Increasing complexity of cancer care:
How displaced treatments impact efficiency, cost-effectiveness and equity

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Certificate of Original Authorship

I, Philip Haywood, declare that this thesis, is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Business School at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

This document has not been submitted for qualifications at any other academic institution.

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Abstract

Background

Medical technology is increasing the number of available treatments for cancer. For advanced cancer an increasing number of treatments can result in an increasing treatment sequence. Treatments are given one after another in a cycle of treatment, failure and then another treatment. Newly added treatments may not replace existing treatments. The movement of existing treatments into later lines of therapy is displacement.

Displacement poses challenges for economic evaluation. This thesis addresses three questions.

1. Does the displacement of a treatment alter its cost-effectiveness?
2. If the cost-effectiveness becomes less favourable can any resulting societal welfare loss be corrected by changing the price?
3. Can the required price change be calculated in Australia?

Methods

A theoretical framework is developed for displacement in cancer treatment. The implications of decision-making criteria and information gaps are assessed. Real-world data is used to estimate the number of treatments and lines of therapy received by patients, and costs of care. A systematic review and meta-analysis of randomised controlled trials which reported treatment outcomes of multiple lines of therapy is undertaken. The cost-effectiveness of displacing treatments for breast cancer, colorectal cancer and non-small cell lung cancer are modelled.

Results

The displacement of a treatment may result in dynamic and allocative inefficiencies. Real-world data showed 13-18% of participants received four or more lines of therapy. The mean health services cost of cancer care was approximately $4 000 per month. Displacement resulted in decreased effectiveness, an increased toxicity per unit time and reduced treatment length.

In the modelling, there was an increase in the incremental cost-effectiveness ratio with displacement. After displacement, reducing the price of cancer treatments by 32% was required to restore cost-effectiveness.

Conclusions

There is the potential for displacement in Australia. Displacement results in an increasing incremental cost-effectiveness ratio of a treatment. This can be corrected with price changes in most circumstances.

The Australian real-world data did not record all the treatments that were received by patients. Therefore, it is not able to be used to calculate the price changes that are required with displacement.

The addition of new treatments in Australia should consider the impact of displacement on currently subsidised treatments. A failure to do this results in biased assessments of the benefits and costs of new treatments. It will likely underestimate the cost and overestimate the benefit. Therefore, the potential for displacement should be considered in cancer treatment funding to ensure equity and cost-effectiveness.

Abbreviations

Abbreviation	Full-text
5-FU	5-fluorouracil
5-HT3	5-hydroxytryptamine 3 (receptor antagonist)
AC	a protocol consisting of doxorubicin and cyclophosphamide
ACIM	Australian Cancer Incidence and Mortality (Books)
AIC	Akaike information criterion
AIHW	Australian Institute of Health and Welfare
AR-DRG	Australian Refined Diagnosis Related Groups
ASM	additive separate model
ATC	Anatomical Therapeutic Chemical Classification System
AUD	Australian dollar
Aus.	Australian
BSC	best supportive care
C/E	cost-effectiveness
Ca	Cancer
Cet	Cetuximab
Cet+I	cetuximab and irinotecan
CHEERS	consolidated health economics reporting
CHeReL	Centre for Health Record Linkage
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPAP	Chemotherapy Pharmaceutical Access Program
CRC	colorectal cancer
CTCAE	common terminology criteria for adverse events
D	Docetaxel
DC	disease control
DEALE	Declining Exponential Approximation of Life Expectancy
DRG	Diagnostic Related Groups
ED	emergency department
EGFR	epithelial growth factor receptor
EM-CaP	Economic Models of Cancer Protocols research project
EoCC	Elements of Cancer Care
EQ-5D	European Quality of life-5 Dimensions
EViQ	Cancer Treatments Online
FEC	a protocol consisting of 5-fluorouracil, epirubicin and cyclophosphamide
FOCUS (trial)	fluorouracil, oxaliplatin, CPT11: use and sequencing
FOLFIRI	a protocol consisting of 5-fluorouracil, leucovorin and irinotecan
FOLFOX	a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin
G-CSF	granulocyte-colony stimulating factor

Gem	gemcitabine
Gem and Carbo	a protocol consisting of gemcitabine and carboplatin
HCD	high cost drug
HR	hazard ratio
HTA	Health Technology Assessment
HUI3	Health Utilities Index Mark 3
ICER	incremental cost-effectiveness ratio
IHPA	Independent Hospital Pricing Authority
IV	intravenous
KRAS	Kristen rat sarcoma
LYS	life year saved
MBS	Medical Benefits Schedule
Met	metastatic
MRC	Medical Research Council
N/A	not applicable
NCCN	National Comprehensive Cancer Network
NHCDC	National Hospital Costs Data Collection
NHMRC	National Health and Medical Research Council
NHS	National Health Service
NICE	National Institute of Health and Clinical Excellence
NMB	net monetary benefit
NSCLC	non-small cell lung cancer
NSW	New South Wales
Onc	oncologist
OR	odds ratio
OR	overall response
OS	overall survival
P	price
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PFS	progression free survival
Pharm	pharmaceutical
PPP	purchasing power parity
PSA	probabilistic sensitivity analysis
Q	quantity
QALY	quality adjusted life years
QHES	Quality of Health Economics Studies
RCC	renal cell carcinoma
RCT	randomised controlled trial
RECIST	Response evaluation criteria in solid tumours
RPBS	Repatriation Schedule of Pharmaceutical Benefits
RR	relative risk

s100	section 100
SD	standard deviation
SPP	survival post-progression
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TGA	Therapeutic Goods Administration
TNM	Tumour Node Metastasis staging system
UK	United Kingdom
US(A)	United States of America
USD	United States of America dollars
XELIRI	a protocol consisting of irinotecan and capecitabine
XELOX	a protocol consisting of oxaliplatin and capecitabine

Symbols

Abbreviation	Full-text
$	dollar
%	per cent
g	gram
K	thousand
kg	kilogram
M	million
mg	milligram
mm	millimetre

Chapter 1 Introduction

1.1 What is the problem?

Medical technology is one of the acknowledged drivers of growth in medical spending in many countries, including Australia.[5] There is enormous optimism generated by new technologies because of the expected clinical benefit, but there are also difficult choices to make because these technologies are costly.[6] The cost of new technologies is contributing to increasing pressure on healthcare budgets. A significant portion of the financial burden is borne by the public purse, particularly in healthcare systems that are based on social insurance, such as Australia.[7]

Australia has mandated the use of economic evidence for national decision-making in the healthcare system since 1993.[5] The Australian Federal Government has a subsidy scheme for medicines (the Pharmaceutical Benefits Scheme [PBS]), which has existed since 1954. The National Health Act requires that the comparative cost and effectiveness of a medicine must be assessed before it is recommended for subsidisation.[8] In practice, this requires the economic evaluation of new medicines.

Economic evaluation, or more broadly economic analysis of healthcare services, is the comparative analysis of alternative courses of action in terms of costs and outcomes.[9] To make the best choices, alternatives need to be assessed using relevant, accurate and comprehensive information. These evaluations should be relevant in answering the appropriate question, accurate in minimising and understanding bias, and comprehensive in the potential alternatives that are included. It is therefore important that the theoretical and practical framework of economic evaluation correctly handle the increasing complexity of decision-making occurring in clinical practice.

Options for treatment of many diseases are increasing with advances in medical technologies. As a result, these medical advances make decision-making more complex. This complexity can relate to the number of decision-making points required and the increased number of alternative treatments available at each decision-making point. The complexity is a developing feature of the treatment pathway for most chronic diseases, for example, hypertension,[10] diabetes[11] or arthritis,[12] in which advances in technology have led to more treatment options and greater treatment choice.

One clinical area in which this is a crucial issue is oncology. Cancer is an important source of morbidity and mortality in Australia. One in two Australians will be diagnosed with cancer and one in five will die from cancer before the age of 85.[13] In the case of advanced cancers, the disease is usually considered incurable, and the goal of treatment is prolonging survival and improving quality of life.[14] The number of available treatments for cancer has increased in recent years and is expected to further increase in the future.[15] Increasing options allow for a longer period of treatment. These treatments options may be administered one after another in succession in response to the failure of a previous treatment.[16-18]

Patients with advanced cancer can now expect a period of initial treatment, followed by disease progression, which is then addressed by "salvage" treatments. The use of additional treatments increases the length of the treatment pathway as measured by the number of treatments received (the treatment sequence). In colorectal cancer, for example, the use of increasing numbers of anticancer treatments available to treat metastatic disease is one reason for the decrease in colorectal cancer mortality in the last thirty years. The availability of additional treatments has resulted in the transformation of advanced cancers into a chronic disease.[19]

Similarly, technology has increased the number of potential treatments for metastatic breast cancer. There are more alternative agents listed for the initial treatment of breast cancer in 2016 than in 2012 (for example Ado-trastuzumab emtansine).[20,21] The newer treatments can be costly, with annual costs well over AUD (2015) $100 000.[22] Other cancers have also seen the same type of rapid change in the therapeutic landscape[23] At the time of writing, some cancers have not yet become chronic diseases, such as pancreatic cancer or brain cancer which have a low long term relative survival rate.[13]

The rapidly rising cost of medical treatments in oncology, both within Australia[24] and internationally,[25-27] is an issue for funders. In Australia, conservative estimates are that colorectal cancer, non-small cell lung cancer (NSCLC), breast cancer and prostate cancer together cost the healthcare sector $1.3 billion in 2009.[7] Less conservative estimates place the expenditure in the Australian community as high as $4.7 billion for cancer care in 2012.[28] In 2012, the expenditure on the PBS for cancer medicines was $587 million.[28] In 2016-2017, the expenditure on the PBS for anti-neoplastic and immunomodulating agents was $3.2 billion.[29] The expectation is that these costs will continue to rise in the future.[30]

Each treatment option requires an evidence base to support its safety, effectiveness and cost-effectiveness. Ideally, this evidence should relate to the proposed use within the treatment pathway. This is a major challenge with increasing treatment options. There is a paucity of high quality data available to analyse the impact on costs and outcomes of the rapidly increasing length of treatment sequences.[14] The clinical evidence to support the use of cancer treatments in metastatic disease beyond the initial three to four treatments is not well developed.[14,31] However, for some cancers there are more chemotherapy agents available for treatment than this. The practical guidance offered for treating metastatic breast cancer is that patients can receive further treatments, provided a patient has responded to one of the last three treatments received.[32]

These additional treatments may be offered despite poor evidence of their clinical effectiveness after the initial lines of therapy.[33] This occurs because of the perceived benefit (and demand) of clinicians or patients. The lack of clinical evidence represents a challenge for economic evaluation, requiring that assumptions be made about effectiveness. These assumptions flow through to decision-making, both for clinical and reimbursement purposes.

Economic evaluation aids the allocation of resources between competing demands. Thus, it contributes to maximising the total societal welfare that is generated when the right choices are made. Poor or inappropriate choices can result in the reduction of welfare.

Guidelines for economic evaluation recommend that all relevant costs and consequences be included in the alternatives.[9] It is also long-standing advice that a high quality and comprehensive economic evaluation consider all relevant alternatives.[9] However, there are no specific recommendations about how to implement this recommendation in the context of oncology.[34] Mittmann et al. (2012)[35] suggested that the selection of alternatives may require minor adaption because of the considerations of oncology. Usual care, recommended care and the most frequently replaced treatment are all potential recommendations.

The guidelines for submission to the Pharmaceutical Benefits Advisory Committee (PBAC), a precursor to subsidisation in Australia, suggest that the alternative assessed should be the treatment most likely to be replaced in practice.[36] The guidelines[36(p16)] also comment that consideration should be given to the movement of current treatment options later in the treatment sequence.

Arguments have been made for 'whole of disease' or full guideline modelling.[37] These models may be beneficial when the costs of developing them are less than the benefits they provide,

but they require clinical information to be available and are complex to produce.[37] This clinical information is often not available in Australia.[38]

Therefore, economic evaluation in oncology is often undertaken to evaluate competing alternative courses of action at a specific small number of decision points. For example, evaluations often consider the choice of first treatment[39] or the second treatment[40] or perhaps the last treatment received,[41] without always assessing the subsequent treatments. This represents a partial analysis of the expected treatment sequence. It assumes that treatments are mutually exclusive when in reality they are not. Therefore, published economic evaluations often evaluate the increasing number of options as substitutes for one another at a specific point in the treatment sequence rather than evaluating them as probable complements over the course of metastatic treatment. The evaluation at a specific point in a treatment sequence may be a pragmatic response to a lack of evidence for the benefit of treatments later in a sequence.

Failure to consider the entire treatment sequence has an unknown impact on the results of economic evaluations and its subsequent impact on decision-making. This thesis analyses this problem and its clinical, economic, policy and equity implications.

1.2 Oncology treatment

Cancer is a diverse group of conditions characterised by the abnormal growth of cells.[13] There are five main categories of cancer: carcinoma, sarcoma, leukaemia, lymphoma and myeloma, and brain and spinal cord cancers.[42] Carcinomas begin in skin or the tissues that line or cover the internal organs. Examples include melanoma, breast cancer, colorectal cancer, pancreatic cancer and lung cancer.

Cancer is categorised by the organ of origin or site - for example, breast cancer or pancreatic cancer.[43] This categorisation can be further subdivided by the cells (or other characteristics) found in the cancer, for example, non-small cell lung cancer and small cell lung cancer.[42]

The spread of cancerous cells from one site to another is termed metastasis, while the original site is the primary cancer.[13]

Another method of subdividing cancer is on the degree of spread.[44] the TNM (tumour node metastasis staging system) describes the size and extent of the primary tumour (T), the number of nearby lymph nodes that have cancer (N) and whether the cancer has metastasised (M).[45] The TNM system describes the cancer in great detail.[45]

A simpler framework is based on the Stages (I to IV), where Stage IV is spread to distant parts of the body and Stage I to III are not spread but the higher numbers represent a larger cancer and greater local spread.[45]

These divisions are important because outcomes and effective treatments differ between the divisions.[43]

Early stage cancer is early in its growth and has not spread.[42] Advanced cancer is cancer that is unlikely to be cured because of its spread and thus the aim of treatment is to control the cancer.[42] Exactly what is considered advanced can differ between cancer types.[42] For example, advanced breast cancer is breast cancer that has spread beyond the breast to other organs (Stage IV). Advanced breast cancer can be contrasted with early breast cancer, where there is curative intent and surgery is often the main treatment.[46] Recurrence after treatment for early cancer can occur at the original site or as metastasis.

A variety of treatment modalities are available for cancer treatment. These include, but are not limited to: chemotherapy, radiotherapy, surgery, endocrine therapy, immunotherapy and targeted therapy. Some of the modalities can overlap, for example, immunotherapy is a type of treatment where the immune system is used to treat cancer.[42] Some of the immunotherapy treatments involve the use of antibodies that encourage the immune system to identify and destroy cancer cells. These antibodies may also be considered targeted therapy.[42]

When cancer has spread, systemic treatments are used. Systemic treatments are those that travel through the bloodstream, potentially reaching all cells in the body and so treat the metastatic disease as well as the primary cancer.[42] Other therapies, such as surgery and radiotherapy, are still used in advanced cancers to control symptoms from the primary site and in other circumstances.[47] Treatment is used in advanced cancer to improve the quality and quantity of life. Treatments, even in the non-curative setting, can extend life expectancy by slowing or reversing cancer growth.[47]

Chemotherapy, endocrine therapy, immunotherapy and targeted therapy are all systemic treatments that involve the use of pharmaceuticals. Standard cytotoxic chemotherapy is a treatment that uses pharmaceuticals to stop the growth of cancer cells, either by stopping division or killing cells.[42] Some noncancerous cells that also divide quickly, for example, blood cells or the cells that line the gastrointestinal tract are also affected by this type of chemotherapy. Targeted therapies are those that block the growth and spread of cancer by interfering with specific molecules identified in cancerous processes. Some cancers have

specific molecules for which interference or inhibition results in effective treatment.[47] Endocrine therapy (also known as hormone therapy) adds, blocks or removes hormones that may be involved in the growth or spread of specific cancer types (for example, breast cancer or prostate cancer).

Chemotherapy and targeted therapies are often administered orally or intravenously. Antibody-based immunotherapy is typically administered intravenously. Intravenous therapy requires an infrastructure to deliver the pharmaceutical safely, including facilities, gaining intravenous access, staff time, disposables and supportive treatments (such as antinausea treatments).[48]

All therapies are associated with adverse events, sometimes significant or life-threatening.[49] Monitoring, treating and avoiding adverse events is a major component of the safe treatment of cancers.[47,48] The cost and burden of adverse events in oncology treatment is substantial.[49,50]

This thesis focuses on pharmaceutical treatment sequences for advanced carcinomas for which curative treatment is not the intent. The examples of breast cancer, colorectal cancer and non-small cell lung cancer are used throughout this thesis. These are common carcinomas which exemplify the issues this thesis addresses and were included in the data collection described and analysed in Chapter 4.

1.3 What is the magnitude of the problem?

Opportunity cost is benefit forgone in the most favoured alternative use of the resources.[51,52] Minimising the opportunity cost of using existing treatments while ensuring efficiency is increasingly important to healthcare funders globally. Several features of oncology treatments and cancer care in Australia exemplify the magnitude of the challenge ahead.

These features include increases in: the number of people developing cancer; the number of oncology treatments available for use; the use of treatments in multiple cancers, and the cost of oncology treatments. Together, these trends place immense pressure on health technology assessment in oncology to ensure correct decisions are made.

The number of cases of cancer in Australia is expected to increase in the future.[53] This is due both to ageing and an increased population. The Australian Institute of Health and Welfare has estimated a 40% increase in cancer cases from 2007 to 2020, with approximately 150 000 diagnoses in 2020.[53] The potential for the demand for anticancer treatment to increase because of an ageing population is well recognised.[54]

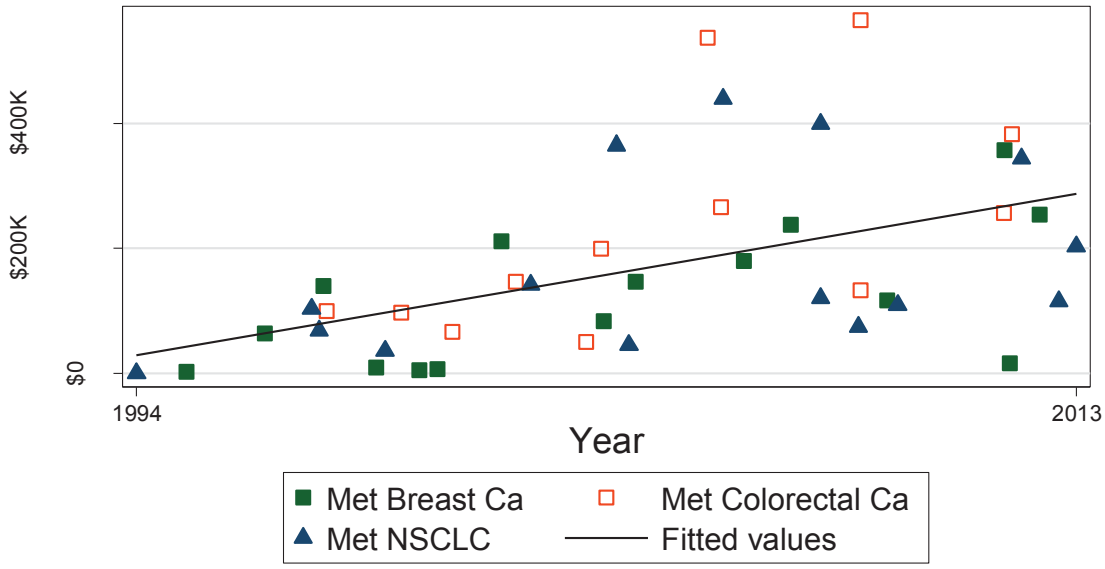
There are also increasing numbers of pharmaceuticals in the pipeline for the treatment of cancer. Increasing numbers of pharmaceuticals are being approved and oncology pharmaceuticals are a priority. Buffery (2015)[15] reported that over 700 new pharmaceuticals and vaccines were in development. In Australia, seven new pharmaceuticals have been approved since 2009 for breast cancer and four for non-small cell lung cancer (see Section 6.2). A growing number of pharmaceuticals may result in an increased length of treatment sequence and potentially an increase of the use of treatments where the clinical evidence is weak. It is assumed a treatment sequence develops when new pharmaceuticals are used prior to existing pharmaceuticals. The movement of an existing pharmaceutical backwards in a treatment sequence is termed displacement. This is defined formally in Chapter 2.

The emergence of genetic technologies and genomic sequencing of tumours has created the potential for pharmaceuticals previously used to treat one type of cancer to be used to treat other cancers types. This use is due to the detection of genetic sequences in tumours that have been associated with treatment response in other cancers. For example, it is now possible to screen rare cancer types and suggest treatments based on driver mutations observed in the cancer genome.[55] Previous research has suggested a high use of off-label treatment for this purpose in the oncology setting in Australia.[56] This creates a growing potential for new lines of therapy for more and more cancers, and an additional complexity about where in the treatment sequence the pharmaceutical will be used.

The high cost of oncology treatments is already a source of concern for decision-makers and reimbursement agencies.[57] Figure 1 is an adaption from Cressman et al. (2015)[58] originally published using Canadian data.[i] It demonstrates how the price has risen over time in purchasing additional progression free survival (PFS, the time before growth of a tumour or death) for three cancers. The trend cost per incremental PFS year purchased is now over AUD (2013) $200 000. The cost-effectiveness of these treatments will be sensitive to small changes in effectiveness or cost.

The development of more targeted agents is also expected to contribute to a rapid increase in the cost of oncology treatment in the near future.[60] This cost increase is due to both the increased numbers of therapies and the requirement of more complex and costly manufacture of biological treatments.[61]

[i] It has been converted to Australian dollars (AUD) using Purchasing Power Parities (PPP).[59]



Adapted from Cressman, 2015 Oncologist

Abbreviations: Ca: cancer; Met: metastatic; NSCLC: non-small cell lung cancer; PFS: progression free survival

Figure 1: Cost per incremental progression free survival gain over time

The total cost of cancer treatments is driven by a combination of the cost of each treatment (including administration and adverse events), the number of treatments each cancer patient receives and the number of cancer patients. As each of these components increases, it follows that the volume and cost of anticancer treatments that are displaced is also likely to increase. The combination of increasing numbers of avaliable treatments and a stronger rationale for their use in individual patients will render the use of large-scale clinical trials to obtain robust comparative evidence on treatment sequences costly. Such trials would be complex, need to be undertaken over many years and may be prohibitively expensive (see Chapter 6).

Therefore, ensuring treatments are cost-effective is an important policy issue for health systems that subsidise anticancer treatments. It is likely that this policy process and the decisions that flow from it will occur in an environment which is not developing the requisite clinical evidence robustly or quickly enough.

1.4 Equity considerations

In the Australian setting, the issue is not simply about ensuring that the Federal Government does not fund pharmaceuticals through the PBS that have not proven to be clinically effective. While this may protect the PBS budget, potential efficiency and health system equity issues remain. Later line therapies may be used by patients even though they are not funded by the PBS, perhaps because of perceived benefit or an assessment of benefit that differs from the societal decision-maker.[62]

Due to the high price associated with newer cancer treatments, use without subsidisation (either by the PBS or another source of funding) can only be achieved by those with significant financial resources (the funding of cancer therapies in Australia is discussed in more detail in Section 4.1). This could result in the inequitable use of these treatments, stratified by wealth. There may also be flow-on effects to the use of public resources, for example, the use of public hospital resources to administer unfunded therapies and to treat adverse events associated with these therapies. The high costs associated with these treatments increases the risk that individuals and their families may face catastrophic health expenses.

This issue is compounded by the fact that a lack of evidence about the size of the benefit does not mean that there is no benefit. Treatments are widely appreciated to have benefit, although the magnitude is not known with certainty. Ensuring that oncology pharmaceuticals are available on the PBS at prices which are sustainable and reflect their opportunity cost is an important way of avoiding inequity in advanced cancer treatment.

1.5 Outline of the thesis

This thesis addresses one way in which a treatment sequence may develop, namely through displacement. Displacement is where existing older treatments are used later in a treatment sequence because of the introduction of new treatments. The new treatments considered in this thesis are those that are chemotherapy and targeted therapy pharmaceuticals.

Three questions are addressed in the context of advanced carcinoma in this thesis.

1. Does the displacement of a treatment, from one line of therapy to a later line, alter its cost-effectiveness compared with alternative treatments or no treatment?
2. If the cost-effectiveness becomes less favourable can any resulting societal welfare loss be corrected by changing the price?
3. Can the required price change be calculated in Australia using administrative data?

Chapters 2 and 3 outline the framework and the previously existing literature. Chapters 4 to 7 are the analytical component of the thesis and Chapter 8 the contribution to the literature and future research requirements.

Chapter 2 describes the framework of lines of therapy and defines displacement. It describes and assesses some of the potential clinical and economic implications associated with displacement of treatment in advanced cancer. It also evaluates the potential inefficiencies

associated with an increasing treatment sequence. It proposes and justifies price adjustment as a solution to these inefficiencies.

Chapter 3 examines the current economic literature. A systematic review of economic evaluations involving a choice in multiple lines of therapy is undertaken. The evidence used, modelling and the approach taken to displacement (and other ways a treatment sequence develops) is reviewed and critiqued to establish if the current literature answers the questions this thesis poses. A case study of economic evaluations of cetuximab is undertaken. Cetuximab is used in different lines of therapy. The modelling approach undertaken and the approach to cetuximab's use in different lines of therapy is critiqued.

Chapter 4 describes the current funding of anticancer pharmaceutical treatments in Australia using a specific dataset that was developed as part of a previous program of research, the Elements of Cancer Care study (EoCC). The EoCC data collection is used to assess the completeness of the administrative data in Australia for three cancer types: breast cancer, colorectal cancer and non-small cell lung cancer. The EoCC is also used to estimate the number of lines of therapy in a sample of patients with advanced cancer. An assessment is made whether the administrative data could be used to identify the lines of therapy. There have been papers published on the adverse events and costs associated with the EoCC cohort.[63,64]

Chapter 5 estimates the cost per month of each line of therapy. A panel data econometric framework is used to calculate the incremental monthly cost associated with an increasing line of therapy. The incremental monthly cost is used to calculate the price changes required to return the cost per month to its original value. The feasibility of implementing these price changes based on Australian administrative data is evaluated.

Chapter 6 reviews contemporary clinical guidelines to assess the number of lines of therapy for which there is high quality evidence for breast cancer, non-small cell lung cancer and colorectal cancer. The number of new anticancer pharmaceuticals and new protocols (collections of pharmaceuticals) becoming available in Australia is tabulated. A systematic review and meta-analysis of randomised controlled trials where treatments were used in different lines of therapy for carcinomas is conducted.

Chapter 7 uses the results of the Chapter 6 meta-analysis in an economic model. The model estimates the impact of displacement on cost-effectiveness and net monetary benefit. The feasibility of price changes is evaluated as a mechanism for minimising the opportunity cost of displaced treatments.

Chapter 8 sets out the generalisability of displaced and makes recommendations for research, modelling of economic evaluation and data collection in the Australian setting.

This thesis is supported by a series of Appendices that detail the searches and data extraction for Chapter 3 and Chapter 6. Additional tables and work from Chapter 4, Chapter 5 and Chapter 7 are included in the Appendices.

Chapter 2 Framework and efficiency

Displacement is where existing older treatments are used later in a treatment sequence, because of the introduction of new treatments rather than being replaced.

The motivation of this Chapter is to understand the consequences of displacement. The aim of this Chapter is to conceptualise displacement and establish a theoretical framework. The framework is used to outline the potential economic consequences of displacement in terms of costs and benefits.

The potential outcomes, the resultant inefficiencies and potential inequities resulting from displacement are discussed. Three scenarios are assessed:

1. not modelling displacement when it occurs;
2. assuming an average cost of displaced treatments; and
3. full information of displaced treatments with value-based pricing.

Not modelling displacement is only appropriate when the assumption is made in an economic evaluation that the new treatment replaces the existing treatment rather than both treatments potentially being used.

Even with full information and value-based pricing, inefficiencies can still occur. These inefficiencies occur because the prices of existing treatments are based on prior evaluations. These evaluations may be invalid after existing treatments are displaced by newly introduced treatments. The cost-effectiveness of existing treatments may have altered.

Altering the price of displaced treatments is offered as a potential solution to restore cost-effectiveness and improve the efficiency of a treatment sequence.

2.1 Framework of lines of therapy

A treatment sequence is defined as the sequential administration of a series of treatments, each separated by the failure of the previous treatment, in patients with advanced cancer. Each treatment may consist of one or more pharmaceuticals. This collection of pharmaceuticals is also referred to as a protocol.

A protocol can include chemotherapy, endocrine, immunotherapy and targeted therapy[ii]. Other therapy modalities such as radiotherapy and surgery are used to treat advanced cancer

[ii] Endocrine therapy is not included in the analysis of subsequent chapters because the focus of this thesis is on chemotherapy and targeted therapy.

and could be included within a protocol. For the purposes of this thesis they are not considered because they do not alter the treatment sequences. A protocol can also include pharmaceuticals and other therapies to avoid or minimise adverse events, such as antinausea medication, intravenous fluids and corticosteroids.

The first line of therapy is the initial protocol (set of pharmaceuticals) given for advanced cancer.[65] Failure of a line of therapy occurs if there is progression or growth of a tumour[iii] and potentially the development of unacceptable toxicity.[68] Unacceptable toxicity is toxicity that is severe enough to require the cessation of treatment.[iv] Failure of the first line of therapy can result in the administration of the second set of pharmaceuticals or protocol (second line of therapy) and, if that then also fails, there may be a third line of therapy and so on.[69] This change in treatment is sometimes referred to as treatment switching.[70]

The reasons for failure of treatment because of progression or growth of a tumour are complex and include multiple mechanisms.[47] One mechanism is selective pressure encouraging the growth of tumour cells that are resistant to the treatment received.[47]

The length of the treatment sequence is enumerated by the number of distinct lines of therapy that could be given. When a patient has received first, second and third line therapy the treatment sequence is of length three.

2.2Framework of displacement

Initially, for a specific cancer there may be no effective treatment and supportive and palliative care is offered. Palliative care and supportive care is treatment directed at reducing symptoms and improving quality of life.

Then, the first treatment A is introduced and is compared to no active treatment (consisting of best supportive care or palliative care). Treatment A is found to be effective and cost-effective compared to no treatment and is subsidised for use. Thus, the new treatment pathway is the use of A in the first line and, when this treatment fails, supportive care follows it. In this case, the length of the treatment sequence is one. In countries that require cost-effectiveness, such

[iii] One commonly used definition of progression in clinical trials involving metastatic disease is the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 which defined progressive disease as at least an absolute 5mm increase in the sum of the longest diameter of the target lesion in addition to at least a 20% increase in the sum of the diameters of target lesions.[66] The appearance of a new lesion is also considered progression.[67]

[iv] Toxicity and adverse events are discussed in greater detail in Chapter 6

as Australia, a price is determined for the subsidisation of treatment A that ensures its cost-effectiveness.

Sometime later a new treatment, treatment B, is developed; it is tested against treatment A (either directly through a clinical trial or indirectly through modelling) and found to be effective and cost-effective relative to treatment A. Treatment B is subsidised for use and replaces A as the first line of therapy. A price is determined for subsidisation of treatment B that ensures its cost-effectiveness. However, now when a patient experiences progression of cancer or intolerable toxicity, and treatment B no longer offers a benefit, best supportive care is not the only option. Treatment A is a potential option in the second line of therapy. Depending on the rules of subsidisation, treatment A may still be subsidised at its original price or funded through some other means (private payment, health insurance etc.). This results in the development of treatment sequence from individual decisions in the first line of therapy (see Table 1).

Table 1: Development of a treatment sequence from individual adoption decisions

Decision	New treatment pathway	First line therapy	Second line therapy	Third line therapy
Treatment A vs No treatment	A	A	No active treatment	N/A
Treatment B vs Treatment A	B → A	B	A	No active treatment
Treatment C vs Treatment B	C → B →A	C	B	A

Abbreviation: N/A: not applicable

Treatment A is unlikely to have been assessed for effectiveness and cost-effectiveness in the second line of therapy, that is, after the use of treatment B. Therefore, there may not be clinical evidence developed for the use of treatment A in the second line of therapy. However, it is likely that, given that there is evidence that treatment A has a clinical effect on the cancer, it will be considered for use in later lines of therapy after the failure of treatment B.

For this thesis, the movement of treatment A from one line of therapy to a later line of therapy because of the addition of another treatment is termed “displacement.” In this example, treatment B has replaced treatment A in the first line of therapy, and treatment A has been displaced from the first line of therapy to the second line of therapy. That is, there has been “replacement” within a line of therapy and then “displacement” into a new line of therapy,

and a treatment sequence has developed. The length of the treatment sequence has increased to two, and treatment A has been displaced one line of therapy.

If another new treatment, treatment C, is now introduced, a similar series of alterations to the treatment sequence is likely to occur once treatment C is assessed as effective and cost-effective relative to treatment B and replaces treatment B in the first line of therapy. It will also receive a price for subsidisation.

Treatment B is displaced from the first line to the second line, and treatment A is displaced from the second line to the third line. From the original assessment in the first line of therapy, treatment A is now being used in the third line. The length of the treatment sequence has increased to three, treatment B has been displaced one line of therapy, and treatment A has been displaced two lines of therapy. Treatment A and treatment B may not have evidence of their clinical effectiveness in their new line of therapy.

A problem that emerges from this process is that there is a difference between the evaluation of a single line of therapy and the entire treatment sequence. This has implications for the cost-effectiveness of each treatment in the setting in which it will now used.

In this framework, the introduction of a new treatment at a single decision point create changes at several other subsequent points in the treatment sequence. Treatment A was evaluated in the first line of therapy but is subsequently used in the second and third line of therapy. Treatment A may not have been evaluated in terms of effectiveness and cost-effectiveness in those later positions in a treatment sequence.

Sometimes a new treatment can be introduced in a later line of therapy and then move forward to the first line of therapy. This is demonstrated with the example of cetuximab for use in metastatic colorectal cancer which is discussed in Cetuximab economic evaluations. The evolution of the use of cetuximab for colorectal cancer is illustrated in Table 2.

Table 2: Displacement due to cetuximab in metastatic colorectal cancer

Scenario	Treatment pathway	First line treatment or protocol	Second line treatment or protocol	Third line treatment or protocol	Fourth line treatment or protocol
Current treatment	FOLFIRI → FOLFOX → other treatments	FOLFIRI	FOLFOX	Other treatments	No active treatment
Introduction of cetuximab	FOLFIRI → FOLFOX → cetuximab→ other treatments	FOLFIRI	FOLFOX	Cetuximab	Other treatments
Movement of cetuximab	FOLFIRI + cetuximab → FOLFOX → other treatments	FOLFIRI + cetuximab	FOLFOX	Other treatments	No active treatment

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Prior to the introduction of cetuximab, treatment for colorectal cancer consisted of three lines of therapy. The evidence for two lines of therapy were reported in several publications[71,72]:

- FOLFOX- a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; and
- FOLFIRI- a protocol consisting of 5-fluorouracil, leucovorin and irinotecan.

The third line of therapy consisted of one of several other treatments with less evidence.[73] With the introduction of cetuximab (a genetically targeted immunotherapy) into the third line of therapy, there was displacement of the "other treatments" into the fourth line of therapy. The first two lines of therapy were unchanged.

Subsequently, cetuximab was combined with chemotherapy (FOLFIRI + cetuximab) in the first line of therapy and the "other treatments" moved back to the third line of therapy. 5-fluorouracil is used in two different lines of therapy, in combination with other pharmaceuticals, demonstrating that individual pharmaceuticals may be present in several lines of therapy.

Thus, displacement is not the only way for a treatment sequence to develop over time. For example, if each new protocol was added at the end of the current treatment sequence then there would be no displacement. Alternatively, the currently available treatments being organised to maximise benefit would also not be displacement.

Another way new treatments do not result in displacement is when they are added to an existing protocol (as cetuximab was in the third row of Table 2) or are used exclusively as a replacement (substitute).

However, displacement has three interrelated features that makes it of interest when considering the economic evaluation of treatment sequences.

1. The adoption of a new treatment alters the use of existing treatments but does not replace them.
2. Adoption of new treatments occurs over time.
3. The new use (of the existing treatment) may not have been evaluated in terms of clinical effectiveness and cost-effectiveness.

Displacement, as it is characterised here, assumes a temporal ordering of treatment, namely that the newly introduced treatments are used before the displaced existing treatments.

2.2.1 Economic evaluation for oncology pharmaceutical adoption

In Australia, as in other countries, economic evaluation is part of the system of health technology assessment (HTA), reimbursement and adoption. The importance of an economic evaluation is emphasised by its contribution to decision-making in order to minimise the opportunity cost.[26]

Australia funds a significant portion of the pharmaceutical budget for oncology care through the Pharmaceutical Benefits Scheme (PBS). The PBS aims to provide timely, reliable and affordable access to medicines for Australians (see Section 4.1 for discussion of funding of pharmaceuticals in oncology).[74] Applications are made for listing on the PBS (with access to subsidisation by reimbursement), usually by manufacturers.[75] The listing of a pharmaceutical on the PBS involves a process that assesses the effectiveness and cost-effectiveness of proposed treatments compared to their alternatives before subsidisation.[76]

The price of the new treatment as proposed in the economic evaluation is chosen by the applicant.[75] The clinical evidence is used for the economic evaluation in submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) but may require extrapolation beyond the trial timeframe. Once a pharmaceutical is recommended for listing on the PBS, a process of price negotiation may occur which is usually followed by approval for listing by the Health Minister or Cabinet. This negotiation may alter the price suggested by the applicant.[75] The

negotiation results in the price of the pharmaceutical to the Government being fixed and the subsequent listing of the pharmaceutical for reimbursement.

The process of pharmaceutical listing on the PBS provides a theoretical framework within which an exploration can be undertaken of the potential impacts of displacement within a treatment sequence. The actual process of listing on the PBS involves more than the simple process described above. PBS listing can include risk-modification strategies associated with high cost pharmaceuticals, including restricting the use of pharmaceuticals to one of more specific lines of therapy or to use with other pharmaceuticals. For example, cetuximab is listed for first line treatment with chemotherapy in metastatic colorectal cancer, as a subsequent lines of therapy with or without chemotherapy in metastatic colorectal cancer, or with radiotherapy in advanced head and neck cancer.[77]

The efficiency of resource utilisation within healthcare systems can be affected when displacement occurs. Three dimensions of efficiency can be considered: allocative, productive and dynamic efficiency.[78] Productive efficiency (or technical efficiency if resources are used) is defined as the production of a given output at the least cost,[52] allocative efficiency refers to ensuring that the community obtains the greatest return from scarce resources (in the case of health care ensuring that it is not possible to increase overall benefits by reallocating benefits between programs)[52] and dynamic efficiency is concerned with the allocation of resources over time (investment decisions).[78,79] The research undertaken for this thesis addresses these three definitions of efficiency.

Economic evaluation may also be used in the context of value-based pricing. In this context, the results of the economic evaluation estimate the value that will be added by the introduction of a new treatment or pharmaceutical. This value, in turn, can be used to calculate a reimbursement price for the new treatment that is consistent with (or at least does not exceed) its added value.[80] There are many components to the value-based pricing of treatments. These components include identifying what is of value, measuring it, valuing it, aggregating it and then using the result to price the treatment.[80]

With the framework of value-based pricing, a biased estimate of the value will result in an incorrect pricing calculation. If the price is lower than it should be then the incentive for the development of a new treatment is diminished, as the manufacturer gains less profit from investing research in this area of oncology. If the price is higher than it should be, there is a welfare loss to society from purchasing the treatment at a higher cost than the opportunity

cost. That is, the resources used to purchase the new treatment would have produced more value if deployed elsewhere. In this situation, although the production of health for cancer patients is productively efficient (it is not possible to produce the same amount of health for cancer patients at a lower cost) the solution is not allocatively efficient (the resources would have more value if deployed elsewhere).

2.2.2 The importance of correct specification of alternatives in an economic evaluation

As discussed above, a new oncology treatment is generally evaluated in terms of its effectiveness and cost-effectiveness relative to an existing treatment. However, when the new treatment is introduced, the old treatment is not always replaced. Instead, it may continue to be used but now after the new treatment. In other words, the old treatment is "displaced" through the lines of therapy to a later line of therapy.

In this context, conducting an economic evaluation of the new treatment compared to the old treatment as replacements (or mutually exclusive substitutes) misrepresents the clinical situation and the economic problem, unless there is a measure in place to prevent the use of both treatments (regulations, disinvestment, removal of funding, etc.). Considering the two treatments as alternatives rather than being used in a treatment sequence is common in healthcare. The consideration of the alternative treatments as replacements for each other may represent the choices in other areas of healthcare accurately, for example in the choice of antidepressants or antibiotics; although there can be treatment failure it is not the expected outcome in these situations.

Additionally, there is very commonly a lack of clinical evidence about the efficacy and/or effectiveness of the old treatment in the new line of therapy. This lack of clinical evidence about later lines of therapy has been recognised for some time (see Chapter 6). The absence of the clinical information makes it difficult to determine the altered incremental benefit and cost of the treatment or even whether it is altered. If the incremental benefit and incremental cost of the existing treatment is altered in its new line of therapy, the opportunity cost associated with the use of existing treatment may change. If the opportunity cost of the existing treatment is altered, then either the price or reimbursement may require reconsideration.

Currently, the pharmaceutical pricing system in Australia does not automatically adjust prices of existing treatments to value. There are mechanisms that alter prices, such as explicit reconsideration, price disclosure within groups of pharmaceuticals that could be used

interchangeably or the introduction of generic pharmaceuticals.[75] However, displacement can occur independently of these other mechanisms.

Table 3 extends Table 1 by adding information about costs and outcomes. That is, it illustrates the sequential introduction of three protocols, each consisting of one treatment, one after the other. It is assumed that each has been the subject of an appropriate clinical trial demonstrating its effectiveness and cost-effectiveness in the first line of therapy compared to the treatment it was most likely to replace at the time of introduction. The benefit of the treatments is expressed in quality adjusted life years (QALYs) gained.

Table 3: Incremental cost-effectiveness analysis for three treatments in the first line of therapy

Treatment	Cost	Benefit (QALY)	Incremental cost	Incremental benefit	ICER
No treatment	$0	0	N/A	N/A	N/A
A	$24 000	1.2	$24 000	1.2	$20 000
B	$32 200	1.4	$8 200	0.2	$41 000
C	$41 200	1.6	$9 000	0.2	$45 000

Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; QALY: quality adjusted life year

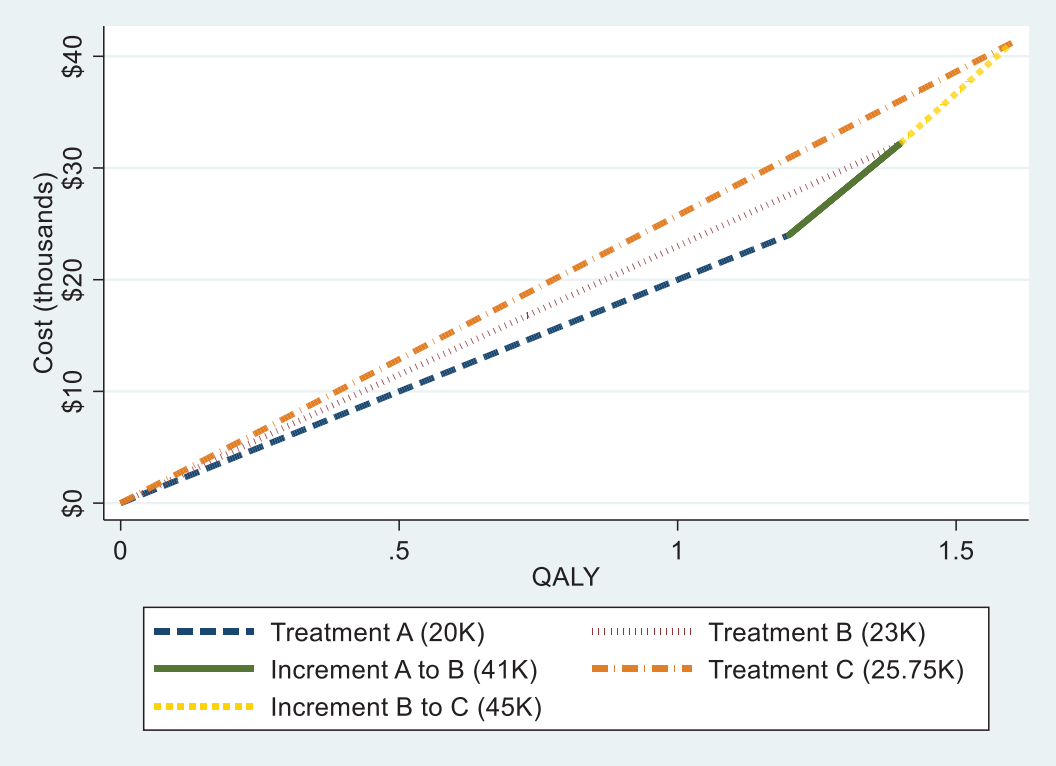
QALYs are a measure designed to combine information about survival and preferences about the quality of life into a single number. They are calculated by weighting the survival time by the quality of life experienced during that time. The weights, also referred to as utility weights, have an upper bound of one reflecting full health, while zero reflects death. Quality of life worse than death can result in negative utility weights. The utility weights are based on preferences of either society or individuals.[51]

The costs and benefits for the use of the three treatments (A, B, and C) are shown in Table 3 and Figure 2. For ease of comparison, “no treatment” is assumed to incur no costs nor produce benefits.

Table 3 demonstrates that moving from No treatment to treatment A and so on produces small incremental gains at an increasing incremental cost relative to the benefit. The incremental cost and the incremental benefit are calculated as the difference between the new treatment and the alternative treatment (the next most recent in this example). The incremental cost-effectiveness ratio (ICER) is calculated by dividing the incremental cost by the incremental benefit. The ICER represents the cost per QALY gained from reimbursing and using the new treatment instead of the next most recent existing treatment.

The same information is displayed in the cost-effectiveness plane in Figure 2. The horizontal axis represents the effectiveness of the treatment (in QALYs) and the vertical axis the cost. The slope from one treatment to the next is the incremental cost-effectiveness ratio.

Each treatment is to the right and above the one preceding it, showing it to be both more costly and more effective. However, the ICER does not exceed $50 000/QALY gained.



Abbreviation: QALY, quality adjusted life years

Figure 2: Cost-Effectiveness plane for replacement with treatments A, B and C

In the context of reimbursement decision-making, the concept of a willingness to pay (WTP) threshold is often used. This is the price that reflects society's willingness to purchase additional QALYs rather than allocate resources to another use. If $50,000 was the (implied or explicit) willingness to pay threshold per QALY all three treatments would have been accepted for subsidisation and reimbursement. The threshold represents the value of an extra QALY to the decision-maker. This may be the cost of QALYs from activities foregone elsewhere in the health system,[81] a benchmark or an explicit threshold.[82] Minimising the opportunity cost would involve accepting the treatment if the incremental cost-effectiveness was less than the threshold and not accepting the treatment for reimbursement if the incremental cost-effectiveness was greater than the threshold.

If the cost-effectiveness threshold was $41 000, then initially treatment A and then treatment B would be chosen for reimbursement. However, treatment C would be rejected for reimbursement. This is because the resources required to gain the additional QALYs (at a cost of $45 000/QALY) exceeds the threshold and could have been better used elsewhere.

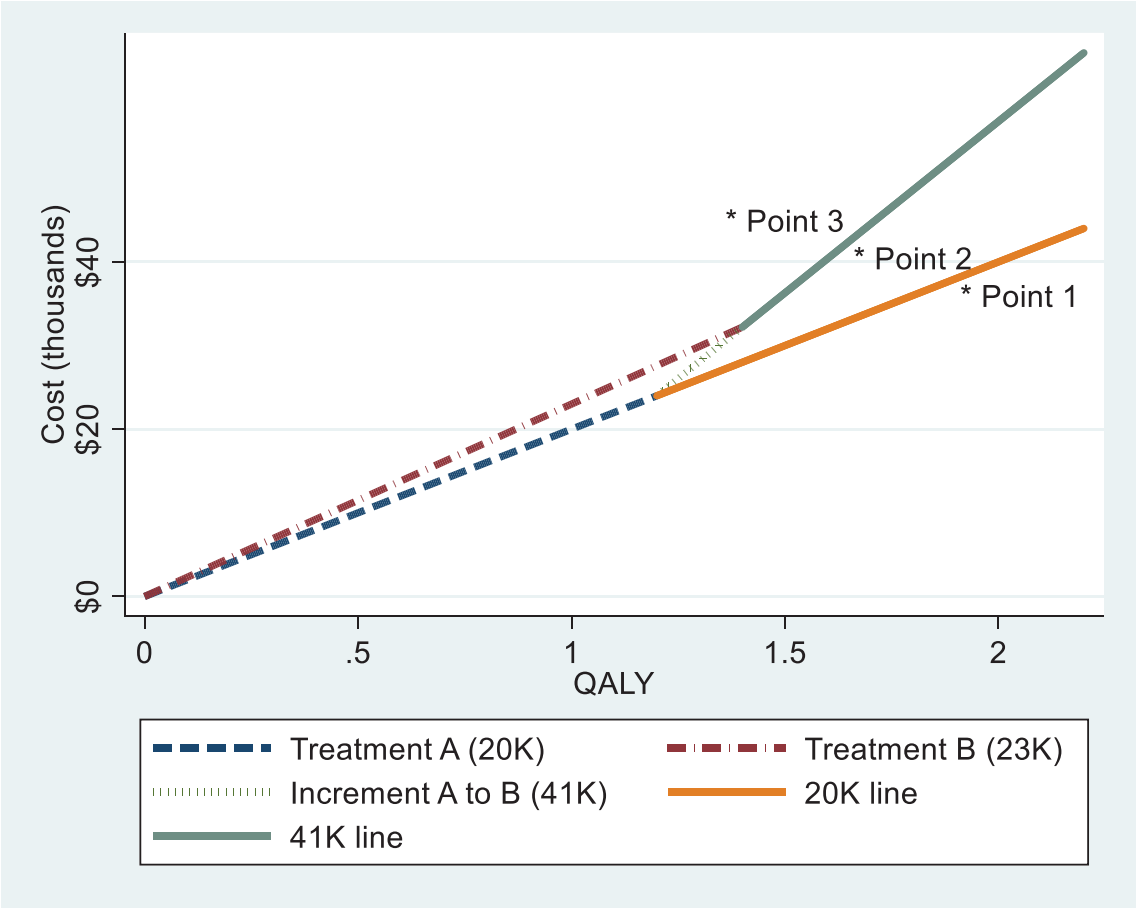
If the threshold was less than $41 000 and above $20 000, only treatment A would be recommended for reimbursement. At a threshold of less than $20 000, no treatment would be recommended for reimbursement.

Each of these calculations and the subsequent decision is made on the assumption that the new treatment replaces the existing treatments. However, as discussed, unless the use of one treatment precludes the use of the others (because of regulation, disinvestment, or incompatible therapies) multiple treatments are available to be used when they are reimbursed through subsidy. Therefore, it is likely that any available effective therapy will be used at some point in the treatment pathway if there is progression.

To examine the situation where two treatments become available, an extension in the cost-effectiveness plane is used. When treatment B is introduced, as well as the use of treatment B in the first line of therapy, treatment A can be used in the second line of therapy. It might be expected that the use of treatment A after the use of treatment B will result in increased costs and benefits compared to treatment B alone. On the cost-effectiveness plane, it will be to the right and above the position of treatment B alone.

There are three broad scenarios that could exist. Examples of these are shown as points 1, 2 and 3 in Figure 3. Each of these shows a potential outcome associated with the use of both treatments A and B.

1. Scenario 1 (Point 1) is when the combination of treatment A and B in a treatment sequence (B→A) is more effective and has a lower incremental cost-effectiveness from treatment A than treatment A has from no treatment.
2. Scenario 2 (Point 2) is when the combination of treatment A and B in a treatment sequence (B→A) has an incremental cost-effectiveness between that of the incremental benefit of treatment A (from no treatment) and treatment B (from treatment A).
3. Scenario 3 (Point 3) is when the incremental benefit of the combination of treatment A and B in a treatment sequence (B→A) (from treatment A or treatment B) is greater than the incremental benefit of treatment B (from treatment A).



Abbreviation: QALY: quality adjusted life years

Figure 3: Cost-effectiveness place of replacement and displacement for treatment A and B

As shown in Table 3, treatment A had an ICER of $20 000/QALY gained compared to no treatment; the 20K line in Figure 3 shows the extension of this cost-effectiveness ratio in the cost-effectiveness plane. Treatment B had an ICER of $41 000/QALY gained over treatment A, and the 41K line shows the extension of this ICER on the cost-effectiveness plane.

Point 1 (Scenario 1) has a lower cost-effectiveness increment compared to treatment A than treatment A compared to no treatment, that is it is below (less costly) and to the right (more effective) of the 20K line.

Extended dominance occurs when one alternative has a higher incremental cost-effectiveness than another more effective alternative.[51] In this example, at point 1 the treatment sequence of treatment B followed by treatment A (B→A) has extended dominance over both treatment A (used alone) and treatment B (used alone). Therefore, the treatment sequence B→A should always be chosen over the option of treatment A alone or treatment B alone. Treatment A alone and treatment B alone are extendedly dominated by no treatment and the treatment sequence B→A. If treatment A was considered cost-effective relative to no treatment, then the treatment sequence B→A is also cost-effective.

Point 2 (Scenario 2) has a higher ICER than no treatment compared to treatment A (i.e. it is above and to the left of the 20K line), but a lower ICER than from A to B (i.e. it is below and to the right of the 41K line). The use of treatment B alone is extendedly dominated by the combination of treatments sequence B→A. If B was considered cost-effective, then the treatment sequence B→A is also cost-effective.

Point 3 (Scenario 3) has a higher ICER compared to treatment B than from treatment A to treatment B (i.e. it is above and to the left of the 41K line), and by extension from no treatment to treatment A (it is above and to the right of the 20K line). In this scenario, the previous decisions do not give an indication of whether the combination of treatments is cost-effective. However, if the ICER from treatment A to B is at the highest acceptable level, then the treatment sequence B→A would not be considered cost-effective because at point 3 it exceeds the highest acceptable level of incremental cost-effectiveness. In this case, the incremental cost-effectiveness of using treatment sequence B→A is higher (less incremental benefit per unit of incremental cost) than all the other calculated ICERs.

The discussion above highlights some of the problems to be considered, depending on whether treatments are, in fact, mutually exclusive - complete substitutes - for each another (replacement) or whether they are, to an extent, complements (both replacement and displacement). It is the combination of treatment A and treatment B in a treatment sequence that needs to be considered in an economic evaluation.

In considering the implications of the above, it is important to understand the regulatory environment, especially if disinvestment and reinvestment in alternative treatments is a viable option. In scenario 3, if disinvestment from treatment A is possible, then treatment B alone is the ideal decision if the acceptable cost-effective ratio is $41 000 or above. If disinvestment is not possible then treatment A would be the preferred option (because the combination of treatment A and treatment B is not cost-effective). That is, the realistic alternatives must be identified.

Correctly identifying the alternatives, whether it is replacement or replacement and displacement, is an important component of constructing an appropriate economic evaluation for decision-making for oncology pharmaceutical adoption.

2.3 What are the efficiency implications of displacement?

The decision to subsidise and the extent of reimbursement of new oncology treatments depends on what clinical evidence is available, how the decision is modelled and how treatments are priced.

Lack of evidence, modelling assumptions and pricing structures may introduce a bias in decision-making that results in a loss of efficiency when displacement occurs.

In this Section, three approaches to subsidising treatments in oncology are evaluated. The three approaches are:

- assuming replacement rather than replacement and displacement;
- assuming a mean cost and benefit for displaced therapies; and
- using value-based pricing with incremental analysis and full information.

The potential biases are identified and efficiency losses are discussed. Emphasis is placed on when a failure to consider displacement may result in allocative inefficiency, productive inefficiency or dynamic inefficiency.

2.3.1 Assuming replacement rather than replacement and displacement

There are several reasons why the economic evaluation of alternative treatments for oncology may be modelled as replacement rather than replacement and displacement.

Most commonly, information may not be available for the outcomes (both costs and benefits) of replacement and displacement. Instead, information may be available for replacement only, for example, a clinical trial where two alternative treatments (treatment A and treatment B) are compared within a line of therapy.[83] Therefore, the economic decision (that is the economic model) could be constructed as replacement when the clinical situation that will most likely occur will involve both replacement and displacement- essentially not including a valid alternative.

Table 4 shows the ideal decision that should be made for each of the three scenarios discussed above in Figure 3 (for two different cost-effectiveness thresholds). Table 4 shows whether the same decision would occur, if the treatments are incorrectly assumed to be replacements (substitutes as shown in Figure 2) when they are complements (replacement and displacement, as shown in Figure 3).

Two problems may arise if only the replacement alternatives are considered rather than the full set of alternatives available for replacement and displacement. First, a cost-effective combination of technologies (which may occur in scenario 1) may not be accepted. Second, a cost-ineffective combination of technologies (which may occur in scenario 3) may be accepted.

Table 4: Relationship between cost-effectiveness ratio, replacement and displacement decisions

Scenario	Acceptable ICER is $20 000		Acceptable ICER is $41 000	
	Ideal decision	**Replacement gives the same result as replacement and displacement**	**Ideal decision**	**Replacement gives the same result as replacement and displacement**
Scenario 1: B→A has extended domination of B and A	Treatment A with Treatment B	No	Treatment A with Treatment B	Yes
Scenario 2: B→A has a similar ICER as B from A	Treatment A alone	Yes	Treatment A with Treatment B	Yes
Scenario 3: B→A has a higher ICER than B from A	Treatment A alone	Yes	Treatment B alone, disinvest from Treatment A if disinvestment is not possible Treatment A	No

Abbreviation: ICER: incremental cost-effectiveness ratio

While the situation will become increasingly complicated when the third treatment (treatment C) is introduced, the same principles apply. If the incremental cost-effectiveness of a treatment changes as it is displaced, then a decision about a new technology which causes displacement may be incorrect because the incremental cost-effectiveness of a previously adopted technology changes.

Allocative inefficiency can result if a cost-ineffective combination of treatments is accepted, that is one with a higher (deteriorating) ICER than the threshold willingness to pay. The resources could be used to provide more societal benefit elsewhere and not for the treatment of advanced cancer. Allocative inefficiency can also occur if a cost-effective combination of treatments is not accepted, whereby societal benefit is diminished because the resources would have produced more benefit if allocated to the treatment of cancer rather than their alternative use.

As shown in Table 4, the relationship between the cost-effectiveness of treatments as modelled at the requested prices and the acceptable cost-effectiveness (that is the threshold) for a decision-maker is important. If the cost-effectiveness of a treatment before displacement is close to, but does not exceed, the societal threshold then the possibility of an incorrect decision increases. This is because displacement increases the cost-effectiveness of the displaced therapy (that is, a deterioration in the cost-effectiveness ratio). This problem could be mediated by including costs and benefits from treatments that are used after the treatment in the initial line of therapy.

Therefore, if displacement occurs, it is important that the evaluation of the incremental cost-effectiveness of new treatments takes into consideration use of existing treatments. If the costs and benefits of existing treatments differ when displaced than in the original consideration, not considering them may lead to allocative inefficiency because of the potential for bias in the results.[70]

2.3.2 Inclusion of mean costs and benefits with displacement

One method of including the relevant costs and benefits in the absence of complete information about the cost and benefits of displaced treatment is to use an estimate of average cost and average benefit of displaced treatments. These averages are applied to the period that is identified as attributable to displaced therapies.

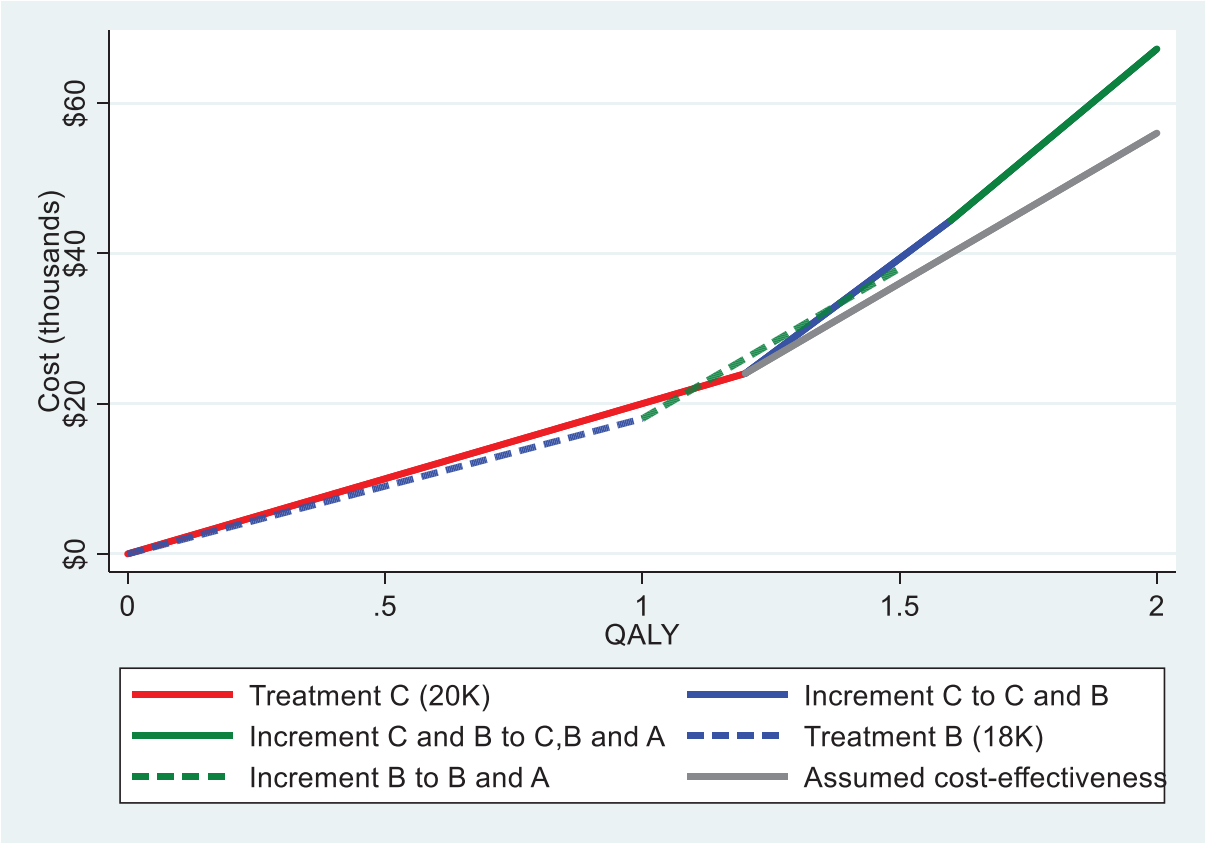
For example, this approach is used when there is evidence of incremental survival from a clinical trial that included displaced treatments. If a new treatment was offered to one arm of a trial and not the other and overall survival was measured as an outcome, then the overall survival of the treatment arm would include the benefit of displaced treatments and the cost would include the cost of displaced treatments (that is the survival benefit of B→A has been estimated correctly). However, the collection of information of costs may cease after the new treatment has ceased and a modelling approach is often required.

Modelling is used to determine the relationship between survival and the costs and benefit, and therefore the cost-effectiveness (see Section 3.1 for a systematic review of the modelling assumptions used in economic evaluations of multiple lines of therapy). A commonly used assumption is to assume a constant cost for the displaced treatments.

The potential problem with this approach is shown in Figure 4, where a two treatment sequence (treatment A and B- dashed line) is compared to a three treatment sequence (treatment A, B and C- solid line). Each displacement is of the type described in scenario 3

above with an increasing cost per incremental benefit (Figure 3). The same cost per unit of effect is assumed for the displaced therapies in the three treatment sequence (solid grey line) as the two treatment sequence (dashed green line).

In this example, the assumed cost (grey line) underestimated the true cost of the displacement of treatments for the three treatment sequence and therefore a cost-ineffective combination of treatments would be more likely to be accepted. This is because the relationship between the costs and effectiveness of displacing treatment A is different from displacing treatment B. Also, the relationship between costs and effectiveness for treatment A might be different when it is displaced once from when it is displaced twice.



Symbol: K: thousand
Abbreviation: QALY: quality adjusted life years

Figure 4: Example of displacement resulting in allocative inefficiency

Including a mean cost and benefit for displaced treatments and protocols potentially results in allocative inefficiency because it assumes a common cost and benefit to multiple different treatments that have been displaced. If the cost and the benefit differ for treatments with displacement or the cost and the benefit for a treatment change with the number of displacements it is an inappropriate assumption with implications for decision-making.

One method of ensuring this allocative inefficiency does not occur is to explicitly include each displaced treatment in the cost-effectiveness analysis to achieve value-based pricing.

2.3.3 Value-based pricing and full information about incremental cost and benefit

The previous two approaches demonstrate that not accounting for each displacement in decision-making may result in inaccurate assessments of the incremental cost and benefit. Inaccurate assessments of the incremental cost and benefit may result in allocative inefficiency.

Allocative inefficiency can be avoided by correctly calculating the incremental cost and benefit of the entire treatment sequence associated with the introduction of a new treatment compared to the previous treatment sequence. A second approach to ensure allocative efficiency is to use value-based pricing, that is, to price the new treatment in such a way as to ensure that a cost-effectiveness threshold is not exceeded (assuming the prices of the existing treatments are fixed). A model of value-based pricing is introduced in this Section, with an example demonstrating the potential inefficiencies.

In the value-based pricing model the identification, measurement and aggregation of the incremental health benefit is via QALYs. The value of the QALY is determined exogenously by a societal willingness to pay threshold.

The incremental net monetary benefit (NMB) is the net benefit to society of adopting the new treatment (defined in Equation 1).[51]

$$NMB = (threshold * incremental\ QALY) - incremental\ cost \qquad (1)$$

There were several assumptions made in the modelling.

1. The treatment of chronic cancer is expected to be limited, with the expected survival of patients and the expected use of treatment being finite.
2. The clinical effectiveness of individual treatments and the treatment sequences are known with certainty.
3. Doctors and patients will use the available treatments without regard for their cost to the funder to maximise benefit for patients.
4. The only restriction on the use of treatments is their availability. Once subsidised the treatment can be used in any line of therapy.

5. New treatments are more effective in the first line of therapy than previous treatments.
6. New treatments displace existing treatments into the next line of therapy, if subsidised.
7. Each treatment is only used in one line of therapy.
8. Unsubsidised treatments are not able to be used.
9. The treatments are the only available disease modifying strategy.
10. Each treatment is a single pharmaceutical with a known usage, consumption or volume of treatment in each line of therapy.
11. The costs of the treatments are the only costs in the model.
12. Manufacturers do not own multiple treatments and are profit maximisers.
13. Manufacturers offer a treatment at a set price and the price does not change after acceptance.
14. The decision-maker agrees to subsidisation by accepting a price for the treatment if the NMB is not negative.

Cancer treatments are not the same as other consumer goods (in which for example non-satiation is assumed). This is because the demand for cancer treatments (like other healthcare) is a derived demand (the underlying demand is for improved survival and/or quality of life). For an individual the marginal utility of a specific treatment will reach zero and afterwards become negative, because of the toxicity of treatment. Therefore, even in the absence of price as a rationing mechanism for an individual (that is the patient in consultation with their doctor) there is not unlimited consumption.

Assumption 14 suggests that the manufacturers extract all the rent from the provision of the treatment. The cost of each line of therapy is the price of the treatment multiplied by its usage (consumption) in that line of therapy.

The natural history of the cancer is no treatment, for which there is an associated survival and QALY gain compared to immediate death (Q_{NH}). There are multiple treatments introduced one after another with each successive treatment being more effective than the previous treatment (or the natural history of the disease for the first treatment), and therefore each becoming the first line of therapy (as shown in Table 3 and Assumption 5).

As each treatment is subsidised the prior treatments are displaced into later lines of therapy (as discussed in Section 2.2, and Assumptions 6 and 7).

The benefit of each treatment j alone in first line of therapy is Q_j with $Q_{NH} < Q_1 < Q_2 < Q_{j-1} < Q_j < Q_{j+1}$.

The required usage or consumption of treatment j in the first line of therapy is d_j.

The benefit from all treatments up to and including treatment *j* (DQ_j) is shown in Equation 2.

$$DQ_j = Q_j + b_{j-1,j}\, Q_{j-1} + \cdots + b_{2,j} Q_j + b_{1,j} Q_1 \quad (2)$$

In Equation 2, $b_{i,k}$ is the change in the outcome of treatment *i* because of displacement with the introduction of treatment *k*, the number of displacements is *k-i*, and the length of the treatment sequence is *k*.

The decision-maker requires that the threshold value of cost/QALY gained not be exceeded with reimbursement (WTP threshold=π). The decision-maker achieves this by accepting or rejecting the prices offered to them for each of the treatments.

To maximise profit the manufacturer will choose the highest possible price that ensures the cost-effectiveness threshold is not exceeded. This is because the use of the treatment is not responsive to price once subsidised (Assumption 3). Therefore, the prices that are offered to the decision-maker are as high as they can be, given the available constraint (Assumptions 12 and 13) of requiring the NMB to not be negative (Assumption 14). That is, the boundary solution will be used.

The price accepted by the decision-maker for treatment *i* is p_i and the usage of treatment *i* with the introduction of treatment *j* (i.e. in the *jth* line of therapy) is d_{ij}.

If only replacement is considered *($b_{i,j}$=0, if i ≠j and $d_{ij} = 0\ if\ i \neq j$)* each of the treatments would be accepted and reimbursed provided the price did not cause the NMB to become negative.

The incremental cost for the first treatment is $p_1 d_{11} - 0$.

The incremental benefit for the first line of therapy is $\pi(Q_1 - Q_{nh})$.

Therefore, the NMB is shown in Equation 3, and is rearranged to make price the subject in Equation 4.

$$NMB = \pi(Q_1 - Q_{nh}) - p_1 d_{11} = 0 \quad (3)$$

$$p_1 = \frac{\pi(Q_1 - Q_{nh})}{d_{11}} \quad (4)$$

The price for the replacement scenario for treatment *j* is shown in Equation 5.

$$p_j = \frac{\pi(Q_j - Q_{nh})}{d_{jj}} = \frac{\pi(Q_j)}{d_{jj}} \; if Q_{nh} = 0 \quad (5)$$

That is, the prices of treatments are related to their benefit and the required amount of treatment that will be consumed in treatment but not the prices or size of the benefit of other treatments if replacement occurs.

When displacement occurs, there is potential benefit from the use of previously adopted treatments (*j-1, j-2, ….,1*). If the cost (price multiplied by volume of the treatment) of displaced treatments decreases relatively more than the benefit, the cost-effectiveness ratio would improve, if they stay the same the cost-effectiveness is unaltered (even when the effectiveness is altered), and if the benefit decreased more than the cost, the cost-effectiveness ratio worsens.

Three scenarios considered in Figure 3 could arise:

- cost-effectiveness could improve for the displaced treatment(s);
- cost-effectiveness could remain the same in next line of therapy as it was in first line for the displaced treatment(s); or
- cost-effectiveness in the next line of therapy could be worse than in the first line for the displaced treatment(s).

The cost from all treatments up to and including treatment *j* when treatment *j* is introduced ($Dcost_j$) is shown in Equation 6.

$$Dcost_j = p_j d_{jj} + p_{j-1} d_{j-1,j} + \cdots + p_1 d_{1j} \quad (6)$$

The incremental benefit is the difference between benefit of one treatment (including all displaced treatments) and the benefit of the previous treatment (including all displaced treatments) (i.e. $DQ_j - DQ_{j-1}$). The incremental cost is the difference between the displaced cost of one therapy and the displaced cost of the previous therapy ($Dcost_j - Dcost_{j-1}$).

The price of the new treatment is determined by total benefit from the treatment sequence multiplied by the threshold minus the other costs that are required for the displaced therapies divided by the required consumption of the new treatment. This is shown in Equations 7 and 8.

$$p_j = \frac{\pi(DQ_j - Q_{nh}) - \sum_{i=1}^{j-1} p_i d_{i,j}}{d_{jj}} \quad (7)$$

$$p_j = \frac{\pi(Q_j) + \pi((\sum_{i=1}^{j-1} b_{i,j} Q_i) - Q_{nh}) - \sum_{i=1}^{j-1} p_i d_{i,j}}{d_{jj}} \quad (8)$$

If it is assumed there is no change in the relationship between cost and outcome for each of the displaced treatments, that is within each line of therapy (i.e. $p_i d_{i,j} = \pi b_{i,j} Q_1$) and $Q_{nh} = 0$, then, the price of the new treatment is the monetary value of the benefit minus the costs (of other treatments) divided by the consumption (shown in Equations 9 to 12).

$$p_j = \frac{\pi(DQ_j) - \sum_{i=1}^{j-1} p_i d_{i,j}}{d_{jj}} \quad (9)$$

$$p_j = \frac{\pi(Q_j) + \pi(\sum_{i=1}^{j-1} b_{i,j} Q_i) - \sum_{i=1}^{j-1} p_i d_{i,j}}{d_{jj}} \quad (10)$$

$$p_j = \frac{\pi(Q_j) + \pi \sum_{i=1}^{j-1} p_i d_{i,i+j-1} - \sum_{i=1}^{j-1} p_i d_{i,j}}{d_{jj}} \quad (11)$$

$$p_j = \frac{\pi(Q_j)}{d_{jj}} = (equation\ 5) \quad (12)$$

That is, if there is no change in the cost-effectiveness of the displaced treatments, the price of the new treatment is the same as when considering replacement only. This occurs even when the effectiveness of existing treatments is reduced with displacement provided there is no change in the relative value of the benefit compared to the cost of the displaced treatments.

The alteration in the relationship between cost and value for treatment *i* with the introduction of treatment *j* ($c_{i,j}$) can be determined by the ratio of the cost to the monetary value of the benefit within each line of therapy (equation 13).

$$c_{i,j} = \frac{p_i d_{i,j}}{\pi b_{i,j} Q_i} \quad (13)$$

If the various $c_{i,j}$ are all greater than one, then the cost of the displaced treatments relative to the value of their benefit increases and the price of the new treatments falls (equation 8).

Alternatively, if the various $c_{i,j}$ are all less than one then the cost of the displaced treatments relative to the benefit decreases and the price of the new therapy would increase to maintain cost-effectiveness of the treatment sequence at the value-based pricing threshold. If there is a mixture of $c_{i,j}$ greater or less than one, the impact on pricing is ambiguous depending on whether the cost of displaced treatments ($\sum_{i=1}^{j-1} p_i d_{i,j}$) is greater or less than the value of the benefit of displaced treatments ($\pi(\sum_{i=1}^{j-1} b_{i,j} Q_i)$).

Displacement has an impact on the price of newer treatments. When $c_{i,j} > 1$, treatments that were introduced earlier and subsequently displaced have higher prices relative to the value of the benefit than later treatments. Conversely, later, superior treatments can have lower prices with displacement compared to the replacement scenario.

At the extreme, the prices could be reduced to below the marginal cost of production or zero. In these cases, the new treatment will not be adopted, either because it would not be offered, or alternatively because it would not be accepted (even at zero price).

Despite the correct calculation of the incremental cost and benefit of a new treatment with consideration of the treatment sequence, there are two potential inefficiencies that can occur if the cost of displaced treatments increases relative to their benefit ($c_{i,j} > 1$).

First, there is allocative inefficiency. This is because displaced treatments have an individual incremental cost-effectiveness that exceeds the cost-effectiveness threshold. Societal welfare would be improved by not using the displaced treatments and diverting the resources to an alternative use.

Second, there may also be dynamic inefficiency. This is because existing displaced treatments have a higher price relative to newer treatments. At the extreme, new treatments would not be adopted, which may reduce the incentive to innovate, that is, to research and develop new treatments. Over time this would result in a reduction in the available treatments and subsequently worse outcomes for cancer patients.

Therefore, the policy of pricing new treatments, assuming the prices of existing treatments do not change may be associated with potential allocative and dynamic inefficiency even with full information. While the incremental cost-effectiveness of a treatment sequences remains consistent with value-based pricing, the individual components of the treatment sequence have different cost-effectiveness. Full information about the costs and effectiveness is necessary but not sufficient to exclude allocative and dynamic inefficiencies.

Returning the cost-effectiveness of displaced existing treatments to their original cost-effectiveness (prior to displacement) would remove the allocative inefficiency of displaced therapies. This can be achieved by altering the price of existing treatments when they are displaced by the introduction of newer, more effective treatments.

Adjusting the price of each treatment by $1/c_{i,j}$ when displacement occurs and the line of therapy changes would restore the incremental cost-effectiveness of displaced treatments to their original assessment. This would eliminate the potential allocative inefficiency associated with the later line displaced treatments.

Additionally, adjusting the price of displaced treatments would potentially improve the price of newer treatments as they are introduced, avoiding dynamic inefficiency.

It is not simply the change in the effectiveness associated with a displaced treatment that may produce allocative and dynamic inefficiency but rather the potential change in the cost-effectiveness. Within this model, this can be addressed with price changes.

This is illustrated below in an example, initially showing replacement, then displacement and value-based pricing and finally, displacement, value-based-pricing and price changes. The implications for cost, benefit, allocative and dynamic efficiency are discussed.

Three treatments are introduced one after another as replacements, with each producing more benefit (QALYs gained) than the one prior, and the first treatment (treatment A) producing more benefit than the natural history of the disease (which is zero in this example).

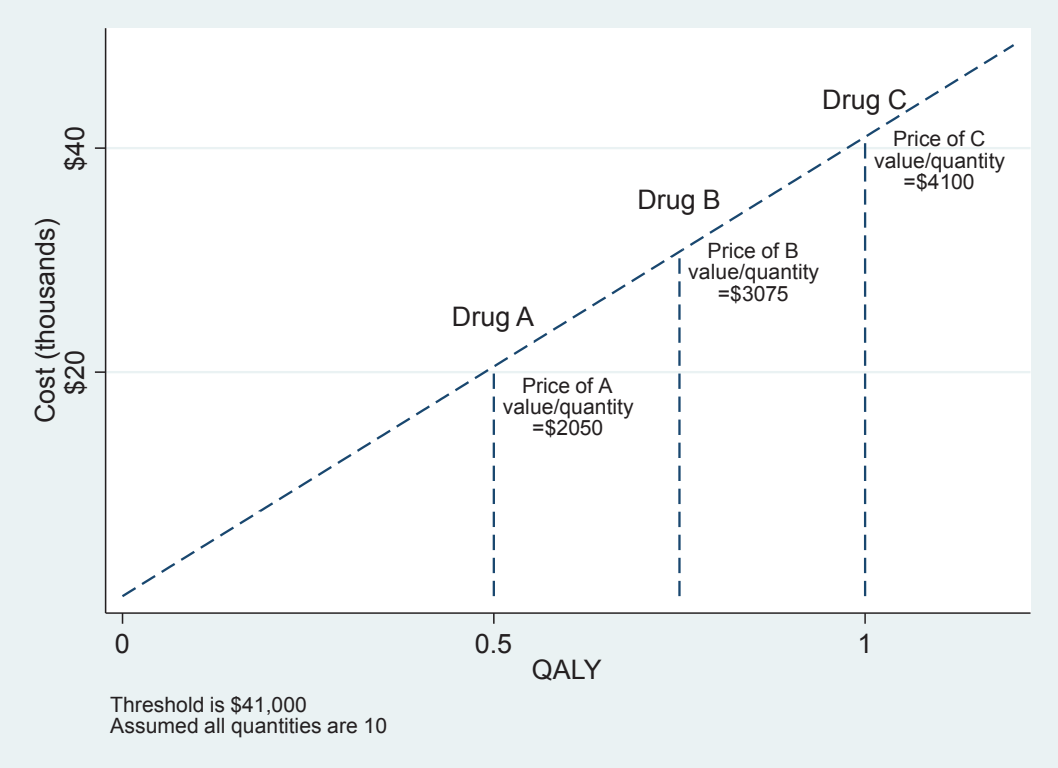
As each treatment replaces the previous treatment, the price is chosen by the manufacturer to ensure that the NMB is not negative. This ensures that the incremental cost-effectiveness remains $41 000 per QALY. The total cost paid by the decision-maker is the product of price and quantity. The information about the costs and benefits of these treatments is shown in Table 5 and in Figure 5, on a cost-effectiveness plane.

Table 5: Incremental cost-effectiveness analysis for three treatments in the first line of therapy

Treatment	Quantity (Q)	Benefit (QALY)	Incremental benefit (QALY)	Price (P)	Cost (P*Q)	ICER
No treatment	0	0	N/A	N/A		N/A
A	10	0.5	0.5	$2 050	$20 500	$41 000
B	10	0.75	0.25	$3 750	$37 500	$41 000
C	10	1	0.25	$4 100	$41 000	$41 000

Note: The decision-maker willingness to pay is $41 000 per QALY
Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; P: price; Q: quantity; QALY: quality adjusted life year

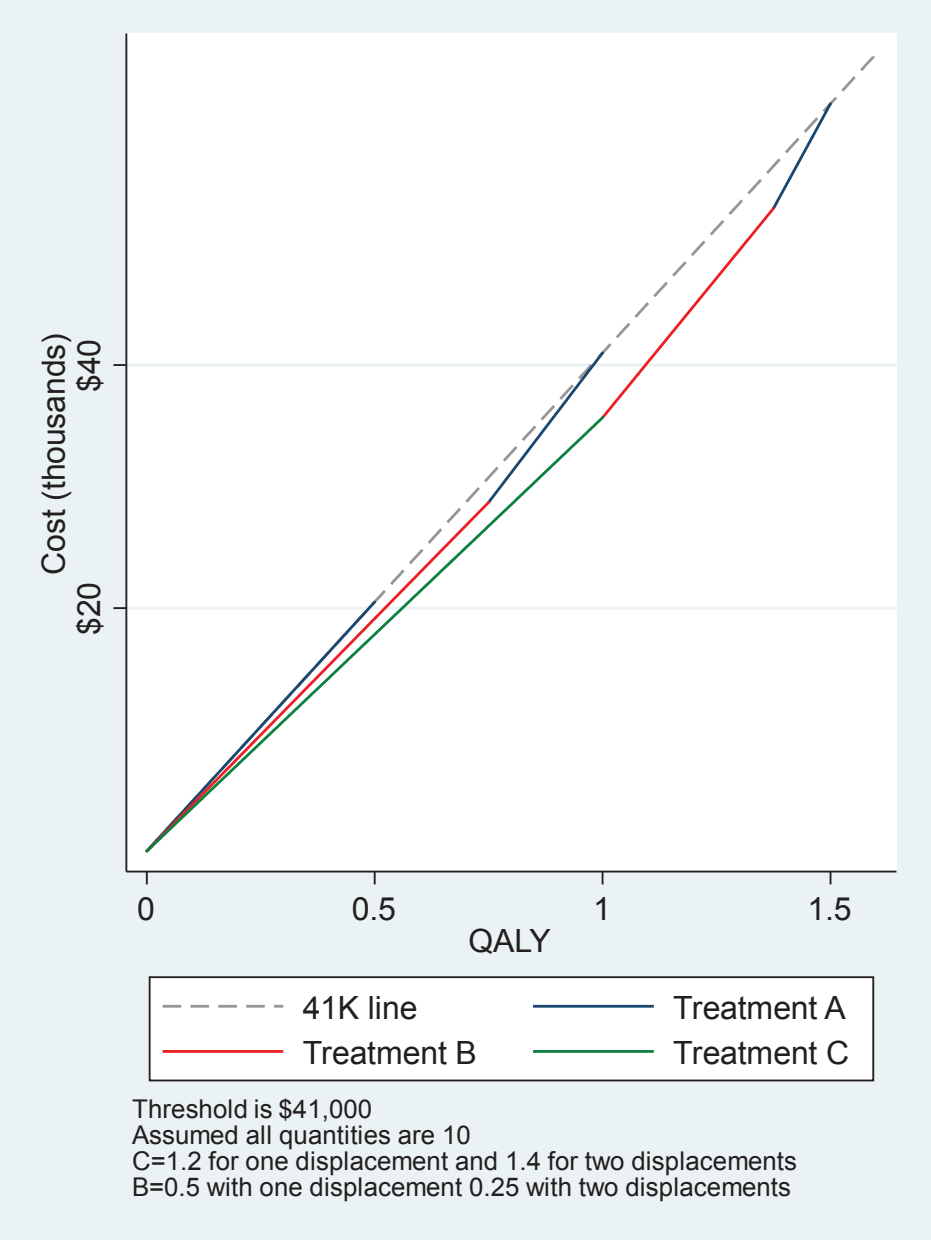
The use of value-based pricing results in the treatments being on the same cost-effectiveness line from the origin on a cost-effectiveness plane (on the $41 000 per QALY line) and the pricing determined by the benefit accruing to each treatment (Figure 5 and Equations 4 and 5).



Abbreviation: QALY, quality adjusted life years

Figure 5: Value-based pricing of alternative treatments with replacement

The example is expanded with displacement and value-based pricing. It is assumed that all the $c_{i,j}$ are greater than one. The results are shown below in Table 6 and Figure 6. The cost-effectiveness of three treatments and the resultant treatment sequences are shown on a cost-effectiveness plane. As Figure 7 shows, increasing cost relative to benefit for displaced treatments results in a decreasing price being paid for the newly introduced treatments. This occurs to ensure the entire treatment sequence does not result in a negative net monetary value (Equation 8). Treatment A is used alone, after treatment B and after both treatment C and treatment B. With each displacement, the benefit from treatment A decreases and the cost per unit of benefit increases. This results in an increase in the slope of treatment A and a shortening of the length of treatment A on the cost-effectiveness plane.



Symbol: K: thousand Abbreviation: QALY: quality adjusted life years

Figure 6: Value-based pricing of A, B and C with replacement and displacement

When displacement occurs, the incremental benefit and incremental cost potentially alter compared to the example consisting of replacement only (Table 6 below). The same assumptions are used as in Figure 6, that is, there is decreasing effectiveness and the relationship between the costs and benefits has deteriorated. In this case the price of treatment B and treatment C falls relative to the situation in which there is replacement only (Table 5). Both the total costs and the total benefits are higher than in the replacement only scenario. Similarly, the incremental costs and the incremental benefits are higher than in the replacement only scenario. This occurs because displaced treatments have costs and benefits

associated with their use in later lines of therapy. Not considering displacement underestimates both the costs and the benefits of the treatment sequence.

If the marginal cost of production for treatment C was less than $4 100 and more than $3 567, then with displacement, treatment C would not be offered for subsidisation by the manufacturer, whereas it would be in the replacement scenario. This is an example of the dynamic inefficiency discussed earlier.

Table 6: Incremental cost-effectiveness analysis for three treatments with displacement

Treatment sequence	Quantity (Q)	Benefit (QALY)	Incremental benefit (QALY)	Price (P) of new treatment	Cost ∑(P*Q)	ICER
No treatment	0	0	N/A	N/A		N/A
A	10 of A	0.5	0.5	$2 050 (A)	$20 500	$41 000
B followed by A (B→A)	10 of B 6 of A	1	0.5	$2 870 (B)	$41 000	$41 000
C followed by B then A (C→B→A)	10 of C 6 of B 4.2 of A	1.5	0.5	$3 567 (C)	$61 500	$41 000

Note: The decision-maker willingness to pay is $41 000 per QALY
The decrease in effectiveness is 50% for one displacement and 75% for two displacements
The increase in quantity (and thus) cost relative to benefit is 20% for one displacement and 40% for two displacements
Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; P: price; Q: quantity; QALY: quality adjusted life year

Table 7 below shows the potential intermediate combinations of treatments, most of which were also shown in Figure 6. The alternatives have been listed in order of benefit (from least to greatest) and then cost (from lowest to highest). The prices of each of the treatments are as shown in Table 6, calculated to ensure that the incremental cost of each treatment sequence does not exceed the monetary value of the incremental benefit. The incremental cost and benefit are relative to the preceding alternative in Table 7.

One treatment is dominated: the treatment sequence B followed by A (B→A) produces the same value of treatment C alone, but at a higher cost. Therefore, the treatment sequence B→A should never be chosen if treatment C is available. This also demonstrates the result in the modelling that if $c_{i,j}$ >1 (as it is in this example), then the relative price of newer treatments is lower than that of existing treatments. This is a reformulation of the dynamic inefficiency issues discussed earlier, namely newer treatments attract lower prices than older treatments for the same benefit. Conversely, newer treatments have a lower cost (price multiplied by quantity) than existing treatments because of their lower prices.

Several alternatives can also be excluded by extended dominance. As discussed earlier (Section 2.2.2), extended dominance occurs when a more expensive and effective treatment has a lower ICER than the one preceding it.[51]

For example, choosing treatment A rather than no treatment has an ICER of $41 000 but choosing treatment B rather than treatment A has an ICER of $32 800. In this case treatment A should not be chosen by the decision-maker, if they are willing to purchase QALYs at a cost of $41 000 then they would purchase them at a cost of $32 800. Therefore, treatment A should never be chosen when treatment B is available.

When the alternatives excluded by extended dominance and the alternative excluded by dominance are removed, and the ICERs recalculated, the results are shown in the final column. The NMB of each treated participant is shown in the second to last column. The NMB is calculated by multiplying the benefit by the threshold and subtracting the cost. As can be seen, the ICER for moving from no treatment to treatment C is below the willingness to pay threshold of $41 000. However, the subsequent ICERs produced by moving to treatment C followed by treatment B (C→B), and treatment C followed by treatments B then A (C→B→A) are $45 920/QALY and $68 800/QALY respectively. Therefore, if these alternatives were used, it would represent an allocative inefficiency, as a greater benefit could be achieved by deploying the resources elsewhere. This inefficiency would occur even without the redeployment of resources, as was assumed in this case. These results occur because the prices of earlier displaced treatments (and therefore their costs) do not reflect their incremental benefit after displacement.

Table 7: Incremental cost-effectiveness analysis for three treatments with displacement including intermediate treatment sequences

Treatment sequence	Quantity (Q)	Benefit (QALY)	Incremental benefit (QALY)	Cost ∑(P*Q)	Incremental cost	ICER ($/QALY)	Net monetary benefit (per participant)	ICER with extended dominance
No treatment	0	0	N/A	$0	N/A	N/A	N/A	N/A
A	10 of A	0.5	0.5	$20 500	$20 500	$41 000	$0	Extended domination
B	10 of B	0.75	0.25	$28 700	$8 200	$32 800	$2 050	Extended domination
C	10 of C	1	0.25	$35 670	$6 970	$27 880	$5 330	$35 670
B followed by A (B→A)	10 of B 6 of A	1	0	$41 000	$5 330	Dominated	$0	Dominated
C followed by A (C→A)	10 of C 6 of A	1.25	0.25	$47 970	$12 300	$49 200	$3 280	Extended domination
C followed by B (C→B)	10 of C 6 of B	1.375	0.125	$52 890	$4 920	$39 360	$3 485	$45 920
C followed by B then A (C→B→A)	10 of C 6 of B 4.2 of A	1.5	0.125	$61 500	$8 610	$68 880	$0	$68 880

Note: The decision-maker willingness to pay is $41 000 per QALY
The decrease in effectiveness is 50% for one displacement and 75% for two displacements
The increase in quantity (and thus) cost relative to benefit is 20% for one displacement and 40% for two displacements
Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; P: price; Q: quantity; QALY: quality adjusted life year

If the prices of the existing displaced treatments were altered when new treatments were introduced to ensure their incremental cost-effectiveness remained constant, it would decrease the prices of older treatments and increase the prices of newer treatments. However, it would not make any difference to the incremental cost and benefit of the treatment sequence (see Table 8). This is achieved by multiplying the prices of displaced therapies by $1/c_{i,j}$. In this example by 0.83 for one displacement and by 0.71 for two displacements.

Table 8: Incremental cost-effectiveness analysis for three treatments with displacement and price adjustment

Treatment sequence	Quantity (Q)	Benefit (QALY)	Incremental benefit (QALY)	Price (P) of all treatments	Cost ∑(P*Q)	ICER
No treatment	$0	0	N/A	N/A		N/A
A	10 of A	0.5	0.5	$2 050 (A)	$20 500	$41 000
B followed by A (B→A)	10 of B 6 of A	1	0.5	$3 075 (B) $1 708 (A)	$41 000	$41 000
C followed by B then A (C→B→A)	10 of C 6 of B 4.2 of A	1.5	0.5	$4 100 (C) $2 562 (B) $1 220 (A)	$61 500	$41 000

Note: The decision-maker willingness to pay is $41 000 per QALY
The decrease in effectiveness is 50% for one displacement and 75% for two displacements
The increase in quantity (and thus) cost relative to benefit is 20% for one displacement and 40% for two displacements
The prices have been altered to ensure the incremental cost-effectiveness remains constant
Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; P: price; Q: quantity; QALY: quality adjusted life year

The results of the intermediate alternatives are shown in Table 9. The prices have been adjusted to ensure that the ICER of displaced treatments remain constant. This results in different prices depending on the number of treatments and the number of displacements. It also results in a constant ICER when the components of the treatment sequences are removed. This eliminates the allocative and dynamic inefficiencies described in this Chapter.

Table 9: Incremental cost-effectiveness analysis for three treatments with displacement including intermediate treatment sequences and price changes

Treatment sequence	Quantity (Q)	Benefit (QALY)	Incremental benefit (QALY)	Price	Cost ∑(P*Q)	Incremental cost	ICER ($/QALY)	Net monetary benefit (per participant)	ICER with extended dominance
No treatment	0	0	N/A	N/A	$0	N/A	N/A	$0	N/A
A	10 of A	0.5	0.5	$2 050 (A)	$20 500	$20 500	$41 000	$0	$41 000
B	10 of B	0.75	0.25	$3 075 (B)	$30 750	$10 250	$41 000	$0	$41 000
C	10 of C	1	0.25	$4 100 (C)	$41 000	$10 250	$41 000	$0	$41 000
B followed by A (B→A)	10 of B 6 of A	1	0	$3 075 (B) $1 708 (A)	$41 000	$0	the same as above	$0	the same as above
C followed by A (C→A)	10 of C 6 of A	1.25	0.25	$4 100 (C) $1 708 (A)	$51 250	$10 250	$41 000	$0	$41 000
C followed by B (C→B)	10 of C 6 of B	1.375	0.125	$4 100 (C) $2 562 (B)	$56 375	$5 125	$41 000	$0	$41 000
C followed by B then A (C→B→A)	10 of C 6 of B 4.2 of A	1.5	0.125	$4 100 (C) $2 562 (B) $1 708 (A)	$61 500	$5 125	$41 000	$0	$41 000

Note: The decision-maker willingness to pay is $41 000 per QALY
The decrease in effectiveness is 50% for one displacement and 75% for two displacements
The increase in quantity (and thus) cost relative to benefit is 20% for one displacement and 40% for two displacements
The prices have been altered to ensure the incremental cost-effectiveness remains constant
Abbreviations: ICER: incremental cost-effectiveness ratio; N/A: not applicable; P: price; Q: quantity; QALY: quality adjusted life year

The framework presented in the previous Sections demonstrates that in a value-based pricing approach, with the possibility of displacement, the prices of new treatments must be related to the prices of existing treatments.

Value-based pricing, as applied in this model, ensures the treatment sequence does not exceed the threshold for societal purchasing of health. Thus, the allocative inefficiency associated with the treatment sequence that occurred in either assuming replacement or assuming a mean cost and benefit is avoided.

The price and cost of newer technologies, if displacement is considered and correctly estimated in the value-based pricing, are altered compared to the replacement scenario. Therefore, unless there are changes to the prices of existing treatments, the costs (price multiplied by consumption) of the existing treatments may exceed their opportunity cost as expressed by the willingness to pay threshold (Figure 6 and the example). Moreover, effective treatments may receive a lower price than less effective treatments and eventually effective treatments may not be funded or offered for reimbursement.

This situation arises if the prices for existing treatments are not altered with new treatments becoming available. This occurs even though there has been a change in the relationship between the cost and benefit of the existing displaced treatments. Adjusting the price to reflect this change restores the relationship between cost and benefit within a line of therapy and would then allow for the new treatments to have a higher price.

Reimbursement or subsidisation based on the line of therapy that the treatment is used is a form of stratified cost-effectiveness, where subgroups may have their own price for reimbursement. In this case, the subgroups are cancer patients who use the treatment in different lines of therapy because of displacement.

Stratified cost-effectiveness by line of therapy has been discussed in the literature.[84] Hawkins and Scott (2011)[84] discussed the use of reimbursement based on value-based pricing which included two examples. The second example was the consideration of a pharmaceutical in the first and second line of therapy for cancer. In the example, the treatment had a benefit of 1 QALY in the first line of therapy and 0.5 QALYs in the second line of therapy. Hawkins and Scott (2011)[84] concluded that there may be impacts on the acceptable price if second line treatment as well as first line treatment is included the coverage decisions. The acceptable price for the payer is lower as the gain of the treatment in the second line of therapy is smaller (than in the

first line of therapy). The average price of a treatment could be the weighted sum of use across the lines of therapy.

The work in this thesis deviates from the example in Hawkins and Scott (2011)[84] by establishing that treatment in the first and second lines of therapy is related to the introduction of new treatments. In Hawkins and Scott (2011)[84] the pricing changes were an extension of a current reimbursement strategy.

2.4 Conclusions

This Chapter provided a conceptual framework for displacement and outlined the economic issues associated with treatment sequences and lines of therapy. It demonstrated the potential to mis-specify the economic problem as a simple replacement of one treatment for another rather than the use of both treatments. Such a mis-specification can lead to allocative inefficiency because a treatment's incremental cost and benefit have been calculated incorrectly and thus an incorrect reimbursement decision made. Therefore, for a correct reimbursement decision to be made, the implications of treatment sequences for cost-effectiveness and pricing needs to be considered.

Displacement is one way in which a treatment sequence develops. Displacement occurs when an existing treatment moves from one line of therapy to a later line of therapy because of the introduction of a new treatment. It assumes that newer treatments will be used prior to older treatments in a treatment sequence.

When displacement occurs, it may alter the effectiveness and the cost-effectiveness of the protocol. The potential for displaced treatments to have an altered effectiveness and cost-effectiveness is discussed and evaluated in Chapter 6. Where cost-effectiveness is altered then allocative inefficiency and dynamic inefficiency may occur. These inefficiencies may occur even with full information at a point in time and a form of value-based pricing, as this Chapter demonstrated.

One method of correcting the inefficiencies is to return the cost-effectiveness of displaced treatments to their original values. Price changes based on restoring the cost-effectiveness within a line of therapy were shown to reduce allocative and dynamic inefficiency. To achieve these price changes, each line of therapy will need to be identified (Chapter 4) and its cost and effectiveness assessed (Chapter 5 and Chapter 7).

The features of displacement emphasised in this Chapter may be present in other methods of producing a treatment sequence. The contemporary economic evaluations of treatment sequences, including how they are conceptualised, is evaluated and critiqued in Chapter 3.

Chapter 3 Current literature for economic evaluations in oncology

This Chapter reports the results of a systematic review of the current economic evaluation literature on multiple lines of therapy (treatment sequences) in oncology. As discussed in Chapter 2, most economic evaluations in oncology evaluate cost-effectiveness within a line of therapy at a specific point in a treatment sequence. These economic evaluations usually compare one treatment to another active treatment or to best supportive care.[83] It is less common for a treatment sequence including multiple lines of therapy to be considered in an economic evaluation.[70] Therefore, reviewing the economic evaluations of pharmaceuticals known to be used in multiple lines of therapy may be useful. Common modelling assumptions and the approach to subsequent treatments (including displacement) can be compared to the potential problems outlined in Chapter 2.

Cetuximab is used in different lines of therapy for the treatment of metastatic colorectal cancer (CRC).[85] It has also been the subject of numerous economic evaluations[86] and CRC is one of the three tumour types involved in the Elements of Cancer Care (EoCC) cohort (see Chapter 4). Cetuximab has the added complication of genetic heterogeneity in tumour response to treatment, which is characteristic of the more recent personalised oncology pharmaceuticals.[87] Therefore, a review of economic evaluations of cetuximab was also undertaken.

The motivation for the reviews is to compare the results of the economic evaluations to:

- the conceptual framework of displacement (outlined in Chapter 2);
- treatment sequence length in real-world data (the comparison is conducted in Chapter 4);
- costs in real-world data (the comparison is conducted in Chapter 5); and
- the clinical literature (the comparison is conducted in Chapter 6)

Additionally, the reviews outline the common modelling approaches to displacement in a treatment sequence or in economic evaluations of a single pharmaceutical.

The specific aims of the two reviews are to describe, evaluate and critique the modelling methods used in economic evaluations of multiple lines of therapy in carcinomas.

The components of Chapter 3 are shown diagrammatically below.

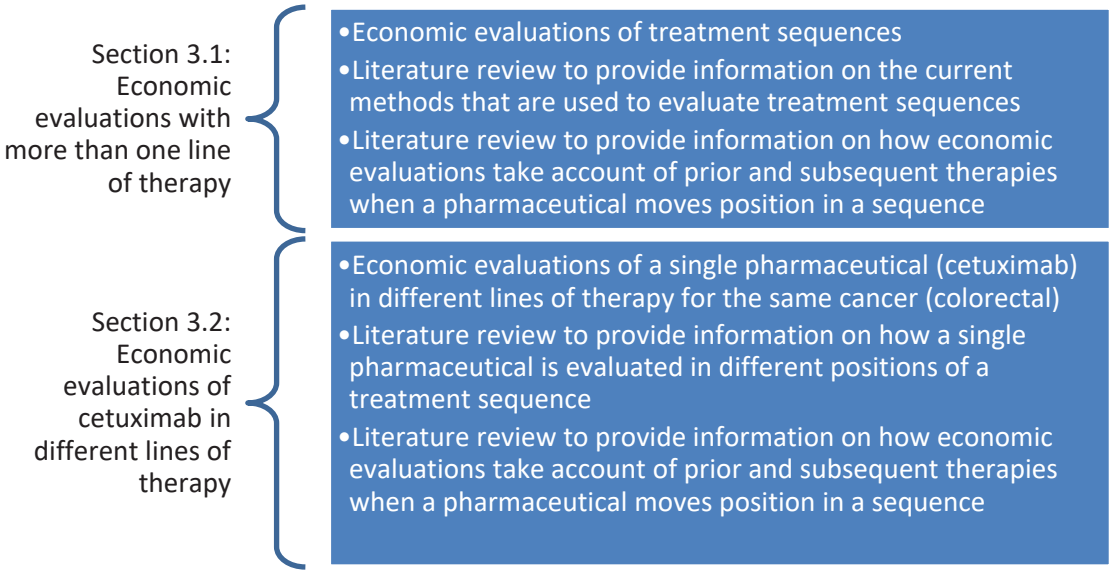


Figure 7: Components of Chapter 3

Section 3.1 comprised a systematic review of economic evaluations that included a choice in more than one line of therapy. That is, there was a choice of at least two protocols in at least two lines of therapy. The assumptions made in the economic evaluations with respect to the lines of therapy were identified. The detailed literature search and data extraction are presented in the Appendices A and B.

Section 3.2 comprised a systematic review of economic evaluations of cetuximab. This allowed for comparison, evaluation and critique of the economic evaluations for cetuximab in different lines of therapy. This comparison included the type of evidence used, the model used and the modelling assumptions. The detailed data extraction is presented in the Appendix C.

3.1 Economic evaluations of multiple lines of therapy in oncology

The aims of the research in this Section are to undertake a comprehensive literature review:

1. to identify, evaluate and critique the current published literature on economic evaluations of multiple lines of therapy (i.e., a treatment sequence) in carcinomas; and
2. to describe the modelling assumptions and outcomes that are important when evaluating the impacts of displacement.

3.1.1 Search strategy

The search strategy comprised four steps.

1. A literature search was undertaken for economic evaluations that involved consideration of multiple lines of therapy in carcinomas (the topic of the thesis). This was undertaken in Medline, PubMed and EconLit (keywords are reported in Table 10).
2. The recovered papers were hand searched for further references. Articles that cited the recovered papers were searched in PubMed.
3. Health Economics, Journal of Health Economics, PharmacoEconomics, Journal of Cancer Policy and Journal of Medical Economics were also hand searched for the period 2010 to 2016. Additionally, the National Institute of Health and Clinical Excellence (NICE) website was searched.
4. As an additional search the articles that cited the randomised controlled trials (RCT) discussed in Chapter 6, where a treatment protocol was used in different lines of therapy were also included.

Papers were included if they reported on the conduct and results of an economic evaluation that included more than one line of therapy. To qualify for inclusion, the paper had to report a choice of interventions (at least two protocols) involved in at least two lines of therapy. Economic evaluations that included post-progression costs, including other active treatments, but did not model a choice in the later lines of therapy were excluded.

To qualify as an economic evaluation, both costs and benefits had to be assessed. The benefits did not have to be expressed in terms of quality adjusted life years. An incremental analysis was not required for inclusion (although was considered good practice for reporting in the Consolidated Health Economic Reporting Standards [CHEERS] guidelines).

Several studies were identified outside the first step of the search strategy, one from the reference list of a recovered study,[88] two from the review of seminal journals[2,89], one from the NICE website[90] and one from the articles that cited the RCTs.[4]

The exact terms used for the initial search in Medline, PubMed and EconLit are shown below (last updated on the 3/05/2016) as well as the reasons for exclusion. Exclusion was undertaken in a sequential order, for the following reasons:

- not being a study of a carcinoma; then
- not being an economic evaluation; then

- not being an economic evaluation of multiple lines of therapy; and then
- not having choice of treatment in multiple lines of therapy.

The precise steps undertaken are tabulated in Table 10.

Table 10: Search strategy for economic evaluations of treatment sequences in carcinomas

Step	Term	Number of articles
1 from Medline	exp Antineoplastic Combined Chemotherapy Protocols/ec [Economics]	656
Retained for full-text		108
2 from PubMed	((Health Care Costs[MeSH Terms]) AND Disease Progression[MeSH Terms]) AND Cancer	75
Retain for full-text review		15
3 from EconLit	Cancer	1258
Retain for full-text review		34
Included from journal search for full-text review and NICE		14
Included from search of authors and citings		159
Total for full-text review		330
Removal of duplicates		23
Exclusion because not carcinoma		15
Exclusion because not an economic evaluation		215
Exclusion because not economic evaluation of multiple lines of therapy		53
Exclusion because a lack of choice in multiple lines of therapy		12
Retained		12

Several articles are not strictly economic evaluations of multiple lines of therapy in carcinomas but are of interest to this discussion. These articles are mentioned below in the discussion of other articles of interest. A CONSORT flow chart is shown below in Figure 8. The full-text exclusions and inclusions are presented in Appendix A.

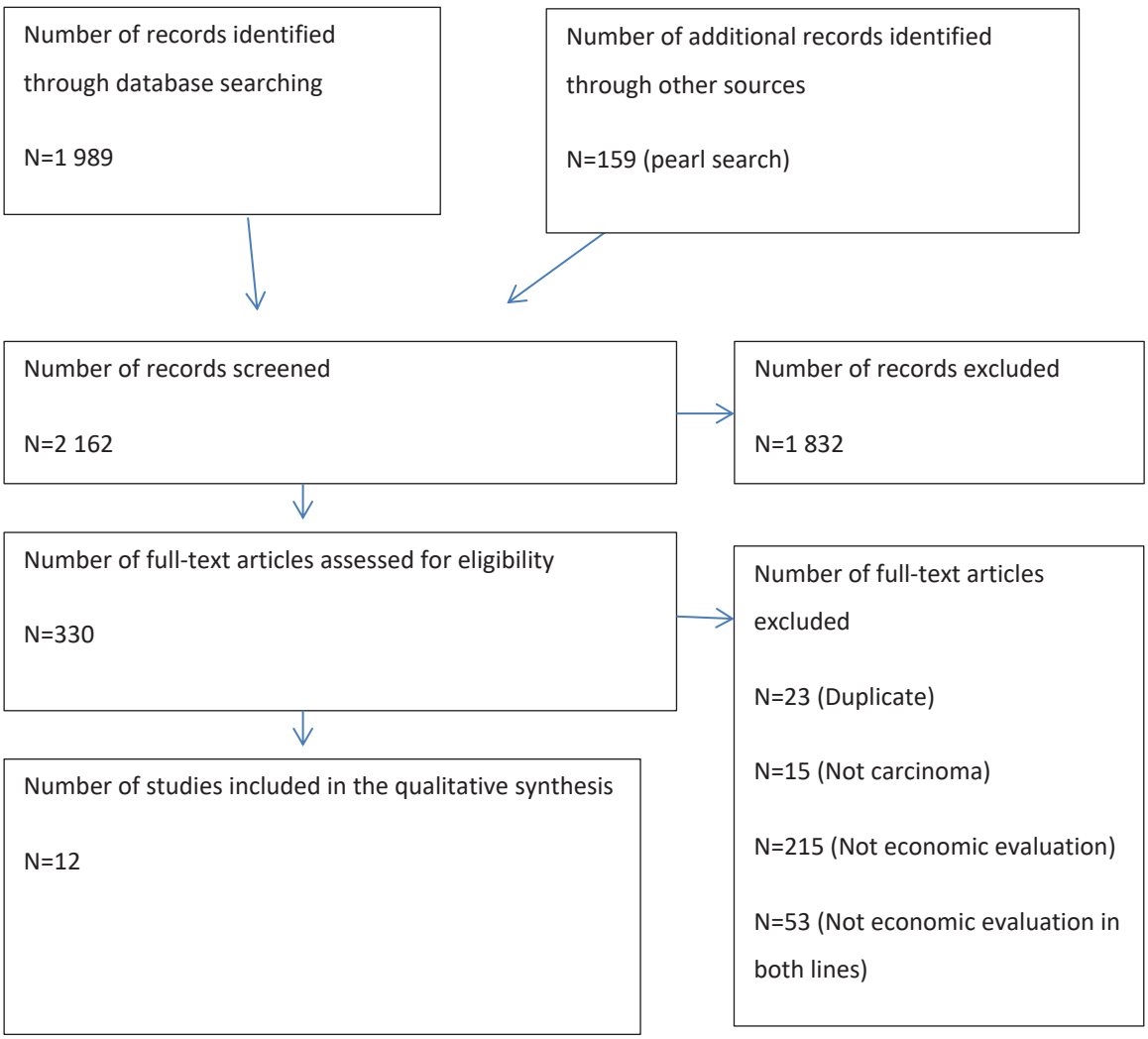


Figure 8: CONSORT diagram for the literature search of economic evaluations of treatment sequences in carcinomas

3.1.2 Overview of recovered literature

The recovered literature - a total of 12 papers - is shown in Table 11. Economic evaluations of multiple lines of therapy are a recent and infrequent addition to the literature; the first recovered paper was published in 2008. Ten of the recovered papers were published journal articles and two were formal Health Technology Assessment (HTA) reports.

One paper, published in 2007, contained the results of an economic evaluation[91] which was very similar to a conference abstract. Although the conference abstract was not referenced, the same authors produced a very similar set of results in the same disease with the same treatments in 2009.[1] Only the later paper was included in this review to avoid potential duplication.

Most of published papers suitable for the qualitative synthesis were economic evaluations of the treatment of CRC (nine papers). Less common were economic evaluations of non-small cell lung cancer (NSCLC) (two papers), and breast cancer (one paper).

All 12 papers were evaluated according to the CHEERS guidelines.[92] The papers were grouped by the type of cancer examined and the commonalities and differences assessed. Additional information was extracted about the methods of combining treatments, whether mortality from other causes was included and the proportion of participants who received multiple lines of therapy.

For those evaluations that involved the same protocol being used in more than one line of therapy, (analogous to displacement) information was extracted on how the same protocol was used within the model in the different lines of therapy.

Nine of the 12 included an incremental analysis. Of the three that did not, one was because the analysis was formally constructed as a cost-minimisation exercise with the assumption of equal outcomes.[93] The second argued that a traditional incremental analysis was inappropriate.[94] The third compared the most expensive treatment sequence to the least expensive sequence but did not provide the incremental cost-effectiveness ratio for the intermediate treatment sequence alternatives.[2]

Table 11: Recovered economic evaluations of multiple lines of therapy

Reference	Title	Year	Disease	Length of sequence	Protocols used in alternative treatment sequences	Outcome measure	Model/Trial for alternatives	OS/PFS effectiveness measure
Hind et al.(2008)[94]	The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation	2008	CRC	2	FOLFOX FOLFIRI	QALY	Trial (two separate trials)	Overall survival
Miyazaki et al. (2009)[93]	Cost-minimization analysis of sequence changes between FOLFIRI and FOLFOX6 therapy for advanced colorectal cancer in Japan	2009	CRC	2	FOLFOX FOLFIRI	LYS- cost-minimisation	Trial based (one trial)	Overall survival
NICE (2009)[90]	A cost-utility analysis of chemotherapy sequences for the treatment of patients with advanced breast cancer	2009	Breast	3	Capecitabine Docetaxel Gemcitabine Paclitaxel Vinorelbine	QALY	Synthesis of multiple trials (model)	Overall survival
Shiroiwa et al. (2009)[95]	Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials	2009	CRC	2	XELOX FOLFOX	Quality adjusted days	Trial (two separate trials)	Progression free survival
Wong et al. (2009)[1]	Cost implications of new treatments for advanced colorectal cancer	2009	CRC	3	5-FU FOLFOX FOLFIRI Bevacizumab Irinotecan Cetuximab	LYS	Synthesis of multiple trials (model)	Overall survival
Chouaid et al. (2012)[96]	Cost effectiveness of erlotinib versus chemotherapy for first-line treatment of non-small cell lung cancer (NSCLC) in fit elderly patients participating in a prospective phase 2 study (GFPC 0504)	2012	NSCLC	2	Erlotinib Docetaxel Gemcitabine	QALY	Trial based (one trial)	Overall survival

Reference	Title	Year	Disease	Length of sequence	Protocols used in alternative treatment sequences	Outcome measure	Model/Trial for alternatives	OS/PFS effectiveness measure
Manca et al. (2012)[97]	The cost-effectiveness of different chemotherapy strategies for patients with poor prognosis advanced colorectal cancer (MRC FOCUS)	2013	CRC	2	5-FU Oxaliplatin Irinotecan	QALY	Trial based (one trial)	Overall survival
Chouaid et al. (2013)[88]	Cost analysis of erlotinib versus chemotherapy for first-line treatment of non-small-cell lung cancer in frail elderly patients participating in a prospective phase 2 study (GFPC 0505)	2013	NSCLC	2	Erlotinib Gemcitabine	QALY	Trial based (one trial)	Overall survival
Tappenden et al. (2013)[98]	Using whole disease modelling to inform resource allocation decisions: economic evaluation of a clinical guideline for colorectal cancer using a single model	2013	CRC	2	FOLFOX FOLFIRI XELOX XELIRI 5-FU Irinotecan Capecitabine	QALY	Synthesis of multiple trials (model)	Overall survival
Rautenberg et al. (2014)[2]	Economic outcomes of sequences which include monoclonal antibodies against vascular endothelial growth factor and/or epidermal growth factor receptor for the treatment of unresectable metastatic colorectal cancer	2014	CRC	3	FOLFOX FOLFIRI Bevacizumab Cetuximab Panitumumab Irinotecan	LYS	Synthesis of multiple trials (model)	Overall survival
Goldstein et al. (2015)[89]	First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis	2015	CRC	2	FOLFOX FOLFIRI Bevacizumab	QALY	Trial (two models)	Overall survival

Reference	Title	Year	Disease	Length of sequence	Protocols used in alternative treatment sequences	Outcome measure	Model/Trial for alternatives	OS/PFS effectiveness measure
Riesco-Martinez et al. (2016)[4]	Cost-Effectiveness Analysis of Different Sequences of the Use of Epidermal Growth Factor Receptor Inhibitors for Wild-Type KRAS Unresectable Metastatic Colorectal Cancer	2016	CRC	3	FOLFOX FOLFIRI Bevacizumab Cetuximab Panitumumab	QALY	Synthesis of multiple trials (model)	Overall survival

Abbreviations: 5-FU: 5-fluorouracil; CRC, colorectal cancer; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; LYS: life years saved; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression free survival; QALY: quality adjusted life years; XELIRI: a protocol consisting of irinotecan and capecitabine; XELOX: a protocol consisting of oxaliplatin and capecitabine

Eight studies evaluated a treatment sequence that involved the use of two lines of therapy, while four involved the consideration of a treatment sequence of up to three lines of therapy.

Results from a single trial were used as the basis for four evaluations. Two evaluations used two trials, but alternatives were from one trial or the other (no synthesis of new alternatives not contained within an arm of a trial). The basis for the six other evaluations involved modelling new alternatives from multiple sources of evidence.

The economic evaluations based on single trials were based on four separate RCTs.[68,72,99,100] These trials are discussed further in Chapter 6. There is a close relationship between the availability of clinical literature including multiple lines of therapy and the corresponding development of economic evaluations. Most economic evaluations used a preference weighted form of overall survival (quality adjusted life years (QALY) or quality adjusted days).

All the economic evaluations examining a sequence length of three lines of therapy involved the use of models to construct the alternatives.

The results of the evaluation using the CHEERS checklist are presented below in Table 12. Each of the 24 checklist items was given one row; a yes in the appropriate box demonstrated that the relevant element of the checklist was reported to a sufficient standard, a no meant that the element was not considered to be reported on to a sufficient standard. Partial was used when there was an important element of an element that was often missing, but the remainder was considered of a sufficient standard.

An example of an element that was often missing from the evaluations was model selection. Often the papers included a very clear description of the model and some justification for its choice, but not enough to be confident that the authors had considered other approaches and disregarded them as inferior. For some features, such as a structured abstract, the inclusion of appendixes or chapters from HTA reports meant this was not applicable (recorded as N/A). The percentage in the final column was the number of yes and a weighting of one-half for the partials divided by the total number of responses (excluding the N/A). The detailed data recovery is described in Appendix B. This Appendix also contains a discussion of the economic evaluations as compared to each cancer type.

Table 12: CHEERS checklist for economic evaluations of treatment sequences

Number	Category	Hind et al. (2008)[94]	Miyazaki et al. (2009)[93]	NICE (2009)[90]	Shiroiwa et al. (2009)[95]	Wong et al. (2009)[1]	Chouaid et al. (2012)[96]	Manca et al. (2012)[97]	Chouaid et al. (2013)[88]	Tappenden et al. (2013)[98]	Rautenberg et al. (2014)[2]	Goldstein et al. (2015)[89]	Riesco-Martinez et al. (2016)[4]	Percentage
1	**Title**	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	83%
2	**Abstract**	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
3	**Background and objectives**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
4	**Target population and subgroups**	Yes	Yes	Yes	Yes	Yes	Yes	Partial	No	Yes	No	No	Yes	71%
5	**Setting and location**	Yes	Partial	Yes	Partial	Yes	No	Yes	No	Yes	No	Yes	No	58%
6	**Study perspective**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
7	**Comparators**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
8	**Time horizon**	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	83%
9	**Discount rate**	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	No	Yes	Yes	75%
10	**Choice of health outcome**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	96%
11	**Measurement of effectiveness**	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	83%

Number	Category	Hind et al. (2008)[94]	Miyazaki et al. (2009)[93]	NICE (2009)[90]	Shiroiwa et al. (2009)[95]	Wong et al. (2009)[1]	Chouaid et al. (2012)[96]	Manca et al. (2012)[97]	Chouaid et al. (2013)[88]	Tappenden et al. (2013)[98]	Rautenberg et al. (2014)[2]	Goldstein et al. (2015)[89]	Riesco-Martinez et al. (2016)[4]	Percentage
12	**Measurement and valuation of preference based outcomes**	Yes	N/A	Yes	Yes	N/A	Yes	Yes	Yes	Yes	N/A	Yes	Yes	100%
13	**Estimating resources and costs**	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	92%
14	**Currency, price date and conversion**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
15	**Choice of model**	Yes	Partial	Yes	No	Partial	Yes	Yes	Yes	Partial	No	No	Partial	58%
16	**Assumptions**	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	92%
17	**Analytic methods**	Yes	No	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	No	67%
18	**Study parameters**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
19	**Incremental costs and outcomes**	No	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	82%
20	**Characterising uncertainty**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
21	**Characterising heterogeneity**	Yes	No	No	Partial	No	No	No	No	Yes	No	No	No	21%
22	**Study finding & limitations**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
23	**Source of funding**	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	83%
24	**Conflicts of interest**	No	Yes	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	67%

Abbreviations: CHEERS: consolidated health economics reporting; N/A: Not applicable

Overall, the papers as a group scored adequately on most criteria. Papers scored poorly on three features of the CHEERS checklist: the justification for the choice of model (58%), the discussion of the setting (58%) and the assessment of heterogeneity (21%).

The model justification was weak in most of the papers reviewed with the exception of Hind and colleagues, who discussed why the model used was chosen and why other models would be less appropriate.[94] Tappenden et al. (2013)[98] used a whole of disease model which may account for the lack of detail about the component associated with the metastatic treatment. The other economic evaluations based on modelling explained the type of model used, but not why that model was superior to other potential choices.

The setting was another feature not explained in sufficient detail. The potential use of other treatments might be considered when discussing the setting, alongside other issues (patient co-payments etc.).

The other major checklist feature poorly reported upon was the characterisation of heterogeneity; most evaluations did not consider this feature. The lack of this feature is potentially important as cancer patients are heterogeneous in terms of outcome based on clinical and genetic features. Even simple sources of heterogeneity, such as sex or age, were not considered. In later economic evaluations, such as Rautenberg et al. (2014),[2] well recognised markers of treatment effect heterogeneity (such as genetic factors) were not discussed or included.

3.1.3 Economic evaluations of colorectal cancer

Nine economic evaluations were identified for CRC (see the CRC Section in Appendix B for more detail).

The rationale for the economic evaluations varied across the publications:

- establishing the relative cost-effectiveness of alternative planned treatment sequences[1,2,4,89,94,97];
- establishing the least costly sequence for treatment sequences of known equivalent effectiveness[93];
- establishing the relative cost-effectiveness of two treatments in different lines of therapy[95]; and
- establishing the feasibility of a whole of disease modelling.[98]

The standard of care for CRC changed over the period of the publication of these papers. This was reflected in the interventions considered in the economic evaluations, with chemotherapy (irinotecan, oxaliplatin and 5-FU [and an oral version- capecitabine]) and antibodies therapies (cetuximab, panitumumab and bevacizumab) used for treatment. Combinations of these pharmaceuticals were used within some protocols within a line of therapy. For example, FOLFOX is a combination of 5-FU and oxaliplatin, and FOLFIRI is a combination of 5-FU and irinotecan.

The conclusions across similar economic evaluations were not consistent. Hind et al. (2008),[94] Miyazaki et al. (2009),[93] Manca et al. (2012)[97] and Tappenden et al. (2013)[98] compared similar regimes of treatment with the economic evaluations being based on RCTs. However, they reached different conclusions.

Miyazaki et al. (2009)[93] concluded that, for a treatment sequence length of two, FOLFIRI used prior to FOLFOX was the least costly. Hind et al. (2008)[94] suggested that either a treatment sequence of one containing FOLFIRI or treatment sequence length of two with 5-FU followed by FOLFIRI or 5-FU followed by FOLFOX would be cost-effective. Tappenden et al. (2013)[98] noted treatment sequences with a first line of therapy including oxaliplatin dominated a treatment sequence including irinotecan in the first line of therapy. These differences were driven by the relative costs of the pharmaceuticals within the jurisdictions that were examined. In Tappenden et al. (2013),[98] Manca et al. (2012)[97] and Hind et al. (2008)[94] the cost of oxaliplatin-containing protocols was less than irinotecan-containing protocols, whereas in Miyazaki et al. (2009)[93] it was the reverse.

Economic evaluations that included antibody therapy reached different conclusions based on the range of alternatives. For example, Rautenberg et al. (2014)[2] and Wong et al. (2009)[1] compared a similar group of pharmaceuticals but reached different conclusions. Rautenberg et al. (2014)[2] claimed that the incremental benefit was worth the incremental cost for the most expensive protocol while Wong et al. (2009)[1] reached the opposite conclusion. Differing assumptions employed in the modelling underlie this apparent disparity. First, Wong et al. (2009)[1] assumed a background rate of death while Rautenberg et al. (2014)[2] did not. Perhaps, more importantly, Rautenberg et al. (2014)[2] did not consider a no-antibody therapy option (which means that the main cost driver was not subject to an incremental analysis), while Wong et al. (2009)[1] included alternatives without antibody therapy. Additionally, Rautenberg et al. (2014)[2] only compared the best to the worst option rather than calculating the incremental cost-effectiveness through the non-dominated options.

3.1.4 Economic evaluations of breast cancer

NICE conducted an economic evaluation in 2009 which considered multiple lines of therapy in breast cancer.[101] In the discussion, the authors mentioned that the neglect of sequential therapy (or treatment sequences) as a comparator had been an identified concern in previous guidance published by NICE. They also highlighted that their literature review did not identify economic evaluations that considered more than one line of therapy.

Consequently, the authors constructed a new economic model in which treatment sequences were explicitly considered. As there was no evidence for third line therapy, each agent was assumed to work as effectively as it did in second line therapy. It was noted in the discussion on clinical evidence that new therapies are often introduced into clinical practice prior to formal treatment comparisons being undertaken.

The pharmaceuticals considered were taxanes, vinorelbine and capecitabine. The existing clinical evidence did not consider the use of these agents in different lines of therapy so a modelling approach was undertaken to inform this decision.

Alternative treatment sequences were considered. Essentially the review considered each of the pharmaceuticals as a contender for first, second or third line therapy. Some therapies were only available in later lines of therapy, for example capecitabine or vinorelbine monotherapy. Combinations of pharmaceuticals in a protocol were allowed but only in the first line of therapy.

Unlike most of economic evaluations considered in this Section, a network meta-analysis was undertaken where the results of several trials were combined to generate the effectiveness results. However, the network meta-analysis was only conducted for protocols in the first line of therapy.

Seventeen alternative sequences were assessed, including those with a sequence length of one protocol (4 alternatives), a sequence length of two protocols (7 alternatives) and a sequence length of three protocols (6 alternatives). The differences in protocol length allowed the calculation of the incremental costs and outcomes of extending sequences.

In the model, therapies were stopped based on either progression or intolerable toxicity. Median numbers of cycles reported by pivotal trials were used to develop the number of cycles in each arm.[90] A network meta-analysis (described as an indirect analysis) was

undertaken to calculate the relative effectiveness of different treatments.[v] Another indirect analysis was undertaken to calculate the number of deaths due to treatment toxicity and discontinuations from each arm. The effectiveness of third line therapy was assumed to be equal to that reported in trials of second line therapy. Overall survival was the sum of the progression free survival calculations.

The approach used to calculate survival was that after the lines of therapy with active treatment there was a fixed period in palliative care. Utility weights were assigned to each line of therapy, based on response and toxicity from trials. Costs were calculated for treatment, assessment, adverse events, palliative care and death.

A total average cost and QALYs gained was produced for each of the considered strategies. The strategies were then ordered, and several strategies were excluded by extended dominance.

A threshold willingness to pay was considered in the analysis. The main strategies recommended in the clinical section of the document were assessed as being the most cost-effective at the cost per QALY gained likely to be considered acceptable by the third party payer.

There was assumed to be no difference in rates of toxicity or response to chemotherapy between second and third line treatment. In the sensitivity analysis, the effectiveness of third line therapy was reduced and did not impact significantly on the results.

This study is important because it evaluated the inclusion of a line of therapy (the third line in this case) for which the clinical evidence was absent. The study explicitly altered the effectiveness of treatment in this line of therapy within the sensitivity analysis. This was the only economic evaluation to undertake this process.

3.1.5 Economic evaluations of non-small cell lung cancer

Two economic evaluations were conducted with respect to NSCLC. [99,100] Both were conducted by the same group of authors, evaluated similar treatment sequences and are therefore considered together. The rationale of the economic evaluations was to consider the cost-effectiveness of preplanned treatment sequences.

[v] An indirect comparison is a comparison between different trials using a common comparator (for example placebo, no active treatment or a common treatment). A network meta-analysis contains multiple different treatment comparisons.[102]

Both studies were based on RCTs conducted in France, involved similar populations (the elderly) and the same pharmaceuticals (docetaxel and erlotinib). The main difference between the studies was that one trial recruited fit participants[96] and the other frail participants.[88]

In both trials, all costs were collected until the second progression of the cancer occurred. There were four disease states in the model: stable disease with oral therapy, stable disease with intravenous therapy, progressive disease and death. Utilities were assigned to health states based on the literature. The costs of adverse events were included in the model but not the disutility associated with such events. The estimation of include utilities and costs from the end of the second progression to death assumed that the last observation was equal to overall survival. That is, there was no extrapolation of observed survival to account for the censored nature of the data. Costs in the post-treatment phase were allocated based on a previous study which investigated the cost of palliative care. The authors acknowledged that the use of published utility estimates and costs of palliative care was less than ideal.

3.1.6 Other relevant articles recovered in the literature search

Additional articles were identified that did not include an economic evaluation of carcinomas but are included here because of their relevance to the topic.

A series of articles considered displacement in the context of haematological proliferative disease. Multiple myeloma is a disease for which there has been a rapid increase in the number of treatments available.[103] The incremental benefit of the rapid introduction of these treatments has been assessed in several articles, which have produced conflicting results.[103] The authors of this study also observed that the validity of the current studies was weak because of the rapid changes in the options and combinations available.[103]

Zheng et al. (2017)[70] undertook a review of treatment sequences in NICE assessments. Forty assessments of treatment sequences were identified. Oncology was the most common disease assessed, with 13 assessments (nine of these were assessments of early cancer disease). The next most numerous disease was autoimmune diseases with seven assessments.

Of the four assessments undertaken by Zheng et al. (2017)[70] of advanced cancer types, one concerned a sequencing of radiotherapy, surgery, implanted chemotherapy infused wafers and chemotherapy in high grade gliomas.[104] Another involved the consideration of the addition of cetuximab to first line therapy for metastatic CRC. A treatment sequence was modelled including second line therapy.[105] The third assessment considered the impact of different doses of imatinib in the second line treatment of gastrointestinal stromal tumours.[106] The

fourth was an evaluation of ipilimumab in metastatic melanoma.[107] The treatment sequence consisted of alternative choices in the first and second line treatment. There was a degree of patient heterogeneity in terms of mutation status (BRAF V600) and the patient population was divided into two subgroups.[107] The redacted information available about this research meant that it was not included in the economic evaluations reviewed in this Section.

The most common approach used in the assessments undertaken by Zheng et al. (2017)[70] was cohort modelling with tracker states. Tracker states involve introducing memory into the model, so, for example, the chance of progression might be related to the number of cycles that the cohort had already received. The biggest challenge was acknowledged to be the lack of clinical data.[70] Additional issues identified were patient heterogeneity and the choice of the number of lines of therapy.

de Mello-Sampayo (2014)[108] discussed the implications of a treatment sequence for adoption decisions for technologies. The author found the option value of a technology for deployment by a clinician or patient in the future impacts on the current decision-making around technologies. The author observed that preserving future options has a value and should be included in the calculation of net benefit. This includes the situation where future benefits are not known with certainty.[108]

Two additional broad areas of interest are covered in the literature: the economic consideration of crossover or switching within oncology trials; and the use of dynamic treatment strategies within oncology treatment. In trials where these approaches are used, statistical techniques are employed which attempt to assess the relative survival attributable to treatments. These statistical methods are important in the context of assessing the relative cost-effectiveness of two or more treatments. These concepts are briefly described below.

3.1.7 Crossover/Switching literature

Crossover or switching in an oncology trial occurs when the treatment specified for one group within the trial is also received by members of other arms of the trial.[109] This commonly happens in the context of treatment failure as determined by progression of the disease; when this occurs the control arm receives the intervention treatment.[109] Several arguments have been advanced to explain the increased prevalence of switching. These include the inability to recruit participants without offering the intervention of choice at some point in time and a concern it would be unethical not to offer the new treatment to one group if initial results suggest that it is useful.[109]

However, switching produces a situation where the impact of the intervention is obscured because it is received by both arms of a trial.[109] Therefore, in an intent to treat analysis, the difference between the two arms of a trial is biased to the null.[109] A range of statistical techniques are available to correct for the resulting bias, each with their own required set of assumptions.[109] These techniques have been applied to anticancer treatments to determine an unbiased estimate of treatment impact.[110] This approach can also be used to assess the impact of using non-standard treatments on outcomes within an RCT.[110] Adjustment for treatment switching is considered an important issue in the approval and funding of new anticancer agents.[111]

A similar attribution problem is the potential for other therapies to be given in the post-progression period. In this situation, overall survival, or more correctly, the difference in overall survival is not due solely to the treatments given in the progression free survival phases (Tappenden et al., 2006).[38] The economic evaluations in this review did not correct for crossover although some included post-treatment sequence protocols.

3.1.8 Dynamic treatment strategies

The use of dynamic treatment strategies is another approach when evaluating multiple treatments for an individual. The rationale is that for every multistage treatment strategy (in this case the sequence of cancer treatment), the dose or treatment is modified according to the patient's current history and disease status. The selection of a new treatment, for example a new line of therapy, is determined partly by the patient's experience of past treatments. These are also called adaptive treatment strategies.

Work has been undertaken on the design of RCTs in cancer (and other diseases) comparing different adaptive strategies or comparing adaptive strategies to non-adaptive strategies. This includes the estimation of effects of dynamic treatment strategies in observational data and RCT, including cancer.[112,113]

Dynamic treatment strategies are an area closely related to the topic of this thesis. They involve multiple treatments and an understanding that the assessment of a combination of treatments may result in different outcomes from those produced by the summation of the assessment of individual treatments. However, dynamic treatment strategies can be broader than cancer treatment. No economic evaluations of dynamic treatment strategies in cancer were identified in the current literature review. However, it is anticipated that RCTs based on

dynamic treatment strategies and the corresponding economic evaluations will become more common in the future.

3.1.9 Approach to modelling within the current literature

Most of the published economic evaluations selected the evidence to use for effectiveness and the alternatives simultaneously. Three broad approaches were taken to the selection of alternatives (and these have different requirements for the synthesis of effectiveness).

The first (single trial based) approach was to select the alternatives, measurement and estimation of effectiveness from within a single trial. This was the approach taken by the NSCLC economic evaluations, and Miyazaki et al. (2009)[93] and Manca et al. (2012)[97] in CRC. This approach has the advantage of a more complete collection of data within the trial (and afterwards), allowing a greater inclusion of costs and more information about the use of post-treatment sequence protocols. While this approach has the most internal validity, it potentially has the least external validity. The lack of external validity is because the number of alternatives that are considered is necessarily limited to those explored in the trial and they may been replaced as standard treatment by the time the results are available. There are limited number of RCTs involving multiple lines of therapy and this restricts the available evidence to inform modelling.

The second (trial arm based) approach was to combine different alternatives from the arms of distinct RCTs but not synthesise new alternative strategies. Thus, each combination of first line, second line and third line therapy was contained entirely within an arm of an RCT. This approach requires evidence from multiple RCTs to be available from similar populations for valid comparisons. It has less internal validity than using a single trial because there may be differences between the trials in population characteristics and health systems. At the same time, it still suffers from the same problem as using a solitary trial in that feasible alternatives not considered in the trial cannot be evaluated. Hind et al. (2008)[94] was an example of this approach.

Specifying realistic alternatives, in most cases, requires the modelling of alternatives that have not been considered wholly within an arm of an RCT. This was the third (synthesis of alternatives) approach. In this approach, the first line treatment, the second line treatment and the third line treatment are not contained in an arm of RCT. Examples included Wong et al. (2009)[1] and Rautenberg et al. (2014).[2] Therefore, the alternative and the estimated effectiveness of the alternative were modelled.

Progression free survival (PFS) and overall survival (OS) are key outcomes used to investigate the impact of cancer treatments. They are often the endpoints used in clinical studies.

Progression free survival in advanced carcinomas (also known as metastatic progression free survival) is the time interval between entry into the study and the date of growth of metastasis, new metastasis or death (from any cause).[114] Overall survival is time interval from entry into the study and death.[115]

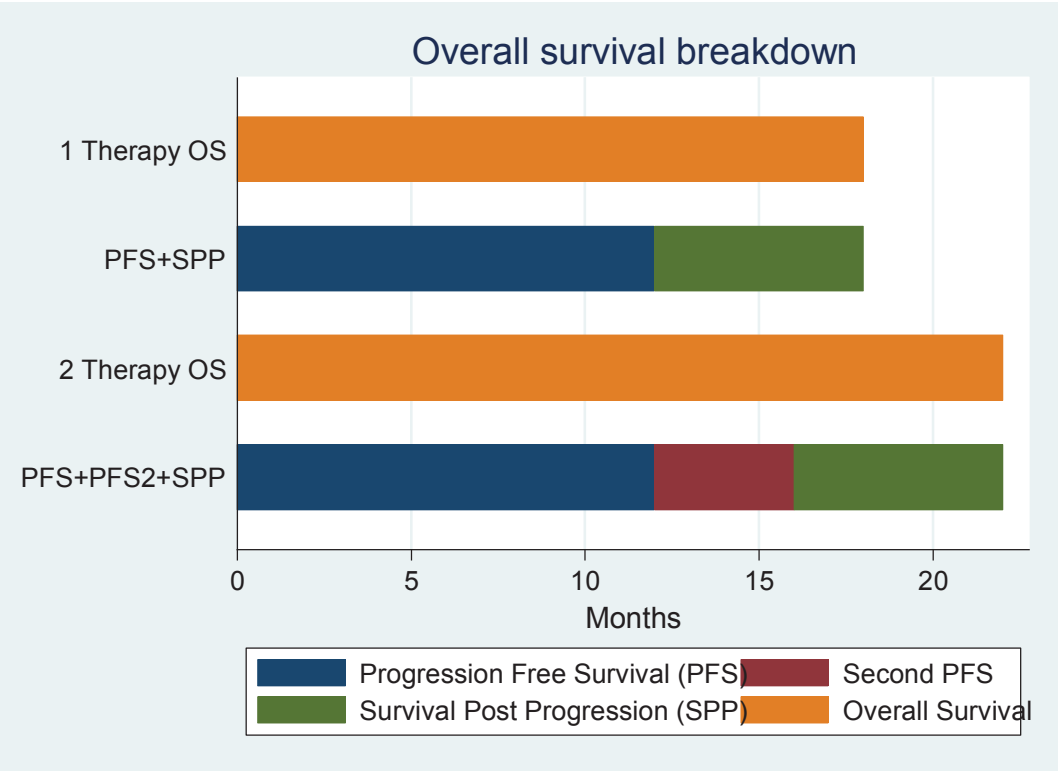
The relationship between overall survival and progression free survival is demonstrated in Figure 9. The top line shows the mean overall survival associated with a cancer population; this can be divided into a period of time before an initial progression and a time after progression in the second line.[116] These periods are both survival periods. The first period can be defined as PFS and the second period as survival post-progression (SPP)[vi]. This is shown in the second line; overall survival is equal to the sum of PFS and SPP.

This breakdown is not based on whether there were prior progressions experienced by the participants. That is, the population under consideration could already have been given a treatment and progressed, and therefore be a second line of therapy population. The population overall survival from entry into the study can still be segmented into a PFS and SPP.[116]

Progression free survival is becoming increasingly used to determine if a treatment is beneficial for regulatory approval, that is, to estimate whether a treatment´s incremental benefit is greater than zero.[117] This assumes an increase in PFS results in an increase in OS.

Multiple progression free survivals can be calculated for a treatment sequence. After the first progression, a second treatment may be given, and a second progression free survival calculated (the third and fourth rows in Figure 9).

[vi] Survival post progression is also termed post progression survival (PPS) in some articles



Abbreviations: OS: overall survival; PFS: progression free survival; SPP: survival post-progression

Figure 9: Overall survival breakdown

There is a relationship between the duration of treatment and progression free survival. However, they are two distinct durations and there may be differences between them. Treatment may be ceased prior to progression because of toxicity, declining patient resilience or because the treatment had finished.[71] Additionally, multiple treatments and lines of therapy may be given prior to progression. For example, if toxicity caused the failure of one treatment and a second treatment is started. The initiation of a second line treatment after progression usually does not start immediately after progression. A gap in treatment often occurs between lines of therapy to ensure that the toxicity of combined treatments is not experienced.[118]

Conversely, there could be treatments given after progression, in the SPP period when they have not been considered in the construction of the treatment sequence. This occurred in the Seymour et al. (2007)[72] trial associated with the economic evaluations of Hind et al. (2008)[94] and Manca et al. (2012).[97]

The economic evaluations often assumed a higher utility (that is, a better quality of life) associated with a pre-progression state (see Table 14). The economic evaluations also attributed different costs to the different periods.

In those economic evaluations which used results from a single trial (for example Manca et al. [2012][97]) and the trial captured overall survival, overall survival can be directly extrapolated from the trial.

As these trials included additional planned treatments given after progression and until a further progression, the possibility of identifying multiple progressions arises (and therefore estimating PFS at multiple time points). This may lead to a situation as shown in the third and fourth line of Figure 9. Overall survival is associated with two treatment protocols and two periods of progression free survival, followed by a post-progression survival.

For modelling purposes, each progression free survival can potentially be related to costs and to utilities. Therefore, a Markov model structure was a common modelling technique used, for example, in Manca et al. (2012)[97] and Miyazaki et al. (2009).[93] Alternatively, the costs and benefits can be measured within the trial independently of the progression periods and calculated directly. This occurred in Chouaid et al. (2012).[96]

The use of additional therapies in the post-progression period was not considered in most economic evaluations. The exceptions were Hind et al. (2008)[94] and Manca et al. (2012).[97] Hind et al. (2008)[94] considered that missing therapies were an indication that a traditional incremental cost-effectiveness would be misleading, and this was the reason for not including an incremental analysis. Manca et al. (2012)[97] included the costs of additional therapies in the analysis but made assumptions about their length (and therefore total cost).

The trial arm based approach could also use overall survival as an effectiveness measure sourced from the relevant trials.

Most of economic evaluations that synthesised new alternatives focused on overall survival as the effectiveness measure. This was then adjusted by a preference measure (usually expressed as QALYs gained).

The approach taken by all except one[98] of the recovered economic evaluations that synthesised the alternatives was to estimate the PFS associated with a protocol within a line of therapy. The next step was to model participants transitioning from one line of therapy to the next and eventually to a post-progression survival state. Each alternative was modelled as a series of protocols in first, second, third and then a post-progression survival period. The post-progression survival in this case was usually measured explicitly as best supportive care or

treatment without the use of chemotherapy. For this modelling, decision tree and Markov modelling techniques were common.

In this approach, a series of decisions were necessary: the selection of the protocols in each line of therapy; the number of lines of therapy (these first two define the alternatives being compared); how to estimate the effectiveness of each line of therapy; and how to combine this information (the model). This information for those economic evaluations which created alternatives is shown in Table 13.

Table 13: Alternatives and modelling for alternatives synthesised from a combination of sources

Economic evaluation	Selection of protocols in each line	Selection of the number of lines of therapy	Estimation of effectiveness of each line of therapy	Combination
NICE (2009)[90]	"Standard treatment"	Up to three lines of therapy	Indirect meta-analysis	Decision tree, time to progression in each line of therapy was added
Wong et al. (2009)[1]	"Selected to reflect sequential advances in colorectal cancer treatment"	Up to three lines of therapy	Index trial for each line of therapy	Markov model, progression, competing death, death and toxicity
Tappenden et al. (2013)[98]	Current mix of palliative chemotherapies	Up to two lines of therapy	Network meta-analysis	Calculated from OS, divided into three components (PFS1, PFS2 and SPP)
Rautenberg et al. (2014)[2]	"Based on licenced indications" validity checked with clinical oncologists	Up to three lines of therapy	Index (pivotal) trial for each line of therapy	Addition of median progression free survival in each line
Riesco-Martinez et al. (2016)[4]	"Alternative treatment strategies"	Based on use of both antibody therapies- EGFR used in third lines	From published literature- literature search undertaken, choice not clear	Markov model, progression and death

Abbreviation: EGFR: epithelial growth factor receptor; NICE: National Institute of Health and Clinical Excellence; OS: overall survival; PFS: progression free survival; SPP: survival post-progression

Consideration of overall survival and its relationship to sequential progression free survival periods is an important modelling choice within an economic evaluation. A Markov model or decision tree process is a natural fit with the disease process. However, this makes

assumptions about the relationship between progression free survival and overall survival. It assumes that additional PFS results in additional OS. This assumption is contested in the clinical literature, as improvements in PFS do not always translate to similar improvements in OS.[119]

Most of the evaluations that constructed alternatives assumed that overall survival was the sum of progression free survival periods. The switch from one protocol to the next was based on progression (all economic evaluations) or toxicity (most economic evaluations). One economic evaluation.[98] constructed the length of treatment by subtracting calculated progression free survival periods from the calculated overall survival.

The modelled relationship between costs and progression free survival was usually estimated as linear. That is, the cost of treatment was proportional to the progression free survival period. This was the assumption made in most economic evaluations that constructed alternatives (see Table 17).

In a modelled economic evaluation, the impact on participants of disease progression or toxicity is considered. It is usually assumed that they result in a lower utility level for an individual. Therefore, it is plausible that later lines of therapy are associated with lower utility compared to earlier lines of therapy.

Four different approaches were used to take account of this issue in the economic evaluations reviewed: measuring the utility within the trial; assuming an unchanging utility; adopting state specific utility values; or not attempting to calculate utility (instead using life years saved as the outcome measure). Table 14 shows the source of utility estimation in the economic evaluations. Utility weights were often selected based on administration, for example for oral versus intravenous therapy, or based on the line of therapy. The majority, but not all, of the economic evaluations demonstrated a reduction in utility weights associated with increasing lines of therapy.

Table 14: Derivation of utility in economic evaluations of treatment sequences

Reference	Method	Diminishing, stable or increasing as line of therapy increases	Source
Hind et al. (2008)[94]	Assume unchanged	Stable	Mean of all utility scores in FOCUS trial
NICE (2009)[90]	State specific- according to response and toxicity	Stable/Diminishing	2002 paper.[90]
Shiroiwa et al. (2009)[95]	State specific – calculated according to method of administration	Stable	Time trade-off within original paper
Chouaid et al. (2012)[96]	State specific – calculated using standard gamble – based on method of administration and progression	Stable/diminishing	Literature – 2008 paper – standard gamble.[96]
Manca et al. (2012)[97]	Within trial and based on state specific	Not assessable	Based on the EQ-5D questionnaire.[97]
Chouaid et al. (2013)[88]	State specific – calculated using standard gamble – based on method of administration and progression	Stable/diminishing	Literature – 2008 paper – standard gamble.[88]
Tappenden et al. (2013)[98]	Single utility value for all metastatic disease	Stable	1997 paper.[98]
Goldstein et al. (2015)[89]	State specific – based on first and second line therapies	Diminishing	Literature – 2010
Riesco-Martinez et al. (2016)[4]	State specific based on adverse events and progression	Diminishing	Based on the EQ-5D questionnaire survey of oncologists.[4]

Abbreviations: EQ-5D: European Quality of life-5 Dimensions; FOCUS (trial): fluorouracil: oxaliplatin: CPT11: use and sequencing; NICE: National Institute of Health and Clinical Excellence

Information about the approach to treatments with a similar structure to displacement, that is the same protocol being used in different lines of therapy within the same economic evaluation, was extracted from the recovered literature. The information extracted included the method of assessment of benefit, the method of assessment of cost and a comparison of the two between the different lines of therapy.

One or more treatments in different lines of therapy was common to the majority of recovered economic evaluations. Technically, this may not be the same as displacement as defined in Chapter 2, because the use in a later line of therapy might not be because of the introduction of another treatment.

An economic evaluation could have been identified from the literature involving the comparison of different treatment sequences which did not involve displacement. For

example, an economic evaluation comparing the choice of A and B in the first line of therapy and C and D in the second compares different sequences but does not involve displacement of a treatment from one line of therapy to another.

However, if displacement is present, the economic evaluation should be designed so that the effectiveness of the protocol is calculated in two different lines of therapy: the original line of therapy and the subsequent line of therapy.

Table 15 below summarises this process. It describes the specific protocols that were displaced, and the evidence used to calculate the effectiveness in each line of therapy. The final column reports the implied change in effectiveness which occurs when the protocol was moved from one line to the subsequent line of therapy.

Across the recovered literature, the most common implication for displacement was a diminished level of effectiveness of the later line of therapy (14 of 22; 64%). One exception to the diminished level of effectiveness was due to the selection of the same effectiveness data for multiple lines of therapy. For example, in the NICE breast cancer study, the same effectiveness data was assumed to apply in the model for both second and third line therapy because of the absence of third line data.[90]

In some studies, the measurement of effectiveness in different lines of therapy was based on the results of trials which recruited different populations, for example, Rautenberg et al. (2014).[2] In this study, the second line population was modelled from a RCT with inclusion criteria with a biomarker[120] while the third line population was from a retrospective review of a population receiving third line treatment without consideration of the biomarker.[121] The results of this naïve comparison of two populations should be treated with caution as their inclusion in the modelling undertaken in the Rautenberg et al. (2014)[2] is inappropriate. The disease of interest in Rautenberg et al. (2014)[2] was metastatic CRC with wild type KRAS tumours but neither Sobrero et al. (2008)[120] nor Pfeiffer et al. (2008)[121] had wild type KRAS tumours as inclusion criteria.

Table 15: Implied impact on effectiveness of displacement in economic evaluations

Number	Article	Protocol displaced	Displacement	Method of economic evaluation	Implication for displacement
1	Hind et al. (2008)[94]	FOLFIRI	From first line of therapy to second line of therapy (1→2)	Single trial for both lines of therapy	Decreased effectiveness
2	Hind et al. (2008)[94]	FOLFOX	1→2	Single trial for both lines of therapy	Decreased effectiveness
3	Miyazaki et al. (2009)[93]	FOLFIRI	1→2	Single trial for both lines of therapy	Decreased effectiveness
4	Miyazaki et al. (2009)[93]	FOLFOX	1→2	Single trial for both lines of therapy	Decreased effectiveness
5	NICE (2009)[90]	Vinorelbine	2→3	Same information used for both lines of therapy	Same/similar effectiveness
6	NICE (2009))[90]	Capecitabine	2→3	Same information used for both lines of therapy	Same/similar effectiveness
7	Shiroiwa et al. (2009)[95]	FOLFOX	1→2	Different trials used for assessment	Decreased effectiveness
8	Shiroiwa et al. (2009)[95]	XELOX	1→2	Different trials used for assessment	Decreased effectiveness
9	Wong et al. (2009)[1]	FOLFOX	1→2	Pivotal trial (different)	Decreased effectiveness
10	Chouaid et al. (2013)[88]	Erlotinib	1→2	Single trial for both lines of therapy	Similar effectiveness
11	Chouaid et al. (2013)[88]	Docetaxel and gemcitabine	1→2	Single trial for both lines of therapy	Decreased effectiveness
12	Tappenden et al. (2013)[98]	FOLFOX	1→2	Indirect meta-analysis used	Decreased effectiveness
13	Tappenden et al. (2013)[98]	XELOX	1→2	Indirect meta-analysis used	Decreased effectiveness
14	Tappenden et al. (2013)[98]	FOLFIRI	1→2	Indirect meta-analysis used	Decreased effectiveness

Number	Article	Protocol displaced	Displacement	Method of economic evaluation	Implication for displacement
15	Tappenden et al. (2013)[98]	XELIRI	1→2	Indirect meta-analysis used	Decreased effectiveness
16	Tappenden et al. (2013)[98]	Capecitabine	1→2	Indirect meta-analysis used	Similar effectiveness
17	Tappenden et al. (2013)[98]	5-FU	1→2	Indirect meta-analysis used	Similar effectiveness
18	Chouaid et al. (2012)[96]	Erlotinib	1→2	Single trial for both lines of therapy	Similar effectiveness
19	Chouaid et al. (2012)[96]	Gemcitabine	1→2	Single trial for both lines of therapy	Decreased effectiveness
20	Rautenberg et al. (2014)[2]	Bevacizumab + XELOX	1→2	Different trials used for assessment	Decreased effectiveness
21	Rautenberg et al. (2014)[2]	Cetuximab + irinotecan	2→3	Different trials used for assessment	Improved effectiveness
22	Riesco-Martin et al. (2016)[2]	FOLFOX/FOLFIRI + Bevacizumab	1→2	Systematic review	Similar effectiveness

Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; XELIRI: a protocol consisting of irinotecan and capecitabine; XELOX: a protocol consisting of oxaliplatin and capecitabine

The approach to costs is another important element in the recovered literature. Exclusion of types of cost could produce biased results. This is because cancer treatment and care is associated with substantial costs and not considering relative changes might result in the incremental costs not being calculated correctly.[63]

Cost could be based on the activities associated with cancer treatments. These costs could include the administration of the anticancer treatments, the treatment of adverse events, the treatment of the cancer (including palliative care and death), or not be directly related to the cancer and its treatment.

Alternatively, the costs could be classified according to the type of input, for example pharmaceuticals, primary care, hospitalisations, out of hospital specialist care etc.

The types of costs included in the published economic evaluations were extracted and are shown in Table 16. Only pharmaceutical costs and administration costs were considered by all the economic evaluations. The economic evaluations that accompanied clinical trials included a wider range of costs. The inclusion of supportive care costs in several economic evaluations meant that costs of the disease were included. A health service perspective was undertaken in most economic evaluations so patient costs were not included.

The omission of costs, especially costs that are directly related to treatment (such as those associated with adverse events), limits the use of these economic evaluations for decision-making based on incremental costs.

Table 16: Included costs for recovered economic evaluations

Type	Subgroup	Hind et al. (2008)[94]	Miyazaki et al. (2009)[93]	NICE (2009)[90]	Shiroiwa et al. (2009)[95]	Wong et al. (2009)[1]	Chouaid et al. (2012)[96]	Manca et al. (2012)[97]	Chouaid et al. (2013)[88]	Tappenden et al. (2013)[98]	Rautenberg et al. (2014)[2]	Goldstein et al. (2015)[89]	Riesco-Martinez et al. (2016)[4]	Percentage
Cancer Treatment activities	Administration	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Adverse events costs-out of hospital	Yes	No	Yes	Yes	No	Yes	Yes	Yes	No?	No	Yes	Yes	67%
	Adverse events costs - hospital	Yes	No	Yes	No	No	Yes	Yes	Yes	No?	No	Yes	Yes	58%
	Costs of disease	No	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	67%
	Other costs	No	No	No	No	No	Yes	Yes	Yes	No	No	No	No	25%
Input type	Pharmaceuticals	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100%
	Diagnostics	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	No	Yes	75%
	Primary Care	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	No	No	58%
	Out of hospital specialist care	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	75%
	Hospitalisation	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes	Yes	66%
	Patient costs	No	No	No	No	No	No	No	No	No	No	No	No	0%

The costs for displaced therapies are shown in Table 17, including how the costs for the initial line and the subsequent line of therapy were calculated. For some evaluations, there was not an attribution of costs to a line of therapy, for example Chouaid et al. (2013).[88] Therefore, it was not possible to compare the costs of displaced treatments. The remainder of the evaluations costed treatments in one of two ways, either by the number of cycles or by the time in the progression free state.

Table 17: Implied cost changes for displaced treatments in the recovered economic evaluations

Article	Protocol displaced	Displacement	Costs structure for initial treatment	Cost structure for subsequent line	Implied change
Hind et al. (2008)[94]	FOLFIRI	From first line of therapy to second line of therapy (1→2)	Costs per cycle	Costs per cycle	Via the number of cycles
Hind et al. (2008)[94]	FOLFOX	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
Miyazaki et al. (2009)[93]	FOLFIRI	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
Miyazaki et al. (2009)[93]	FOLFOX	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
NICE (2009)[90]	Vinorelbine	2→3	Costs per cycle	Costs per cycle	Via the number of cycles
NICE (2009)[90]	Capecitabine	2→3	Costs per cycle	Costs per cycle	Via the number of cycles
Shiroiwa et al. (2009)[95]	FOLFOX	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
Shiroiwa et al. (2009)[95]	XELOX	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
Wong et al. (2009)[1]	FOLFOX	1→2	Costs per cycle	Costs per cycle	Via the number of cycles
Chouaid et al. (2013)[88]	Erlotinib	1→2	Trial based analysis without individual lines of therapy costs		
Chouaid et al. (2013)[88]	Docetaxel and gemcitabine	1→2	Trial based analysis without individual lines of therapy costs		
Tappenden et al. (2013)[98]	FOLFOX	1→2	Cost per time period	Cost per time period	Via time period
Tappenden et al. (2013)[98]	XELOX	1→2	Cost per time period	Cost per time period	Via time period
Tappenden et al. (2013)[98]	FOLFIRI	1→2	Cost per time period	Cost per time period	Via time period

Article	Protocol displaced	Displacement	Costs structure for initial treatment	Cost structure for subsequent line	Implied change
Tappenden et al. (2013)[98]	XELIRI	1→2	Cost per time period	Cost per time period	Via time period
Tappenden et al. (2013)[98]	Capecitabine	1→2	Cost per time period	Cost per time period	Via time period
Tappenden et al. (2013)[98]	5-FU	1→2	Cost per time period	Cost per time period	Via time period
Chouaid et al. (2012)[96]	Erlotinib	1→2	Trial based analysis without individual lines of therapy costs		
Chouaid et al. (2012)[96]	Gemcitabine	1→2	Trial based analysis without individual lines of therapy costs		
Rautenberg et al. (2014)[2]	Bevacizumab + XELOX	1→2	Cost per time period	Cost per time period	Via time period
Rautenberg et al. (2014)[2]	Cetuximab + irinotecan	2→3	Cost per time period	Cost per time period	Via time period
Riesco-Martinez et al. (2016)[4]	FOLFOX/FOLFIRI + Bevacizumab	1→2	Cost per time period	Cost per time period	Via time period

Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; XELIRI: a protocol consisting of irinotecan and capecitabine; XELOX: a protocol consisting of oxaliplatin and capecitabine

Most economic evaluations modelled displacement as having a similar average cost per unit of time. As most economic evaluations assumed that there was a decrease in the utility value for a displaced therapy this implied that the cost-effectiveness ratio increased with displacement (similar cost per unit time, decreased utility per unit time).

There are mechanisms other than displacement which can be used to determine a treatment sequence from the available protocols.

Sequence heterogeneity refers to the concept that different subgroups of patients may have different ideal treatment sequences which are identifiable prior to the commencement of treatment. An example of such heterogeneity is that patients with wild type KRAS benefit from antibodies and the inclusion of this treatment improves their health outcomes. Correspondingly, those with a mutation do not benefit from EGFR (epithelial growth factor receptor) antibodies and use of this treatment does not improve outcomes. Therefore, the available treatment sequences differ between these groups. This issue is discussed further in Section 3.2 and in Section 8.2.

Dynamic treatment strategies refer to changing the treatment sequence after commencement, for example using the type of adverse events that occurred in the first line of therapy to alter the choice of second line treatment (see Section 3.1.8). None of the recovered studies considered sequence heterogeneity or dynamic treatment strategies in the modelling of the economic evaluations. This weakness is inherent in the construction of an RCT without a dynamic design. This issue flows through to the economic evaluations based on RCTs.

The potential for sequence heterogeneity was raised in the NICE review which discussed the potential for vinorelbine to be slightly less effective but much less toxic than one of the comparators for the elderly.[90] These effects, however, were not modelled.

3.1.10 Conclusions

The literature reporting the results of economic evaluations involving multiple lines of therapy is very limited. The literature recovered only discussed three sites of cancer origin (breast, lung and colorectal) and only a selected number of anticancer agents within each cancer type were evaluated.

The approach used in economic evaluations of multiple lines of therapy is heavily dependent on the available clinical literature. All the evaluations identified for the review reported here used information derived from RCTs to develop the estimates of effectiveness.

Four economic evaluations used a single trial based approach to develop the potential alternative treatment sequences. The remaining studies used different trials to develop the alternatives. Some gathered entire treatment sequences from different trials (trial arm based approach) while the most common approach was to synthesise the treatment sequences from different trials - one for each line of therapy (synthesis of alternatives approach).

Only one economic evaluation conducted an indirect analysis between different trials,[101] another used a published indirect analysis.[98] That all the evaluations used RCT data means that it is very important to understand the limitations of these data. A key limitation is that data on alternative treatment sequences are limited to those for which RCT data exists. As discussed in Chapter 2, RCT data may not exist for the displaced treatment in its new line of therapy.

Several potential limitations arise where a single trial was used as the source of all alternative lines of therapy. The first is the issue of the comprehensiveness of the alternatives. A trial with only two arms may not represent all the potential alternatives. The second limitation is the external validity of the trials; these trials may not represent usual practice. However, there are also significant advantages to using a single trial when considering multiple lines of therapy. The most striking is that actual trial outcomes can be included, for example the fact that some patients cease treatment, that is, they do not move from one line of therapy to the next. The second advantage is that a wider variety of costs can be included in the evaluation. Costs of additional treatments after the planned treatment sequences were available in the economic evaluations based on a single trial. Overall, these economic evaluations are more likely to possess higher internal validity but lower external validity.

Alternatively, for the economic evaluations not based on a single trial, the external validity is likely to be higher due to an ability to include currently realistic treatment sequences. However, the internal validity is lower with potentially different populations included. Also, a smaller range of costs were generally included in those economics evaluations based on more than one trial.

No treatment sequences were longer than three lines of therapy. This is consistent with the available evidence circa 2010 (see Section 6.1) but is not consistent with the treatment of patients in 2010 (see Chapter 4).

The lack of clinical data is a key limitation that may have resulted in the small number of economic evaluations that modelled treatment sequences.[70] This shows the published

evaluations to date are not keeping pace with the extent of clinical practice using multiple lines of therapy, although they are consistent with the evidence base.

Generally, the economic evaluations were considered as good quality, as judged by the CHEERS checklist. The selection of the modelling techniques, discussion of the setting and inclusion of participant heterogeneity were weaknesses in the literature.

In the modelled economic evaluations, it was commonly assumed that all participants received all treatments unless death occurred prior to the final line of therapy. This is not consistent with the RCT literature which is discussed in Chapter 4 and Chapter 6, which demonstrates a substantial minority of all patients do not receive all the available therapies.

The studies that used modelling exhibited a heterogeneous approach and the results were strongly influenced by the scope of modelling undertaken. The lack of trial data involving multiple lines of therapy is likely to be a reason for some of the choices made during the modelling development.

The use of medians (rather than means) for the outcome measure is a result of the dominant reporting in the cancer literature being time to event. This, however, does not necessarily equal the true survival benefit - the mean difference.[38] For the modelled evaluations the lack of justification for the selection of the effectiveness measure, the limited range of costs included and the common assumption that participants received all treatments appear to be weaknesses and may have biased the results.

If the adverse events differ by the line of therapy (see Chapter 6) their exclusion will also have biased the results. If it is assumed that all patients receive all treatments, the resulting calculated cost-effectiveness will be biased by the over-emphasis on the later lines of therapy on the cost-effectiveness of the entire treatment sequence. Most pharmaceutical costs and monitoring were assessed as per cycle or per time. This may not be a reasonable assumption if treatment is ceased prior to progression or the cost of a cycle is dependent on the number of cycles previously given (see Section 2.3.2 and Chapter 6). The exclusion of potential real-world alternatives might be important in determining the incremental cost-effectiveness. This was most noticeable with some CRC economic evaluations excluding a no-antibody comparator.

Additionally, studies using the modelling approach which combined the results of multiple trials assumed that overall survival was the additive combination of the PFS and best supportive care/palliative care. This assumed that the average benefit from another line of

therapy was equal to the incremental benefit from including that treatment. Only one study varied the post-treatment period by the number of lines of therapy received.[4]

These economic evaluations also commonly assumed that the cost of a protocol was directly proportional to the progression free survival time of the line of therapy. That is, there is a constant cost per unit of progression free survival. Whether this is supported by the empirical evidence is examined in Chapter 5.

The economic evaluations and other articles presented here also demonstrate that there are other methods of developing a treatment sequence than displacement. The treatment sequence may be determined by ordering the available treatments to generate the greatest benefit, least cost or most cost-effective outcome. These approaches do not consider the dynamic nature of the number of available treatments over time.

Heterogeneity in the population may result in heterogeneity in the sequence which is the most cost-effective. This was not considered in the economic evaluations within this Section.

Stratified prices were not included in how these economic evaluations estimated costs. The cost of pharmaceuticals was constant, independent of the line of therapy. This results in the conclusion, if the outcomes are equivalent, of using the less expensive protocols initially. As discussed in Chapter 2, it may also result in allocative and dynamic inefficiency if a shorter treatment sequence is not considered.

Only one economic evaluation specifically considered displacement for treatments without clinical evidence.[90] Several economic evaluations had a protocol modelled in different lines of therapy. The implied cost-effectiveness worsened with displacement with these economic evaluations. The benefit, as estimated by the QALYs, fell per unit time while the costs stayed constant.

The assumption that all patients will move from one line of therapy to the next was used in several of the modelled economic evaluations. The chance that a proportion of those taking an initial line of chemotherapy will not receive a second line treatment or perhaps a different more benign treatment was not included in the evaluations. The impact of changing this assumption on the results was not evaluated.

Although this review identified heterogeneity in the methods used, a common feature of the evaluations that synthesised information from several trials was the use of the same functional form to combine the information. This functional form is the addition of the progression free

survival periods from each line of therapy and then an additional period of palliative or supportive care. This model will be defined as the additive separate model and is used in Chapter 5 and Chapter 6 to consider the impact of displacement.

There were five common assumptions made in the economic evaluations of treatment sequences reviewed in this Chapter.

1. Equating progression free survival to the treatment period.
2. Assuming a constant treatment cost per time.
3. Assuming that adverse events do not impact on the results.
4. Assuming participants receive all treatments.
5. Assuming a common post-progression survival.

These assumptions are challenged in Chapter 6 and their consistency with the empirical findings in Chapter 5 evaluated. The change in cost-effectiveness of displaced treatments is examined in Chapter 7.

3.2 Cetuximab economic evaluations

This Section aims:

1. to identify, evaluate and critique the current published literature on economic evaluations of cetuximab in CRC; and
2. to identify the modelling assumptions and outcomes that are important when evaluating the impacts of displacement for cetuximab.

This was achieved by the use of a comprehensive literature review.

3.2.1 Introduction

Cetuximab is a targeted pharmaceutical directed towards the Epithelial Growth Factor Receptor (EGFR) in tumours. However, its activity is not completely correlated with EGFR expression and the marker most commonly used for identification of benefit is the genetic KRAS (Kirsten Rat Sarcoma viral oncogene homolog) status of the tumour.[122] Cetuximab is a member of a class of pharmaceuticals (including panitumumab) known as EGFR-inhibitors[123] or anti-EGFR antibodies.[124]

A KRAS mutation results in resistance to anti-EGFR therapy in CRC.[122] Therefore, cetuximab therapy is beneficial in tumours without an activating mutation, or "wild type" tumours.[122] Approximately 60% of patients with metastatic CRC have wild type tumours.[122] The exact definition of which tumours will respond to anti-EGFR therapy is subject to ongoing modification as more is understood about the activating mutations, of which there are several.[124,125]

Cetuximab is also used in the treatment of head and neck cancer[123] and has been investigated as a treatment in other tumour types.[126]

In the treatment of metastatic CRC, cetuximab has been shown to be beneficial both as a monotherapy (used without any other anticancer agents) and in combination with traditional chemotherapy agents (combination therapy). It was initially demonstrated to have an impact in the later lines of therapy and was subsequently tested in the first line of therapy.

Cetuximab as a monotherapy was compared to best supportive care (BSC) in a trial of 572 patients recruited between 2003 and 2005 who had failed treatment with irinotecan, oxaliplatin and 5-FU. Thus, these patients were given cetuximab as a second or later line of therapy.[127] Most patients had been treated with three or more previous lines of therapy. Overall survival was statistically significantly better in the cetuximab arm (6.1 versus 4.6

months). However, a subsequent unplanned subgroup analysis (post hoc analysis) published a year later showed that the benefit only applied to participants without KRAS mutations.[128] Only 70% of patients had tissue available for KRAS analysis. This trial is also referred to in the literature as the C.O.17 trial.[129]

Cetuximab used in combination with chemotherapy was also shown to be beneficial in patients who had failed previous chemotherapy treatment. The EPIC (also known as Sobrero et al., [2008][120]) and BOND (also known as Cunningham, et al. [2004][130]) trials showed improved PFS and response rates when cetuximab was combined with chemotherapy than either chemotherapy alone or cetuximab alone in later lines of therapy.[120,130] An overall survival benefit was not demonstrated. The significant rate of crossover within these trials is likely to have biased the estimates of the differences between arms.[120] The trials were conducted in an EGFR expressing population and then subsequently a post hoc analysis was undertaken to determine the KRAS status of the tumour. In the BOND trial 90% of the tumours had a KRAS test performed whereas in EPIC only 25% of tumours were available for KRAS analysis and the results for EPIC have only been presented as an abstract.[19]

In summary, the benefit of cetuximab was demonstrated in later lines of therapy in the C.O.17 trial, but the magnitude of the overall benefit for wild type KRAS tumours is uncertain because of the post hoc nature of the analyses and high rate of crossover.

Subsequently, the benefit of cetuximab in first line treatment was demonstrated in the CRYSTAL trial in which participants with EGFR overexpressing tumours were randomised to chemotherapy with and without cetuximab.[131] For tumours with wild type KRAS status the median overall survival improved from 20 months to 23.5 months. However, patients were not initially selected based on their KRAS mutation for recruitment into the study. Subsequent trials showed that cetuximab in combination with other chemotherapy agents was beneficial in first line therapy.[132]

In summary, there are multiple lines of therapy for which cetuximab has been shown to be effective. For the initial lines of therapy, cetuximab has only been used in protocols that include additional pharmaceuticals (combination chemotherapy). For later lines of therapy, it has been used both with and without other treatments.

Table 18: Important clinical trials involving cetuximab

Study	Population	Line of therapy	Comparators	HR PFS	HR OS
Jonker et al. (2007)[127]	Unselected with regard to KRAS status	Third	Cetuximab versus BSC	0.68 (0.57-0.8)	0.77 (0.64-0.92)
Karapetis et al. (2008)[128] from Jonker et al. (2007)[127]	Selected post hoc to include only KRAS wild type	Third	Cetuximab versus BSC	0.55 (0.41-0.74)	0.4 (0.3-0.54)
Sobrero et al. (2008)[120]	Unselected with regard to KRAS status	Second	Cetuximab and irinotecan versus irinotecan	0.69 (0.61-0.77)	0.975 (0.85-1.11)
Van Cutsem et al. (2009)[131]	Unselected with regard to KRAS status	First	FOLFIRI and cetuximab versus FOLFIRI	0.85 (0.72-0.99)	0.93 (0.81-1.07)
	Selected post hoc to include only KRAS wild type	First	FOLFIRI and cetuximab versus FOLFIRI	0.68 (0.5-0.94)	

Abbreviations: BSC: best supportive care; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; HR: hazard ratio; KRAS: Kirsten rat sarcoma; OS: overall survival; PFS: progression free survival

In Australia, the current advice of the Therapeutic Goods Administration (TGA) for cetuximab in CRC is that it be restricted to patients in whom KRAS status has been assessed.[133] Cetuximab was considered but not recommended by the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia eight times, prior to being listed in 2010 on the Pharmaceutical Benefits Scheme (PBS) for the second line treatment of patients with wild type KRAS metastatic CRC.[134] The earlier rejections were due to uncertainty over clinical benefit and later because of a high and uncertain cost-effectiveness ratio.[134] The successful submission referenced the Karapetis et al. (2008) study[128] which reported a QALY gain due to cetuximab of 0.25. The weighted ICER was between $45 000 and $75 000/QALY gained (assumed to be a 2010 base on the basis of publication).[134] This allows some comparison to the results of other economic evaluations assessed later in this Section.

3.2.2 Published systemic reviews of economic evaluations of cetuximab

There have been two previously published systematic reviews of economic evaluations for cetuximab.[85,135] One review of economic evaluations of pharmacogenomics profiling that included KRAS mutations and by extension cetuximab has also been published.[122] There have

also been four HTAs published involving cetuximab. Three of these assessments were undertaken in the UK, in 2007,[136] 2013[137] and 2014.[86] The fourth assessment was undertaken in 2010 in Ontario, Canada.[3] These HTAs also included systematic reviews of the economic evaluations.

In 2014, the "NHS HTA Assessment programme" conducted a systematic review of KRAS testing and associated treatment.[86] This involved a systematic review of previously applicable economic evaluations and the production of a new economic evaluation. The focus of this HTA was narrower than that used in this Chapter, and consequently, a smaller number of economic evaluations were included. The quality of the evaluations was assessed using the CHEERS checklist. The conclusion of the HTA was that "the ICER of KRAS testing and treating …. compared with standard chemotherapy alone seems rather high."[86]

In 2014, Lange et al. (2014)[85] published a systematic review of economic evaluations of monoclonal antibodies for CRC which included cetuximab.[85] The conclusion of the review was that the use of monoclonal antibodies (including cetuximab) was generally not cost-effective. The review also found that undertaking KRAS testing was cost-effective compared to not testing for KRAS if anti-EGFR agents were the treatment of choice. That is, if cetuximab is to be given, selecting which patients should receive it based on their KRAS status was cost-effective compared to not testing for KRAS status. Lange also reviewed the quality of the evaluations using the Quality of Health Economics Assessment and found that in general, the papers were of high quality.

In 2013, Frank and Mittendorf (2013)[122] published a systematic review of published economic evaluations of pharmacogenetic profiling in metastatic CRC. One of the tests considered was the KRAS test. The review suggested that there were three major sources of uncertainty in the published economic evaluations: biomarker costs, the performances of the biomarker tests and the limitations of the clinical data. The use of post hoc analysis was noted as a source of uncertainty in terms of the prognostic and predictive aspects of the KRAS mutation.

In 2010 the Ontario Health Medical Advisory Secretariat published a systematic review in which it noted that no economic evaluations were identified which compared the relative effectiveness of KRAS testing for anti-EGFR therapies.[3]

In 2007, a review of cost-effectiveness agents in CRC was published which included a section on cetuximab.[135] No formal economic evaluations were identified in the systematic review of cetuximab.

Also, in 2007, an HTA was published in the UK. [136] No economic evaluations of cetuximab were identified by the systematic review conducted as part of this HTA.

3.2.3 Methods

A systematic search was undertaken using Medline, EMBASE and EconLit. Articles were included if they reported the findings of research which evaluated both costs and health related outcomes within the framework of a comparative evaluation (including cost-minimisation if formally constructed as such). Relevant summary articles and included articles were hand searched for further additional evaluations. Additionally, the articles included in Section 3.1 were included if the economic evaluations included cetuximab. Articles were excluded if they reported costs only, but contained no formal cost-minimisation construction, were a letter or report without a description of methods, contained no comparisons to enable an ICER to be constructed (it was not necessary for the ICER to be constructed in the article) or were not in English.

A standardised electronic form was designed to enable data extraction for each evaluation. The data extracted included the testing method associated with the targeted therapy, sources of efficacy, adverse events, resource use and costs. Costs were adjusted to 2011 Australian dollars using PPP conversion at the base year to Australia and then inflated using the Australian Health Expenditure Index.[59,138] Cost-effectiveness ratios were recalculated using this information. The extraction was undertaken multiple times throughout the thesis period, with the latest extraction having occurred on the 23/02/2017.

The source of utility weights was recorded and, if possible, utility weights were traced back to their original source. The type of modelling used, the comparator and the method of extrapolation were extracted. The approach to post-progression costing, attribution and the use of other chemotherapy agents were also extracted for each alternative.

CHEERS[92] and Quality of Health Economic Studies (QHES)[139] checklists were completed for all articles. When there was overlap in the papers reviewed, the results were compared to published results reported by the systematic reviews.[85,86] Kappa statistics were used to measure the agreement between the results in this thesis and those published in Lange et al. (2014)[85] and Westwood et al. (2014).[86] Any differences between the results of the present study and previous reviews are discussed below.

3.2.4 Results

Twenty-two articles representing 21 unique economic evaluations were identified and data were extracted from them. The CONSORT diagram shows the breakdown of the record identification.

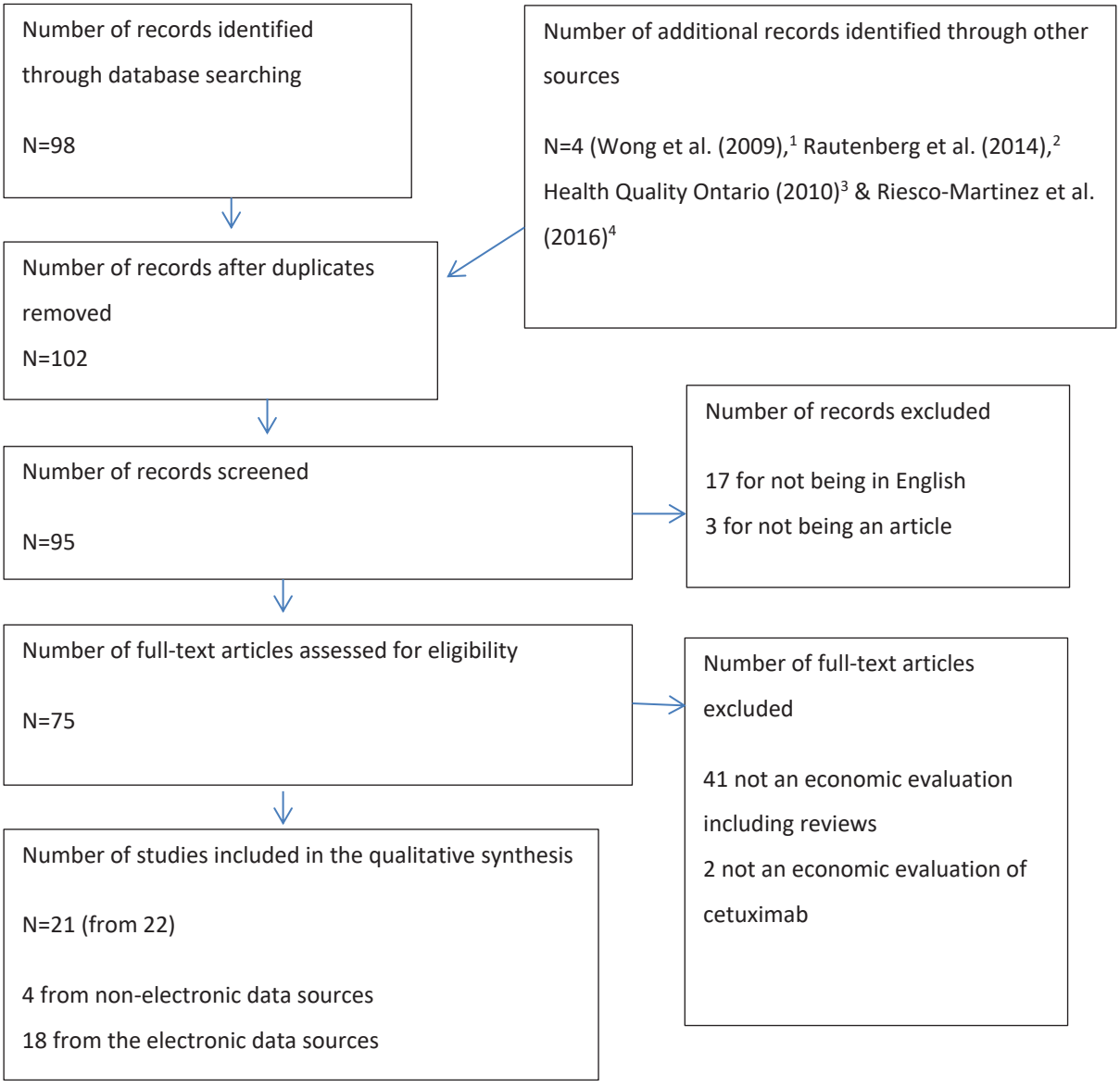


Figure 10: CONSORT diagram for the literature search of cetuximab economic evaluations

Four papers were included which were identified beyond the scope of the electronic searches: Wong et al.(2009)[1] and the Health Quality Ontario (2010)[3] were identified from a review of the reference lists of recovered studies. Rautenberg et al. (2014)[2] and Riesco-Martinez et al.(2016)[4] were identified in another literature search conducted within the thesis and a conference abstract was located in the EMBASE search and the later article was obtained.

Two articles authored by Hoyle and colleagues were recovered, one being a HTA[137] and the other an article in Value in Health.[41] They reported very similar results and used the same methodology so they have been considered one article for the purposes of data extraction.

The 21 evaluations were divided into three groups to aid comparison within a line of therapy. The groups were discussed individually before being compared to each other. Chronologically (in terms of publication date) the groups are:

- later line therapy- therapy after the failure of initial treatment for metastatic CRC;
- first line therapy- initial therapy for advanced or metastatic CRC; and
- treatment sequence- cetuximab was potentially considered in different lines of therapy within the same economic evaluation.

This information as well as the country in which the study was conducted and whether it was included in the previous systematic reviews is shown in the Table below. As can be seen none of the systematic reviews included all the identified papers. Therefore, the current analysis adds to the knowledge base on this issue. The detailed data extraction and the quality assessment are presented in Appendix C.

.

Table 19: Overview of included studies for the cetuximab economic evaluations

Publication	Year	Country	Place in therapy	Group	Conclusion	Included in Frank and Mittendorf (2013)[122]	Included in Hoyle et al. (2013)[137]	Included in Lange et al. (2014)[85]	Included in Westwood et al. (2014)[86]
Norum (2006)[140]	2006	Norway	Latter line therapy	Later line therapy	Cetuximab promising but very expensive	No	Yes	Yes	No
Annemans et al. (2007)[141]	2007	Belgium	Second line therapy	Later line therapy	Cost-effective	No	Yes	Yes	No
Starling et al. (2007)[142]	2007	UK	Second line therapy	Later line therapy	Cost-effectiveness ratio was relatively high	No	Yes	Yes	No
Tappenden et al. (2007)[136]	2007	UK	Latter line therapy	Later line therapy	Difficult to suggest if cetuximab represents value for money	No	Yes	No (included bevacizumab cost-effectiveness but not cetuximab cost-effectiveness)	No
Mittmann et al. (2009)[129]	2009	Canada	Last line therapy	Later line therapy	Cost-effectiveness ratio is high	Yes	Yes	Yes	No
Wong et al. (2009)[1]	2009	USA	Second and third line	Sequence	Most effective regimes still had very high ICERs	No	Yes	Yes	No
Health Quality Ontario (2010)[3]	2010	Canada	Third line treatment	Later line therapy	KRAS testing and cetuximab was considered cost-effective	No	No	Yes	Yes
Shiroiwa et al. (2010)[143]	2010	Japan	Last line therapy	Later line therapy	ICER of cetuximab treatment is too high	Yes	No	Yes	Yes
Asseburg et al. (2011)[144]	2011	Germany	First line therapy (downstaging)	First line Therapy	Cost-effective	No	No	Yes	No

Publication	Year	Country	Place in therapy	Group	Conclusion	Included in Frank and Mittendorf (2013)[122]	Included in Hoyle et al. (2013)[137]	Included in Lange et al. (2014)[85]	Included in Westwood et al. (2014)[86]
Blank et al. (2011)[145]	2011	Sweden	Last line therapy	Later line therapy	Cost-effective	Yes	No	Yes	Yes
Behl et al. (2012)[125]	2012	USA	Last line therapy	Sequence	Incremental cost-effectiveness remains above the generally accepted threshold	No	No	Yes	Yes
Fragoulakis et al. (2012)[146]	2012	Greece UK	Last line therapy	Later line therapy	Cost-minimisation - panitumumab less expensive that cetuximab	No	No	No	No
Vijayaraghaven et al. (2012)[147]	2012	USA Germany	Second line therapy	Later line therapy	KRAS mutation testing is dominant	Yes	No	Yes	Yes
Hoyle et al. (2013)[41,137]	2013	UK	Third line therapy	Later line therapy	Unlikely to be cost-effective	No	Yes	No	No
Lawrence et al. (2013)[148]	2013	Canada	First line therapy	First line Therapy	Cetuximab does not offer best value for money	No	No	No	No
Barone et al. (2014)[149]	2013	Italy	First line therapy	First line Therapy	KRAS testing is cost-effective prior to development of metastatic disease	No	No	No	No
Rautenberg et al. (2014)[2]	2014	Germany	All lines of therapy	Sequence	third line EGFR results in increased survival at a reasonable cost	No	No	No	No
Westwood et al. (2014)[86]	2014	UK	First line therapy	First line Therapy	Testing and treatment expensive	No	No	No	Yes
Graham et al. (2015)[150]	2015	USA	First line therapy	First line Therapy	Cost-minimisation-panitumumab is less expensive	No	No	No	No

Publication	Year	Country	Place in therapy	Group	Conclusion	Included in Frank and Mittendorf (2013)[122]	Included in Hoyle et al. (2013)[137]	Included in Lange et al. (2014)[85]	Included in Westwood et al. (2014)[86]
Wen et al. (2015)[151]	2015	China	First line therapy	First line Therapy	Choice of testing and pharmaceutical is important	No	No	No	No
Riesco-Martinez et al. (2016)[4]	2016	Canada	First line therapy or third line therapy	Sequence	The first line use of EGFR is not cost-effective at its current pricing relative to bevacizumab	No	No	No	No

Abbreviations: EGFR: Epidermal growth factor receptor; ICER: incremental cost-effective ratio; KRAS: Kirsten rat sarcoma; UK: United Kingdom

Two previous systematic reviews used checklists to rate the quality of their included studies. Lange et al. (2014)[85] used the QHES checklist and Westwood et al. (2014)[86] used the CHEERS checklist. For this literature review both checklists were used to measure quality to allow comparison to both Lange et al. (2014)[85] and Westwood et al. (2014)[86].

A comparison using the QHES checklist of the subset of studies included in the Lange review showed a 95% agreement with the assessment conducted for this thesis ($p<0.01$). The main difference was the issue of identification of subgroups. Lange et al. (2014)[85] appeared to interpret the use of KRAS subgroups as decided on prior to the study; in this thesis, the interpretation was made that these were post hoc constructions.

With regard to the use of the CHEERS guidelines there was 100% agreement ($p<0.01$) between the results presented in Westwood et al. (2014)[86] and the assessment conducted for this thesis.

Wong et al. (2009),[1] Rautenberg et al. (2014)[2] and Riesco-Martinez et al. (2016)[4] were also evaluated as part of the systematic review in Section 3.1.

The quality assessment of the papers that were not focused on KRAS testing is shown in Table 20. Barone et al. (2014)[149] was judged as low quality because information was missing several criteria.

Table 20 shows the comparison of the articles using the criteria in the CHEERS checklist. In common with the economic evaluations critiqued in Section 3.1, justification for the choice of model, explanation of the setting and the inclusion of heterogeneity were poorly undertaken in these economic evaluations as a group.

Table 20: CHEERS checklist for economic evaluations of cetuximab (not testing cost-effectiveness)

Category	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007[136]	Mittmann et al. (2009)[129]	Wong et al. (2009)[1]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Asseburg et al. (2011[144])	Blank et al. (2011)[145]	Behl et al. (2012)[125]	Fragoulakis et al. (2012)[146]	Vijayaraghaven et al. (2012)[147]	Hoyle et al. (2013)[137]	Lawrence et al. (2013)[148]	Barone et al. (2014)[149]	Rautenberg et al. (2014)[2]	Graham et al. (2015)[150]	Riesco-Martinez et al. (2016)[4]	Wen et al. (2015)[151]	Percentage
Title	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	95 %
Abstract	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100 %
Background and objectives	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100 %
Target population and subgroups	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	85 %
Setting and location	Yes	Yes	No	Yes	No	Yes	Yes	No	No	No	Yes	No	Partial	No	No	No	No	No	Partial	Yes	40 %
Study perspective	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	No	85 %
Comparators	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	95 %
Time horizon	No	No	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes	75 %
Discount rate	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	No	No	Yes	Yes	65 %

Choice of health outcome	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	94 %
Measurement of effectiveness	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	N/A	Yes	Yes	Yes	No	No	N/A	Yes	No	72 %
Measurement and valuation of preference based outcomes	No	No	Yes	Yes	Yes	N/A	Yes	Yes	N/A	Yes	No	N/A	N/A	Yes	Yes	No	N/A	N/A	Yes	No	64 %
Estimating resources and costs	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Partial	Yes	88 %
Currency, price date and conversion	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100 %
Choice of model	No	No	No	No	No	Partial	Partial	Partial	Partial	Partial	Partial	No	Partial	Yes	Partial	No	No	Partial	Partial	Partial	33 %
Assumptions	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	No	Partial	Yes	Partial	Yes	85 %
Analytic methods	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	No	No	Yes	Yes	Yes	83 %
Study parameters	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	No	Yes	Yes	No	No	80 %
Incremental costs and outcomes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	No	N/A	Yes	Yes	94 %
Characterising uncertainty	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes	88 %
Characterising heterogeneity	No	No	No	No	Yes	No	No	Yes	No	No	No	No	No	No	No	No	No	No	No	No	10 %
Study finding & limitations	Yes	Yes	Yes	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	97 %
Source of Funding	Yes	No	No	Yes	Yes	Yes	N/A	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	89 %
Conflicts of interest	No	No	Yes	No	No	Yes	N/A	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	68 %

Abbreviation: CHEERS: consolidated health economics reporting; N/A: not applicable

Initially, the trials and subsequent economic evaluations of cetuximab occurred in later lines of therapy. At that time, the exact population to benefit from the treatment (i.e. those patients with a wild type KRAS tumour) was not the population recruited to participate in the trials. The early trial participants were patients with EGFR expressing metastatic CRC tumours. However, over time, it became clear that only patients with wild type KRAS tumour would benefit from treatment. Consequently, the population of interest in the economic evaluations changed between economic evaluations (Table 21).

Most, but not all, economic evaluations included an alternative without anti-EGFR treatments. Economic evaluations were less likely to include an alternative without anti-EGFR if KRAS testing was not the purpose of the evaluation. Only one economic evaluation (Annemans et al. [2007][141]) included additional chemotherapy treatment in all alternatives although in different amounts. Starling et al. (2007)[142] and Tappenden et al. (2007)[136] included chemotherapy in the alternative arm only. All the evaluations measured overall survival as the health outcome, with some weighting by a preference measure (i.e. QALYs).

Table 21: Alternatives and use of other treatments in later line cetuximab economic evaluations

Study	Testing as main evaluation	Alternative with cetuximab	Other alternatives	Other treatments in cetuximab alternative	Other treatments in other alternatives
Norum (2006)[140]	No	Cetuximab and irinotecan for EGFR positive patients	No treatment for EFGR positive patients	No	No
Annemans et al. (2007)[141]	No	Cetuximab and irinotecan for EGFR positive patients	Current care for EGFR positive patients	Yes	Yes
Starling et al. (2007)[142]	No	Cetuximab and irinotecan for EGFR positive patients	Current care for EGFR positive patients	No	Yes
Tappenden et al. (2007)[136]	No	Cetuximab and irinotecan for EGFR positive patients	Current care for EGFR positive patients	No	Yes
Health Quality Ontario (2010)[3]	Yes	Cetuximab Cetuximab and irinotecan	Best supportive care (without testing) Panitumumab	No	N/A

Study	Testing as main evaluation	Alternative with cetuximab	Other alternatives	Other treatments in cetuximab alternative	Other treatments in other alternatives
Mittmann et al. (2009)[129]	No	Cetuximab for KRAS wild type patients	Best supportive care for KRAS wild type patients	No	No
Shiroiwa et al. (2010)[143]	Yes	Cetuximab for all, cetuximab for KRAS wild type only	No cetuximab	No	No
Fragoulakis et al. (2012)[146]	No	Cetuximab for KRAS wild type cancers	Panitumumab for KRAS wild type cancers	No	No
Vijayaraghaven et al. (2012)[147]	Yes	Cetuximab Cetuximab and irinotecan	Panitumumab	No	No
Hoyle et al. (2013)[137]	No	Cetuximab for KRAS wild type cancers Cetuximab and irinotecan for KRAS wild type cancers	Panitumumab for KRAS wild type cancers Best supportive care	No	No

Abbreviations: EGFR: epithelial growth factor receptor; KRAS: Kristen rat sarcoma

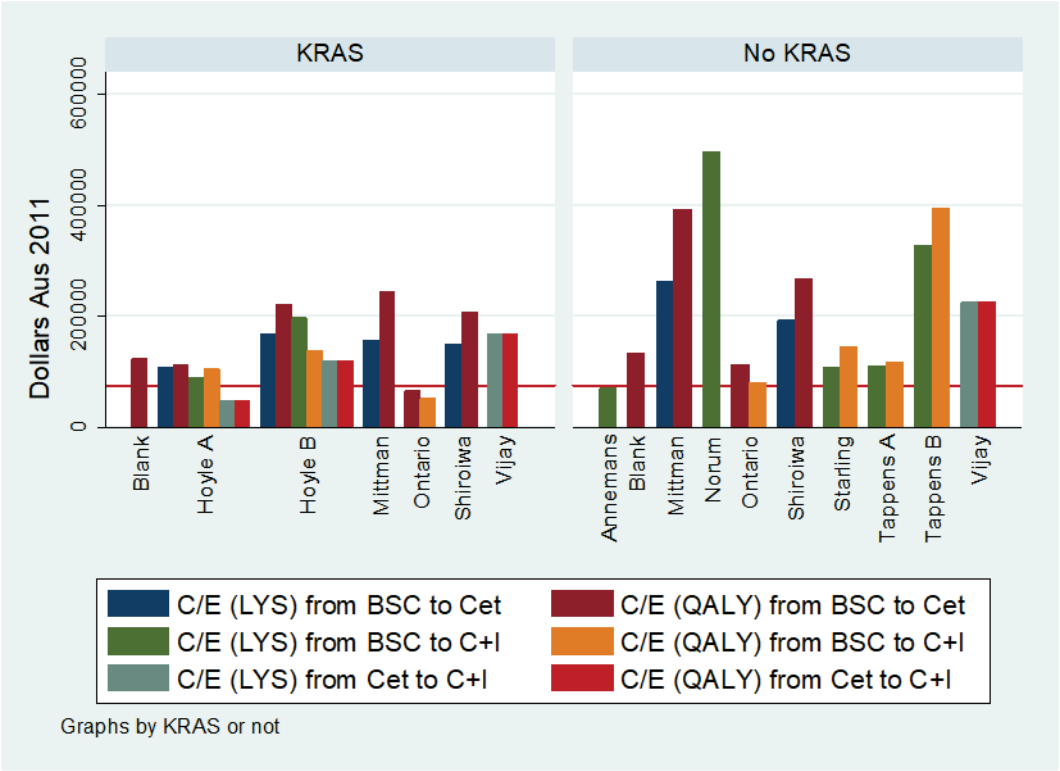
Figure 11 shows the incremental cost-effectiveness results for cetuximab used in a later line of therapy as estimated in the economic evaluations. It illustrates the wide variation of the finding in relation to the cost-effectiveness of cetuximab use. The incremental cost-effectiveness ratio has been shown as both per life year saved and per QALY gained. There are three different increments possible:

- the increment from BSC to the sole use of cetuximab;
- from increment from BSC to the combined use of cetuximab and irinotecan; and
- the increment between cetuximab, and cetuximab plus irinotecan.

The graph has also been divided into whether KRAS testing was included (left hand side of the graph) or not (right hand side of the graph). The highest cost-effectiveness ratios were associated with a lack of KRAS testing.

A line has been added at the level of $75 000 per unit of benefit to aid comparison with the upper level of incremental cost-effectiveness estimated by PBS in the case of cetuximab. The

weighted ICER in the accepted PBAC submission was between AUD (2010) $45 000 and $75 000 per QALY.[152]



Abbreviations: BSC: best supportive care; C/E: cost-effectiveness; Cet: cetuximab; C+I: cetuximab and irinotecan; EGFR: epithelial growth factor receptor; KRAS: Kristen rat sarcoma; LYS: life year saved; QALY: quality adjusted life years

Figure 11: Incremental cost-effectiveness ratio for cetuximab under different strategies (later line)

Three economic evaluations concluded that treatment with cetuximab in the later lines of therapy was cost-effective.

1. Annemans et al. (2007)[141] had a cost-effectiveness ratio of approximately AUD (2011) $70 000 per life year gained in an unselected population.
2. The Ontario HTA[3] estimated a cost-effectiveness ratio of approximately AUD (2011) $50 000 per QALY gained in a population that was tested for KRAS mutation.
3. Blank et al. (2011)[145] suggested that a cost-effectiveness ratio of AUD (2011) $123 000 per QALY was relatively cost-effective. “KRAS/BRAF testing was the most cost-effective approach when compared with the reference strategy (incremental cost-effectiveness ratio: €62 653/QALY).”[145]

Despite the similarity in findings, the key drivers of the relatively low cost-effectiveness ratio varied between these evaluations. The results reported by Annemans et al. (2007)[141] were driven by a relatively small incremental increase in costs between the use of BSC and that of cetuximab. Half of the cost associated with BSC was incurred by the use of subsequent chemotherapy. If additional chemotherapy was removed from all arms in the economic evaluation, the ICER would increase to approximately AUD (2011) $100 000 per life year gained.

Starling et al. (2007)[142] and Tappenden et al. (2007)[136] also had relatively low incremental cost-effectiveness ratios. Both studies included chemotherapy costs in the BSC alternative but not in the cetuximab alternative. Therefore, these studies did not include displacement in the cetuximab alternative.

In the Ontario HTA,[3] the cetuximab group who were tested for KRAS status had a similar QALY gain to other papers but at a lower cost. This result is influenced by several factors, notably that the costs for both BSC and cetuximab were low compared to that reported in other economic evaluations. This was partly driven by the non-inclusion of ongoing costs associated with survival, in contrast to other economic evaluations which attributed an ongoing cost to the post-progression survival. As differences in survival do not incur differences in costs, the incremental increase in costs was lower than might otherwise occur.

The study by Blank et al. (2011)[145] showed an incremental cost-effectiveness ratio similar to other papers that concluded that the use of cetuximab was not cost-effective. The key difference, however, appeared to be the acceptable cost-effectiveness ratio for investment in new health technologies (i.e. a higher cost-effectiveness threshold).

Cetuximab has been used more recently in the initial (or first) line of therapy for metastatic CRC. Its use in the first line is somewhat different to that in subsequent lines. For example, cetuximab is always used with chemotherapy in the initial line of therapy, and therefore the number of alternative treatments is reduced, potentially simplifying the economic evaluation. One potential complication, however, is that in some patients the treatment of advanced cancer in the first line of therapy does not always mirror that of other lines of therapy. Sometimes advanced CRCs are treated with the aim of downgrading (shrinking) liver metastasis so that they become operable which in turn results in superior survival. This potential survival advantage is a dominant feature of some of the economic evaluations of cetuximab use in first line therapy.[144]

Given the small number of economic evaluations of cetuximab as first line of therapy, it is difficult to draw any general conclusions. Additional chemotherapy costs were included in half of the economic evaluations. They tended to be the same in all arms so that the incremental impact was limited. One exception was Wen et al. (2015)[151] which included distinctly different treatments in the second line of therapy for the two alternatives. An assumption was made that the length of treatment in the second line of therapy was equal to the post-progression period. This may have overestimated the costs in second line of therapy, when multiple therapies may be given.

Most economic evaluations did not include an option without antibody therapy, either panitumumab or bevacizumab.

Given that most of the comparisons did not involve the addition of another line of therapy (as compared to the latter lines of therapy) it is possible that the post-progression chemotherapy costs may not represent a displacement scenario. Alternatively, it may be because displacement was not considered.

Table 22: Alternatives and use of other treatments in initial line cetuximab economic evaluations

Study	Testing as main evaluation	Alternative with cetuximab	Other alternatives	Other treatments in cetuximab alternative	Other treatments in other alternatives
Asseburg et al. (2011)[144]	No	Cetuximab plus chemotherapy	Bevacizumab plus chemotherapy	Yes	Yes
Lawrence et al. (2013)[148]	No	Cetuximab plus chemotherapy	Panitumumab plus chemotherapy Bevacizumab plus chemotherapy	No	No
Barone et al. (2014)[149]	Yes	Different testing regimes	Bevacizumab Chemotherapy	No	No
Westwood et al. (2014)[86]	Yes	Cetuximab and chemotherapy	Chemotherapy	Yes	Yes
Graham et al. (2015)[150]	No	Cetuximab and chemotherapy	Panitumumab and chemotherapy	No	No
Wen et al. (2015)[151]	No	Cetuximab and chemotherapy	Bevacizumab and chemotherapy	Yes- different costs	Yes

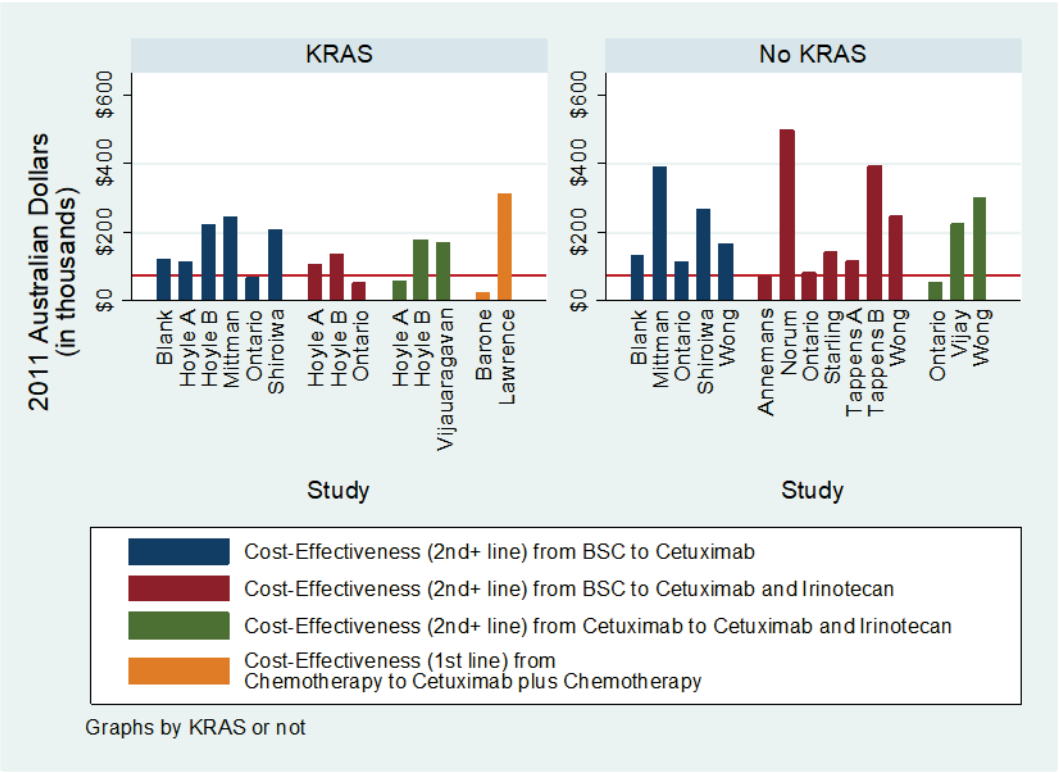
The last category of economic evaluations involved studies of treatment sequences, for which four studies were identified.[1,2,4,125] Within these studies, it is possible to compare the effectiveness and cost-effectiveness of using cetuximab in different lines of therapy. However, in these four economic evaluations, only Rautenberg et al. (2014)[2] and Riesco-Martinez et al. (2016)[4] directly modelled the use of cetuximab in alternative lines of therapy. Only Rautenberg et al. (2014)[2] modelled the same protocol for cetuximab in different lines of therapy. This is discussed in Section 3.1.9.

There are several structural weaknesses in the models used to evaluate the entire treatment sequence. Rautenberg et al. (2014)[2] used median PFS to reflect average survival and treatment and the selection of studies was not consistent with regard to the KRAS status of the population.

Both Wong et al. (2009)[1] and Rautenberg et al. (2014)[2] used a model where all therapies within a treatment schedule were given to all patients; the evidence presented in Chapter 4 of this thesis suggests that this assumption is questionable. Riesco-Martinez et al. (2016)[4] modelled that a decreasing proportion of patients would receive treatments in a later line of therapy. This is consistent with the information presented in Chapter 4.

Wong et al. (2009)[1] and Rautenberg et al. (2014)[2] also did not adjust the different arms of studies that they drew information from to reflect a standard population. Moreover, neither of these studies conducted a meta-analysis of available treatments to estimate an average treatment effect. The use of results from a single study led to a modelling approach that found treatment with cetuximab was superior in a later line of therapy. For example, Rautenberg et al. (2014)[2] found that panitumumab was twice as effective for use in the third line of therapy compared to the second line of therapy.

The variation in the cost-effectiveness ratios within each line of therapy makes comparisons between the lines of therapy difficult. Figure 12 below compares the cost-effectiveness of cetuximab in later lines of therapy to that in the first line of therapy. While it appears that KRAS testing results in a decrease in incremental cost-effectiveness ratios compared to not using KRAS testing, it is difficult to claim there is a difference in the ICER when considering the use of cetuximab in the first line of therapy compared to latter lines of therapy.



Abbreviations: Aus: Australian; BSC: best supportive care; C/E: cost-effectiveness; Cet: cetuximab; Cet+I: cetuximab and irinotecan; KRAS: Kristen rat sarcoma; LYS: life year saved; QALY: quality adjusted life years

Figure 12: Incremental cost-effectiveness of cetuximab with and without KRAS monitoring

3.2.5 Conclusions

The current literature does not allow the assessment of the relative economic benefit of moving cetuximab through lines of therapy.

The limited clinical information and the retrospective or indirect nature of the assessment of benefit resulted in the identified economic evaluations considering multiple alternatives including cetuximab. This variation meant the economic evaluations produced a wide range of incremental cost-effectiveness ratios, despite these evaluations having been based on a small number of trials. In these evaluations, the benefit was modelled using data from more than one RCT because of the lack of prospective trials investigating the intervention of interest, that is, KRAS testing followed by use of an anti-EGFR therapy. This meant that several assumptions were made, which varied between economic evaluations.

These assumptions make it very difficult to assess the relative benefit of cetuximab in the later lines of therapy compared to the earlier lines of therapy. As emphasised previously, more than 90% of the economic evaluations did not consider that the use of cetuximab in a line of therapy was, potentially, at the opportunity cost of using it in another line of therapy.

The results of the two evaluations that did compare the cost-effectiveness of cetuximab between lines of therapy need to be treated with caution. The results within each line of therapy were variable, and a comparison between the different lines of therapy did not reveal any difference in incremental cost-effectiveness. One of these economic evaluations, Rautenberg et al. (2014)[2], had significant weaknesses - only medians were compared and single lines of therapy were taken from trials with different inclusion criteria. A mixture of selected and unselected populations was used with regard to EGFR status. In the other economic evaluation, Riesco-Martinez et al. (2016),[4] modelling showed that the use of cetuximab was less effective (in terms of progression free survival) in a latter line of therapy compared to an earlier line of therapy. However, this conclusion was based on a comparison of different protocols, each containing cetuximab, in the different lines of therapy.

There was an evolution over time in the methods used for modelling and extrapolation among the economic evaluations of cetuximab. The initial economic evaluations used direct calculation, first naively (without adjustment) and then with adjustment for drop-out. The lack of comparability between alternatives reduces the internal validity of these evaluations as does the use of retrospective analysis.

The external validity of an RCT testing an active treatment against placebo may be questioned if the existence of a no treatment arm is not standard practice. In the context of cetuximab there is evidence from both the economic evaluations and previous studies that a significant number of patients received chemotherapy.[72,97] Ideally, then, as part of any RCT, information would have been collected after progression about the use of other therapies and their length of use. In the RCTs that were the basis for the economic evaluations, little is known about the length of treatment with other therapies received by the trial patients received. There is evidence that patients in arms of these RCTs who did not initially receive cetuximab subsequently were treated – that is there was crossover between the arms of the trials.[120]

With regard to treatment sequences, the selection of the alternatives is of great importance. As seen in Section 3.1, only choosing alternatives that include cetuximab does not allow the calculation of the incremental cost-effectiveness of including these expensive agents in a treatment sequence. Ideally, a “no anti-EGFR therapy” treatment should have been included in the selection of alternatives.

The evaluations took a similar approach to the inclusion of post-progression benefits. All included the post-progression benefit of survival as part of the assessment of benefit (unless

constructed as a cost-minimisation economic evaluations). Although most evaluations combined information from two or more RCTs, the outcome used in all the economic evaluations was overall survival (or QALYs based on overall survival). However, a variety of approaches were used in the costing of the use of other chemotherapy agents: they were excluded from both arms, included in only the non-cetuximab arms or included in both arms. This heterogenous approach to the costs of additional chemotherapy was the source of some of the variation in the results of different economic evaluations.

Medians, rather than means, were used as the measure of benefit in a minority of economic evaluations.[2,140] Effectiveness was most commonly estimated using the results of a solitary trial. Meta-analysis was not conducted in the majority of the economic evaluations. Estimations of the pharmaceutical used and therefore costed where based on mean[150] and median progression free survivals.[2] As discussed in Section 3.1, this assumes that the benefit and treatment length are the same.

Despite all studies considering the same pharmaceutical, its use varied over time, initially from use in an unselected population to restricted use for patients with KRAS wild type tumours. The use of post hoc analysis was not restricted to consideration of the genetic material associated with the tumour, decision rules were also used in the economic evaluation to produce a greater number of alternatives. The potential to use cetuximab in combination with chemotherapy also increased the number of alternatives.

The inclusion or exclusion of chemotherapy costs varied markedly between the evaluations and thus was a driver of the results. Any potential benefit from additional chemotherapy was implicitly included on the health side in terms of overall survival, but the incremental cost of chemotherapy could be the same in both arms and therefore not counted from an incremental perspective. This was assumed and could be tested empirically, but this was not always done. The two papers that measured chemotherapy use in both arms found them to be different. However, the results of the economic evaluation of cetuximab in a later line are based on a comparison between an RCT arm and an observational study. Although the authors argued[141] that patients in both studies were matched on age, gender and receipt of previous chemotherapy, an important systematic difference existed between the RCT and the observational study in relation to the use of specific protocols and interventions. This systematic difference may have impacted on the external validity of the results. The economic evaluation of the use of cetuximab in the initial line of therapy assumed that the treatments given after progression in first line continued for the remainder of the patients' survival.[151]

Some economic evaluations included additional chemotherapy in one alternative (the non-cetuximab one) but not the other. Some included additional treatments in both alternatives.

This review demonstrated that there was innovation in the use of cetuximab. A wide range of alternatives included cetuximab. These alternatives included combining its use with genetic testing for predictive and prognostic aspects, using it in combination with other anticancer agents or alone within a line of therapy, in different lines of therapy and with different stopping algorithms. Over the period in which the evaluations were published, most of these alternatives also changed; for example, the genetic testing initially only included testing for KRAS status but subsequently included a wider range of mutations.

When evaluating the use of cetuximab in the first line of treatment, its use in a later line of treatment is a potential option that is foregone by using in the initial line of therapy. There may be alterations in later line treatments with some salvage treatments moving forward a line of therapy. This was not considered in the economic evaluations of the first line of therapy. Only two economic evaluations explicitly modelled cetuximab in different lines of therapy (Rautenberg et al. [2014][2] and Riesco-Martinez et al. [2016][4]), over 90% did not. This confirms, for cetuximab, the majority of the economic evaluations conduct an analysis within a line of therapy.

When it was first introduced into practice in later lines of therapy, cetuximab could have displaced the existing therapies (see Section 2.2.1 and Table 2). Some economic evaluations accounted for the cost of chemotherapy in the non-cetuximab arms but not in the cetuximab arm. The issue of the same chemotherapy protocols being used post cetuximab was not discussed in the economic evaluations. The evidence provided in Chapter 6 suggests that the chemotherapy protocols would not be used for the same length of time if they were displaced. This is consistent with different amounts of chemotherapy (and different costs) being used in each of the arms as occurred in Annemans et al. (2007).[141]

From a theoretical perspective, if the use of non-cetuximab chemotherapy differs between the alternatives and the outcome is overall survival, then it should ideally be included in an economic evaluation. If excluded, the incremental cost-effectiveness ratio will be incorrect and inappropriate decisions may be taken, either adopting a cost-ineffective technology or rejecting a cost-effective one.

If additional chemotherapy use does not differ between the alternatives, then it could be excluded from an incremental analysis because the incremental cost will not be affected. The

timing of the additional chemotherapy should be of interest in this scenario. It is likely that the additional chemotherapy would be received later in the cetuximab alternative and therefore should be potentially discounted relative to a no cetuximab alternative.

The importance of the post-treatment period and the assumption of the allocation of benefit is explored in the modelling of the cost-effectiveness of displaced treatments in Chapter 7. Heterogeneity in the combination of treatments and the proportion of the potential population who receive the treatments are also modelled in Chapter 7.

Chapter 4 Estimating the number of lines of therapy

The motivation for this Chapter is to confirm whether administrative data could be used to accurately estimate the number of lines of therapy in Australia. This information is required to determine the costs and outcomes associated with each line of therapy (the assessment of costs and outcomes is undertaken in Chapter 5) and to assess the potential for displacement in Australia (Chapter 6).

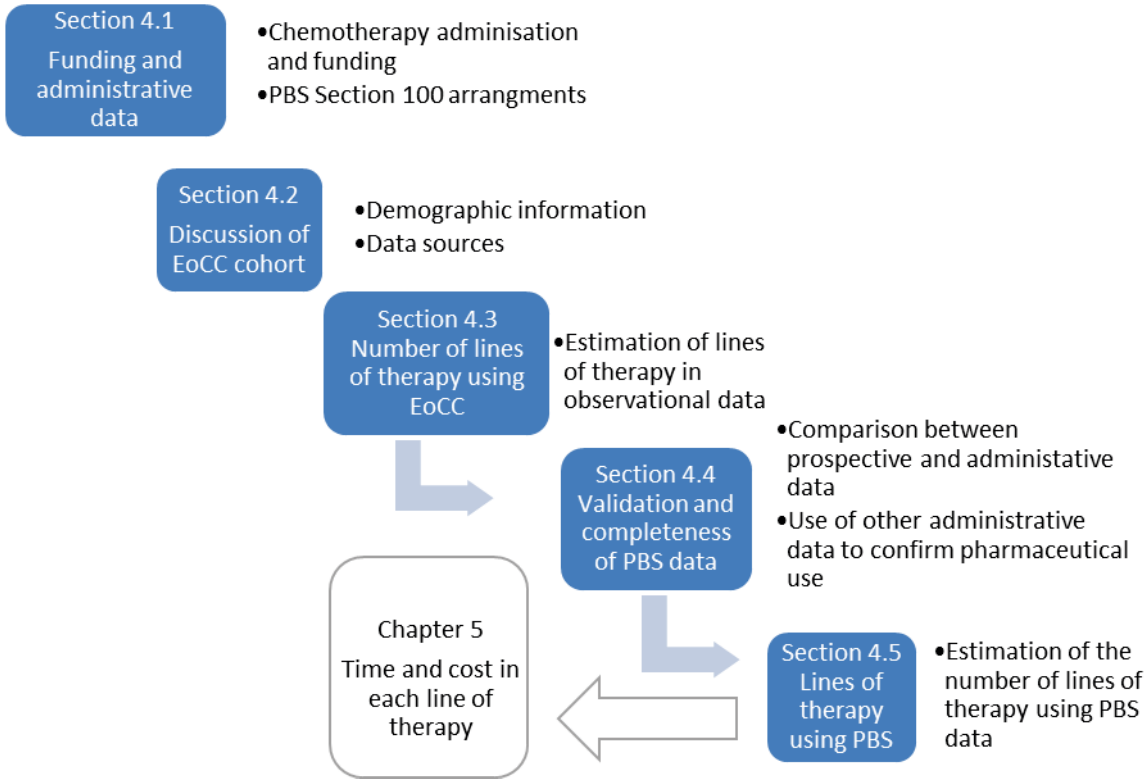
If the administrative data could provide a method to assess the impact of displacement of treatments, it would aid future comparisons of the effectiveness and cost of latter line treatments without significant additional resources for data collection. Conversely, it would be beneficial to understand if and why this cannot be undertaken (without substantial bias) using the currently available administrative data. This information would elucidate the potential biases of such research and identify the potential requirement for additional data collections.

As discussed in Chapter 2 and demonstrated in Chapter 3 the generalisability of trial based economic evaluation is subject to limitations in the context of multiple lines of therapy.[153] Non-randomised studies using secondary databases and prospective observational studies are used to supplement the evidence from randomised trials[154] or compare the results of RCTs to the introduction of treatments in practice.[155]

Available administrative data relates to the funding and management of cancer treatments, specifically chemotherapy. Administrative data, such as billing and reimbursement data, can be used to estimate the treatments received in cancer.[156] It can also be used to generate information about the costs of treatment and the cost drivers.[157] Comparative cost-effectiveness analysis can also be conducted using registry and administrative data.[158] One of the major risks to using observational studies or administrative data for cost-effectiveness is missing data.[158]

This Chapter aims to:

1. establish the validity of administrative data in estimating the number of lines of therapy; and
2. estimate the number of lines of therapy received by the Elements of Cancer Care (EoCC) cohort using administrative data and observation.



Note: Filled boxes are contained in this Chapter, unfilled boxes from other Chapters
Abbreviations: EoCC: Elements of Cancer Care; PBS: Pharmaceutical Benefits Scheme

Figure 13: Scheme of Chapter 4

The research reported in this Chapter and Chapter 5 was undertaken using data provided by the Economic Models of Cancer Protocols research program (EM-CaP).

EM-CaP was a program of work undertaken under the auspices of an NHMRC health services research grant.[vii] One component of this research was a prospective cohort study of New South Wales cancer patients 18 years of age and over, called the EoCC project. The project involved the recruitment of 482 patients undergoing intravenous chemotherapy for breast, colorectal and non-small cell lung cancer at 12 sites within New South Wales.[63] The study was approved by the Human Research Ethics Committee (University of New South Wales, approval number 07014).[63] Research based on the EoCC project, including estimation of the average treatment cost per month for patients and the incidence of adverse events in the EoCC cohort, has been previously published.[63,64]

The flow of the Chapter and the Sections are shown in Figure 13. Section 4.1 outlined the funding of chemotherapy pharmaceuticals in Australia. Section 4.2 described the EoCC cohort

[vii] http://www.uts.edu.au/research-and-teaching/our-research/health-economics-research-and-evaluation-p2/our-research/resear-6

and the associated data. Section 4.3 estimated the number of lines of therapy using the prospective observational data. Section 4.4 compared the administrative data to the prospective observational data and assessed the completeness of the administrative data. Section 4.5 developed an algorithm from the administrative data and used it to estimate the number of lines of therapy in the Pharmaceutical Benefits Scheme (PBS) data.

4.1 Chemotherapy funding and administrative data

The administration and funding of chemotherapy treatment in Australia generates administrative data. These data can be used to study, among other things, real-world use and clinician and patient practices[159] and oncology prescribing.[160] The data have also been used to investigate the relationship between pharmaceutical use and outcomes,[161] and to investigate costs and cost drivers.[63,162]

Guidelines have been produced for the use of real-world data in producing evidence about the comparative cost-effectiveness of treatments[163] and specifically when using secondary or administrative data sources.[154] The guidelines require a clear research question and a selection of data sources. A key source of administrative data is the funding of chemotherapy.

4.1.1 Chemotherapy funding in Australia

The funding of chemotherapy in Australia is complex. There are several ways in which individuals access medical care and the method of access influences who is responsible for funding care.[164] The administrative data included in the PBS records covers the provision of benefits or funding for the consumption of pharmaceutical products on the PBS schedules. Over time the chemotherapy use funded by the PBS has changed. Chemotherapy funded outside of the PBS also differs between Australian jurisdictions. These differences exist currently and were also an issue at the time of the EoCC data collection.

Over time, the PBS has occupied an increasingly central role in the provision of chemotherapy. The results of the oncologist's review of protocols discussed in this Chapter make possible a comparison of the completeness of the PBS administrative data for chemotherapy administered between 2006-2011 for the EoCC cohort.

Chemotherapy pharmaceuticals administered to patients who are public hospital patients have traditionally been the responsibility of the jurisdiction (State or Territory) in which the hospital is located. Patients who receive chemotherapy outside of public hospitals are potentially eligible to have their chemotherapy subsidised by the PBS. Eligibility for subsidisation occurs if the indication and pharmaceutical are listed on the PBS.

There has been an incentive for public hospitals (or the State and Territory jurisdictions) to shift costs onto the Australian Federal Government by treating patients as non-admitted private patients in public hospitals. Over the past 25 years, a series of reforms mitigated the incentives for cost shifting. In 1998, the Australian Federal Government proposed a package of measures that allowed public hospitals to prescribe and dispense PBS medications, and specifically intravenous chemotherapy.

These measures have evolved since their introduction and involve the use of both the general PBS schedule and section 100 (s100) programs (which covers highly specialised medicines). Trastuzumab for early stage breast cancer is funded through the PBS and information about its provision is present in the PBS administrative data. Until recently, however, trastuzumab for metastatic cancer was not available on the PBS, because it had not been recommended by the Pharmaceutical Benefits Advisory Committee for listing.[165] Instead, a separate program operated outside the PBS, called the Herceptin Program.[165] The Herceptin Program was implemented as a special authority program under the subsection 100(1) arrangements of the 1953 National Health Act.[166] This particular section 100 program was administered independently of the PBS by the Australian Department of Human Services.[167] The lack of information regarding the use of trastuzumab for metastatic treatment of breast cancer in linked datasets involving the PBS administrative data has been noted previously.[63,162]

There are other aspects of the listing of pharmaceuticals on the PBS and the funding arrangements that create challenges for the use of administrative data. In particular, the section 100 programs (other than the Herceptin Program) that are part of the PBS have different funding and administrative arrangements than the general schedule (section 85) medicines.[167,168]

These other section 100 programs currently include the Highly Specialist Drugs Program and the Efficient Funding of Chemotherapy Program (among others). Both programs contain listings for pharmaceuticals that are used in cancer treatment. The Highly Specialist Drugs Program includes supportive cancer treatments such as bisphosphonates for treatment of bone metastasis.[168] The Efficient Funding of Chemotherapy Program includes both intravenous chemotherapeutic agents and supportive agents such as antiemetics. The Efficient Funding of Chemotherapy Program contains some of the currently subsidised chemotherapy pharmaceuticals used in the EoCC.

The arrangements associated with the current Efficient Funding of Chemotherapy Program commenced on the 1/12/2011.[169] The characteristics of the earlier arrangements for chemotherapy administration were also reviewed in this thesis because the timeframes associated with the EoCC dataset preceded this date. The predecessors of the Efficient Funding of Chemotherapy Program were the Chemotherapy Pharmaceutical Access Program (CPAP) and the PBS.[167]

The original CPAP ceased on the 1/04/2012.[167] The original CPAP program arrangement "facilitates the supply of chemotherapy pharmaceutical benefits at certain public hospitals to non-admitted patients, day patients and patients on discharge."[170] The CPAP was introduced sequentially in several Australian jurisdictions, beginning in Victoria.[170] Chemotherapy pharmaceuticals that were available to be subsidised by the PBS for patients receiving treatment outside the public hospital setting were also made available for subsidisation in public hospitals provided a series of other arrangements were adhered to. These other arrangements are sometimes collectively referred to as the pharmaceutical reforms. The schedules authorised under the CPAP contained both chemotherapy agents and supportive treatments. As only intravenous pharmaceuticals (or other infusions) require administration in a chemotherapy suite, only those agents were included in the CPAP. Oral chemotherapy agents, such as capecitabine that could be administered outside specialised facilities, were excluded from the CPAP.

Some changes designed to reduce the administrative burden for accessing the CPAP program were introduced in late 2009.[170] Rather than gaining permission via a telephone call for the use of chemotherapy agents, a number was recorded in the patient's notes to indicate the medication was prescribed in accordance with the restrictions in the schedule. At this stage, the section 100 CPAP supplement was added to the Pharmaceutical Benefits Schedule which was published in November 2009. The administrative codes recorded with the use of CPAP were also changed to be more consistent with the PBS codes in the general schedule by having a similar structure. Patients who received chemotherapy funded by the Australian Federal Government in a private setting continued to use the Pharmaceutical Benefits Section 85 Schedule.[170]

New South Wales (and the ACT) did not enter the CPAP, or at the time of writing, the successor to the CPAP, the Efficient Funding of Chemotherapy Program.[171] Treatment in New South Wales for an intravenous anticancer pharmaceutical that is available on the PBS involves the use of one of two alternative mechanisms of funding. For public inpatients, the funding

responsibility falls on the State hospital. For private patients funding is subsidised by the PBS. As New South Wales public facilities have mostly privatised their outpatient chemotherapy treatment arrangements, most patients receive treatment as private patients. The New South Wales privatisation provision is described in the review of funding arrangements for chemotherapy services as "alternative arrangements" whereby public hospitals classified the patients as privately referred non-inpatients and accessed the PBS to fund their chemotherapy treatments. This report also noted that New South Wales and ACT public hospitals are not eligible to receive chemotherapy medicines under the PBS.[164] These were the arrangements in place during the initial six-year long collection of PBS administrative data in the EoCC dataset.

Consequently, treatment received as a (non-day stay) inpatient in a public New South Wales hospital would not be observed in the PBS administrative data. An example would be chemotherapy treatment commenced after cancer was diagnosed as part of an emergency admission and before the patient was discharged if s/he was admitted for multiple days. Another example would be an admission, over several days, as a preventative measure for managing adverse events associated with chemotherapy.

4.1.2 Complexities associated with prescribing and remuneration in the PBS

Previous reports have highlighted the high level of complexity associated with the prescribing and use of chemotherapy, and the presence of many different models for the provision of chemotherapy.[164] One of the complexities is that, for the purposes of PBS remuneration, the chemotherapy script is dispensed and claimed by the pharmacy not by the entity administering the infusion or treatment.[164] These facilities may or may not be physically co-located. This complexity is one reason it is important to confirm if the PBS administrative data is a complete record of cancer treatment/chemotherapy use in Australia.

Another complexity relates to the previous instance where pharmaceuticals dispensed were not recorded. The level of benefit or subsidy offered to patients depends on their beneficiary status. Concessional status exists for those individuals who are receive Government entitlements or Indigenous Australians at risk of chronic illness.[172] There is a PBS safety net that is available for those who have spent over a threshold amount on pharmaceuticals over the period of a year. A co-payment may be required depending on the combination of beneficiary status and whether the PBS safety net has been reached. If the price of a pharmaceutical is less than the co-payment the patient would pay the entire amount. Prior to April 2012 the dispensing records for pharmaceuticals under the co-payment were not recorded.[172]

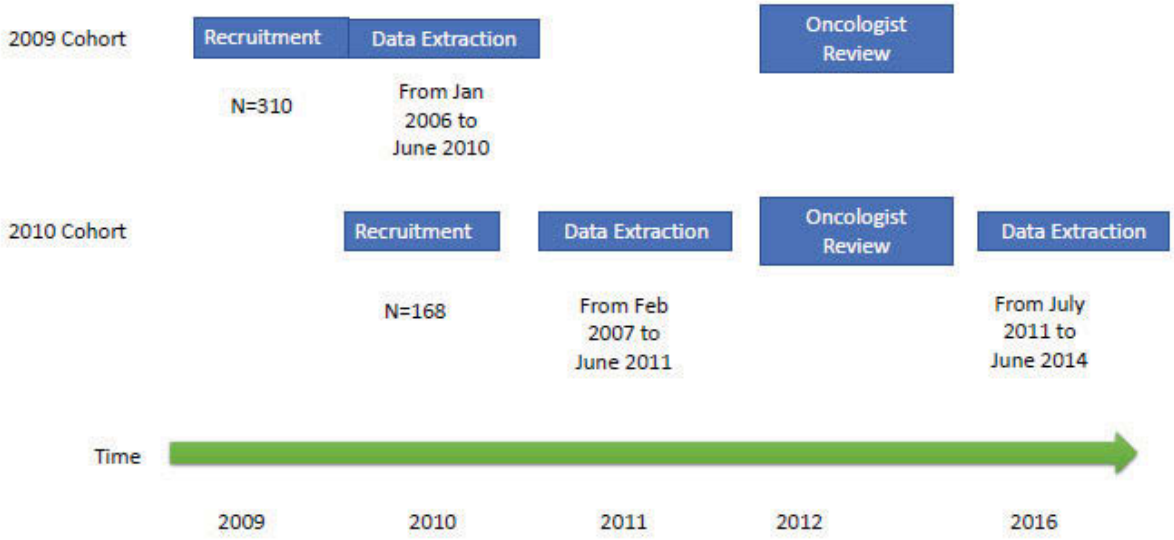
4.2 The Elements of Cancer Care (EoCC) cohort

The EoCC data base was developed using a number of methods. The primary EoCC data collection consisted of a review of the clinical notes and monthly interviews. Consenting participants were interviewed monthly about adverse events, changes in treatment and resource use. The monthly interviews were undertaken until the cessation of chemotherapy and then a further interview was undertaken three months later. Consent was obtained from participants for the primary data from the patient interviews and clinical notes to be linked to several secondary data sources. These sources included the PBS, Medical Benefits Schedule (MBS), and via the Centre for Health Record Linkage (CHeReL), the New South Wales Central Cancer Registry, the NSW Admitted Patient Data Collection, the NSW Emergency Department Data and the NSW Registry of Births, Deaths and Marriages. Two cohorts were recruited, one in 2009 (310 participants) and one in 2010 (168 participants). The consent was designed so that participants could agree to all or some of the data collections.

There were minor differences in the questions asked and the form of the responses between the years. Data collected by field staff were cleaned by the investigators and statisticians. Data inconsistencies were resolved by face to face meetings.[63]

In the initial interview, questions were asked about previous chemotherapy treatments and details of these were extracted from the clinical notes. One extraction of PBS and MBS data was undertaken for each of the cohorts in 2010 and 2011 respectively prior to the review by the investigators and oncologist. A second extraction of hospital, emergency department, PBS and MBS data was undertaken in 2016, updating the 2010 cohort to 30 June 2014. The second extraction for the 2010 cohort occurred after the oncologist's review and data cleaning.

The relationship and cohorts of the data extractions is shown in Figure 14.



Abbreviation: EoCC: Elements of Cancer Care

Figure 14: Data extractions from the EoCC cohort

De-identified data were provided in the form of Stata files which were manipulated using Stata version 15.[173]

The demographic and baseline characteristics of the EoCC participants are shown in Table 23 below. In total there were 258 patients with breast cancer, 157 patients with colorectal cancer and 63 with patients with NSCLC.

It should be noted, the EoCC data collection is not representative of the Australian cancer population. Compared with the gender distribution of cancer diagnoses in the Australian population, there is an imbalance between the numbers of male and female participants. This is to be expected given breast cancer was one of three cancers types specified in the inclusion criteria.[43] There is also a preponderance of Stage IV participants (those with metastatic disease) because recruitment was based on receiving intravenous anticancer treatments. While good quality data are unavailable, the current survival rates suggest a much lower rate of advanced cancer in a general cancer cohort than in the EoCC cohort.[174]

Table 23: Characteristics of the EoCC cohort

Characteristic	Number (%)	Clinical characteristic	Number (%)
Male Sex	126 (26.4%)	Breast cancer	258 (54%)
Female Sex	352 (73.6%)	Colorectal cancer	157 (32.8%)
Age (at recruitment) <= 45	61 (12.8%)	NSCLC	63 (13.2%)
Age 46-65	290 (60.7%)	Previous Chemo	198 (42%)
Age 66-85	127 (26.6%)	Stage I	28 (5.9%)
		Stage II	90 (18.8%)
		Stage III	113 (23.6%)
		Stage IV	247 (51.7%)

Abbreviation: EoCC: Elements of Cancer Care; NSCLC: non-small cell lung cancer

For the purposes of the research in this thesis, a subgroup of EoCC participants identified as having metastatic disease (Stage IV) whose information was linked to the PBS, MBS and the NSW data via CHeReL were included. There were 232 participants included in the EoCC data collection who satisfied these requirements. This is slightly less than the number of patients who had Stage IV disease because administrative data was not available for all participants. The demographic and clinical characteristics of the 232 participants at the time of their recruitment are described in the Table below.

Table 24: Characteristics and administrative data on the 232 EoCC participants with metastatic disease

Characteristic	Categories	Number (percentage)	Percentage conditional on non-missing (percentage)
Sex	Male	79 (34%)	79 (34%)
	Female	153 (66%)	153 (66%)
	Total	**232 (100%)**	**232 (100%)**
Cancer type	Breast cancer	98 (42.2%)	98 (42.2%)
	Colorectal cancer	96 (41.3%)	96 (41.3%)
	NSCLC	38 (16.4%)	38 (16.4%)
	Total	**232 (100%)**	**232 (100%)**
Age (age at recruitment)	<= 45	23 (10%)	23 (10%)
	46-65	132 (56.9%)	132 (56.9%)
	66-85	77 (33.2%)	77 (33.2%)
	Total	**232 (100%)**	**232 (100%)**
Previous chemotherapy	Yes	148 (63.8%)	148 (64.6%)
	No	81 (34.9%)	81 (35.4%)
	Missing	3 (1.3%)	-
	Total	**232 (100%)**	**229 (100%)**
Stage of disease	Stage IV	232 (100%)	232 (100%)
	Total	**232 (100%)**	**232 (100%)**

Characteristic	Categories	Number (percentage)	Percentage conditional on non-missing (percentage)
Country of birth	Australia	132 (56.9%)	132 (69.1%)
	UK	23 (9.9%)	23 (12.0%)
	Other	36 (15.5%)	36 (18.9%)
	Missing	41 (17.7%)	-
	Total	**232 (100%)**	**191 (100%)**
School leaving year	<Year 10	27 (11.6)	27 (14.2)
	Year 10	54 (23.8%)	54 (28.4%)
	>Year 10	109 (47%)	109 (57.4%)
	Missing	42 (18.1%)	-
	Total	**232 (100%)**	**190 (100%)**
Higher education	Yes	120 (51.7%)	120 (63.5%)
	No	69 (29.7%)	69 (36.5%)
	Missing	43 (18.5%)	
	Total	**232 (100%)**	**189 (100%)**
Type of higher education	TAFE/Technical/Diploma	67 (55.8%)	67 (55.8%)
	Under-graduate	40 (33.3%)	40 (33.3%)
	Postgraduate	13 (10.8%)	13 (10.8%)
	Total	**120 (100%)**	**120 (100%)**
Household income at recruitment	Zero	3 (1.3%)	3 (2.7%)
	$1 to $12 999	0 (0%)	0 (0%)
	$13 000 - $20 799	12 (5.2%)	12 (10.6%)
	$20 800 - $31 199	18 (7.8%)	18 (15.9%)
	$31 200 - $41 599	11 (4.7%)	11 (9.7%)
	$41 600 - $51 999	7 (3.0%)	7 (6.2%)
	$52 000 - $67 599	7 (3.0%)	7 (6.2%)
	$67 600 - $83 199	6 (2.6%)	6 (5.3%)
	$83 200 - $103 999	4 (1.7%)	4 (3.5%)
	$104 000 or more	10 (4.3%)	10 (8.9%)
	Unknown	35 (15.1%)	35 (31%)
	Missing	119 (51.3%)	-
	Total	**232 (100%)**	**113 (100%)**
Private health insurance	Yes	134 (57.8%)	134 (70.2%)
	No	57 (24.6%)	57 (29.8%)
	Missing	41 (17.7%)	-
	Total	**232 (100%)**	**191 (100%)**
Concession Card	Yes	97 (41.8%)	97 (50.5%)
	No	95 (41%)	95 (49.5%)
	Missing	40 (17.2%)	-
	Total	**232 (100%)**	**192 (100%)**
Type of concession card	CSHC	36 (37.1%)	36 (37.9%)
	HCC	22 (22.7%)	22 (23.2%)

Characteristic	Categories	Number (percentage)	Percentage conditional on non-missing (percentage)
	Pensioner CC	37 (38.1%)	37 (39%)
	Missing	2 (2%)	-
	Total	**97 (100%)**	**95 (100%)**

Abbreviation: CC: concession card; Chemo: chemotherapy; CSHC Commonwealth seniors health card; EoCC: Elements of Cancer Care; HCC: healthcare card; NSCLC: non-small cell lung cancer

Relative to EoCC participants overall, the metastatic subgroup were older, less likely to be female, less likely to have breast cancer and more likely to have had previous chemotherapy. Compared to other data collections reporting cancer participants, they were more likely to be female and more likely to have private health insurance.[162]

4.3 Number of lines of therapy received by the EoCC cancer cohort

This Section aims to estimate the number of lines of therapy received by the EoCC cohort using the observational data. The prospective observational EoCC data collection is used to estimate the number of lines of therapy that the individuals within the cohort received. There are alternative methods of calculating the number of lines of therapy using the EoCC data.

4.3.1 Data

The EoCC data from the review of clinical notes and from the monthly interviews was reviewed by a senior oncologist from the Prince of Wales hospital and treatments used were attributed to a protocol from the EViQ[viii] website. This occurred prior to the second data extraction in 2016 and excludes that information. Therefore, it is censored information about the treatment of participants.

The data collection form for the review of clinical notes asked specifically about the current chemotherapy protocol and the record of chemotherapy administration over the last 90 days. Additionally, it asked about the previous chemotherapy protocols that had been administered for the current cancer.

The review of patient records and allocation of protocols by the oncologist represents one interpretation of the lines of therapy - that of making equivalent the number of protocols and the number of lines of therapy received by a patient. This is the naïve oncologist review estimation of the number of lines of therapy.

[viii] EviQ is Cancer Treatments Online

There are advantages and disadvantages to the naïve oncologist review method of estimating the number of lines of therapy. These relate to calculating correctly the number of protocols received by a participant and the assumption that the protocols received are an appropriate proxy measure of the number of lines of therapy received by a participant.

The advantages include that the extraction was undertaken on a near complete set of information: clinical notes, letters and administrative data. This results in the oncologist's review including non-PBS lines of therapy. These include trastuzumab which was subsidised via the Herceptin Program for advanced breast cancer prior to 2016.[175]

There are also disadvantages. First, the data potentially does not include the lines of therapy that a patient received prior to the review of his/her notes if these were not recorded in the patient's notes. This might have occurred if a patient had transferred institutions or if the letters and plans were not easily accessible within the clinical notes. Additionally, it does not include information about lines of therapy received after the oncologist's review.

Second, it is also possible that the oncologist's review interpreted what might be one line of therapy as two or more protocols. An example is colorectal cancer (CRC). One of the protocols consists of two pharmaceuticals, oxaliplatin and 5-FU. Oxaliplatin is associated with neurotoxicity which occurs as the cumulative dose of the pharmaceutical increases. Therefore, over time, oxaliplatin might have been ceased and a patient continued 5-FU alone. From the perspective of this thesis, this practice would be considered as the use of one line of therapy as there has been no failure of therapy. However, the oncologist's review may have recorded this as two lines of therapy, for example, scribing one as FOLFOX (the combination of oxaliplatin and 5-FU) and the other as 5-FU. A preliminary review of the data suggested this was the case in several patients.

An alternative method of estimating the number of lines of therapy used is to equate the introduction of new pharmaceuticals with the introduction of a new protocol. For the example of 5-FU and oxaliplatin, only one line of therapy would be recorded. It would not be considered a new line of therapy because the second protocol pharmaceuticals are a subset of the first protocol pharmaceuticals. A new line of therapy is considered to have occurred when a new pharmaceutical is included. This is consistent with the literature which uses the addition of a new pharmaceutical as an indicator of the failure of the previous treatment.[176] This method is referred to as the new pharmaceutical use (oncologist's review).

4.3.2 Methods

The oncologist's review of protocols was used as the basis for constructing the number of lines of therapy received by each participant. The two methods described above were used and the results compared.

The naïve oncologist review consisted of eliminating repeated protocols from the analysis. The oncologist's review of protocols were coded within Stata 15[173] and repeated sequences of protocols (the same protocol more than once in a sequence) were eliminated. The count of protocols was recorded.

The new pharmaceutical use (oncologist's review) consisted of converting each of the oncologist's review protocols into the constituent anticancer pharmaceuticals. A new line of therapy was considered to have occurred when a new protocol was associated with an additional anticancer pharmaceutical when compared to all previously received protocols.

This analysis was performed on the entire EoCC dataset. The results were stratified by type of cancer and stage of cancer. The analysis was undertaken using Stata 15.[173]

4.3.3 Results

Table 25 below shows the mean number of protocols prescribed for each type and stage of cancer as assessed by the naïve oncologist's review. When a protocol was recorded multiple times in a sequence, only one incidence was recorded.

Table 25: Mean number of treatments according to naïve oncologist's review

Stage of cancer	Site of cancer			
	Breast	**CRC**	**NSCLC**	**Total**
Stage I	1.6			1.6
Stage IA	1			1
Stage IB	1.7		2.3	1.9
Stage IC	1.2			1.2
Stage II	2.2	2.5		2.3
Stage IIA	2	1		1.9
Stage IIB	1.5	1	1	1.5
Stage III	2.4	2	1	2.1
Stage IIIA	2	1.7	2	2
Stage IIIB	1.4	2	2	1.9
Stage IIIC	1.5	2		1.6
Stage IV	4.3	3.3	2.8	3.6
Total	**2.8**	**2.9**	**2.5**	**2.8**

Note: This analysis was conducted on the entire EoCC cohort
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

For the analysis restricted to the 232 participants with metastatic disease for whom data were available, the results indicated an average of 4.3 lines of therapy were given for breast cancer, 3.3 for CRC and 2.9 for NSCLC. As might be expected, a higher average number of treatments were prescribed for metastatic disease (ttest, $p<0.01$). This demonstrates that a larger number of lines of therapy are given to patients with metastatic disease as assessed by the oncologist's review. Moreover, the number of lines of therapy is broadly correlated with the length of survival associated with each cancer. That is, because lung cancer has a shorter survival compared with breast cancer, the mean number of therapies given to patients with metastatic NSCLC was less than the mean number prescribed for patients with metastatic breast cancer.

Patients received an average of more than one line of therapy for several cancer stages for which they might have been expected to receive only one, for example, Stage I breast cancer. One explanation for this is that the treatment may have consisted of two distinct sets of pharmaceuticals and both were recorded as a protocol in the oncologist's review. In several breast cancer adjuvant therapies, one set of pharmaceuticals is followed by another; for example, AC (doxorubicin and cyclophosphamide) followed by paclitaxel. This was recorded by the oncologist's review as two protocols in several instances. If the new pharmaceutical use (oncologist's review) method is used the estimated number of lines of therapy decreased. Overall, patients with metastatic disease had 2.5 lines of therapy. Patients with metastatic breast cancer had an average of 3.0 lines of therapy, those with CRC received 1.9 lines of therapy and those with NSCLC received 2.5 lines of therapy. The median number of lines of therapy for participants with all three cancer types was two. The number of estimated lines of therapy for the 232 participants with metastatic disease is shown below.

Table 26: Estimated lines of therapy by new pharmaceutical use (oncologist' review)

Lines of therapy	Site of cancer			Total
	Breast cancer (%)	CRC (%)	NSCLC (%)	
0	1 (1%)	2 (2.1%)	0 (0%)	**3 (1.3%)**
1	12 (12.2%)	33 (34.4%)	6 (15.8%)	**51 (22%)**
2	24 (24.5%)	36 (37.5%)	15 (39.5%)	**75 (32.3%)**
3	30 (30.6%)	19 (19.8%)	11 (28.9%)	**60 (25.9%)**
4	16 (16.3%)	5 (5.2%)	5 (13.2%)	**26 (11.2%)**
5	9 (9.2%)	1 (1%)	1 (2.6%)	**11 (4.7%)**
6	4 (4.1%)	0 (0%)	0 (0%)	**4 (1.7%)**
7	1 (1%)	0 (0%)	0 (0%)	**1 (0.4%)**
8	1 (1%)	0 (0%)	0 (0%)	**1 (0.4%)**
Total	**98 (100%)**	**96 (100%)**	**38 (100%)**	**232 (100%)**

Note: This analysis was conducted on the 232 participants with metastatic disease
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

The two methods of estimating the number of lines of therapy are compared in Table 27. There was a 40% agreement between the two methods of calculation. The new pharmaceutical use (oncologist's review) method reduced the number of lines of therapy relative to the naive method.

Table 27: Comparison between naïve oncologist's review and new pharmaceutical use (oncologist's review) for metastatic patients

Naïve oncologist's review	New pharmaceutical use (oncologist's review)								
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
0	3								
1		24							
2		17	32						
3		7	19	22					
4		2	15	17	9				
5			4	10	9	2			
6		1	1	6	3	4	1		
7			3	4		4			
8				1	1	1	1		
9					3			1	
10					1		2		
11									1
12									
13									
14			1						

4.3.4 Discussion

It was routine for patients in this cohort of cancer patients in New South Wales to receive more than one line of therapy, irrespective of the method of estimation. Moreover, a substantial minority of participants received four or more lines of therapy. Eighteen per cent of participants were assessed as receiving four or more lines of therapy using the new pharmaceutical use (oncologist's review) method of estimation. Using the naïve oncologist´s review method, the percentage of participants who received four or more lines of therapy rose to 46%.

This information is used in Chapter 6 to assess whether the number of treatments given exceeds the available evidence for benefit. It also confirms that the use of multiple lines of therapy is a common practice in oncology, as discussed in Chapter 2.

4.4 Validation and completeness of PBS administrative data

In this Section, the EoCC cohort observational data and other data is used to analyse if the PBS administrative data would be valid and complete with regard to the treatments given and the number of lines of therapy received.

The completeness of the EoCC PBS dataset is assessed through a comparison to other linked data (such as the EoCC MBS administrative data) and the external oncologist´s review (see Section 4.3). The aims of this assessment were to:

- confirm the presence or absence of the other section 100 pharmaceuticals in the EoCC PBS administrative data;
- establish the completeness of the EoCC PBS administrative data using the oncologist´s review as the gold standard comparison;
- determine if any missing pharmaceuticals in the EoCC PBS administrative data could be explained by being below the co-payment threshold; and
- clarify the potential for other administrative data to provide supportive information that provides a fuller picture of chemotherapy use (using MBS infusion data, hospital admissions and other pharmaceuticals).

4.4.1 Presence or absence of other section 100 oncology pharmaceuticals

Trastuzumab prescribed under the Herceptin Program was not expected to be observed in the EoCC PBS administrative data. The aim, however, was to confirm the presence or absence in the EoCC PBS administration data of other pharmaceuticals to treat the three cancer types

available under the other two section 100 programs - the CPAP and the Highly Specialised Drugs Program.

The PBS administrative data were examined for the specific codes representing the actual item number. The chemotherapy agents examined in the EoCC administrative data were paclitaxel, 5-FU and carboplatin. These were chosen because they were more numerous in the EoCC dataset, covered the three cancer types included in the EoCC cohort and were available on the general PBS and the CPAP schedules. The supportive therapy (aprepitant) for the treatment of chemotherapy-induced nausea and vomiting was also included. As 30/06/2011 was the end date within the initial data extraction of the EoCC PBS data, the schedules available on 1/07/2011 were used.

The Medicare statistics program website was used to assess the use of these codes and the corresponding codes in the general PBS schedule over the period 2008 to 2011 (accessed at http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp). The results were stratified by State.

The use of pharmaceuticals from the Highly Specialised Drugs Program in the EoCC dataset was checked by assessing the presence of the codes associated with the use of bisphosphonates for the treatment of hypercalcaemia or metastatic disease in breast cancer (code 6155Y).

None of the codes for CPAP funding of paclitaxel, 5-FU, carboplatin or aprepitant were present in the EoCC PBS administrative data. Table 28 below shows the benefits paid by the Australian Federal Government for the use of items identified in the CPAP Schedule and the PBS Schedule on the 1/07/2011. The totals included only refer to the PBS (not the Repatriation Schedule of Pharmaceutical Benefits [RPBS]). As can be seen in Table 28, only jurisdictions included in the CPAP have a record of the use of the items identified in the CPAP schedule. As is evident, there is no recorded use of the section 100 CPAP in New South Wales. As a check, the use of chemotherapy not subsidised via section 100 was included, and use was recorded in New South Wales (or the ACT). These results provide reassurance that the absence of chemotherapy codes for medicines covered under the section 100 CPAP are not of any significance in assessing the completeness of the EoCC data.

Table 28: Breakdown of prescribed treatments (CPAP and general schedule) 2008-2011 by State

Pharmaceutical	Year	State					
		NSW	VIC.	Queensland	WA	SA	TAS.
Aprepitant (code 5888X) from CPAP	2008	0	4 557	1 231	0	546	0
	2009	0	5 237	1 554	1 039	810	0
	2010	0	5 005	1 446	2,013	1 012	0
	2011	0	6 011	2 717	2 159	1 516	1
Bevacizumab (5850X) from CPAP	2008	0	0	0	0	0	0
	2009	0	513	257	83	30	0
	2010	0	2 532	769	713	212	0
	2011	0	2 908	1 579	762	736	0
Bevacizumab (9443B) from general schedule	2008	0	0	0	0	0	0
	2009	642	404	729	61	345	71
	2010	3 430	2 246	2 498	313	1 523	325
	2011	4 026	2 993	2 544	533	1 260	443

Abbreviation: CPAP: Chemotherapy Pharmaceutical Access Program; SA: South Australia; TAS: Tasmania; VIC: Victoria; WA: Western Australia

The code for bisphosphonates was present in the EoCC data.

There was no evidence of CPAP section 100 program use in the EoCC PBS data. The lack of CPAP is as expected given this program was not used in New South Wales.

It is possible that the EoCC cohort does not fully represent the use of chemotherapy on the PBS that would have occurred in other jurisdictions in Australia over the period of interest because of the differences in administrative arrangements. That is, the external validity of the EoCC dataset may be limited because of the differing funding arrangements.

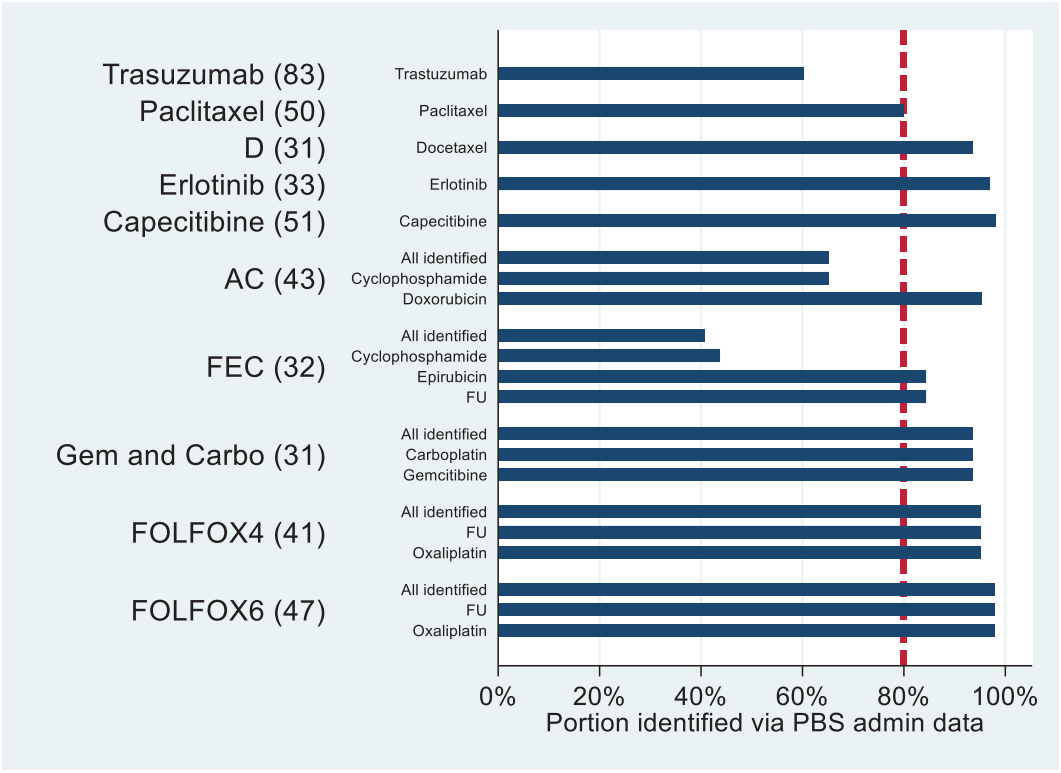
4.4.2 Completeness of the PBS administrative data

The ten most frequent oncologist-assessed protocols recorded in the entire EoCC cohort (including for metastatic and non-metastatic disease) were compared to the EoCC PBS administrative data for those participants. The Anatomical Therapeutic Chemical (ATC) classification for each of the individual pharmaceuticals was searched for in the EoCC PBS administrative data. A count of the number of participants identified with each pharmaceutical was made. A count of all pharmaceuticals correctly identified in each protocol was also made. Eighty per cent was considered a satisfactory level of identification.[177,178]

The individual components of all the protocols identified by the oncologist's review received by the 232 participants of the metastatic group with full data were compared to the PBS

administrative data. The ATC codes for each of the individual pharmaceuticals were searched for in the PBS administrative data. A count of the number of participants identified with each pharmaceutical was made, irrespective of whether it was identified by the oncologist's review. Overall agreement, specificity and sensitivity for the EoCC PBS data (assuming that the oncologist's review was the gold standard) were calculated.

The top ten protocols as determined by oncologist's review for the full EoCC dataset are presented in Figure 15 below. These include all patients in the EoCC dataset, including both metastatic and non-metastatic patients. Three pharmaceuticals - trastuzumab, cyclophosphamide and paclitaxel - were below the prespecified 80% success level.



Note: The figures inside the bracket refer to the number of individuals for which the protocol was observed in the oncologist's review of the full cohort
Abbreviations: AC: a protocol consisting of doxorubicin and cyclophosphamide; D: docetaxel; FEC: a protocol consisting of 5-fluorouracil, epirubicin and cyclophosphamide; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; Gem and Carbo: a protocol consisting of gemcitabine and carboplatin

Figure 15: PBS identification of oncologist protocols

There was a notable difference for some pharmaceuticals between the PBS records and the implied use of pharmaceuticals from the oncologist's review. Of note, five participants had no chemotherapy provision recorded in the PBS administrative data, despite having been recruited based on receiving IV treatment and having available PBS administrative data. Table 29 below shows the breakdown of the pharmaceuticals and the proportion of overall agreement between the PBS and oncologist's review. A large proportion of this agreement is

because most participants did not receive an individual pharmaceutical as measured by either approach. Kappa statistics showed a significant level of concordance.

Table 29: Agreement between oncologist's review and the PBS administrative data for metastatic protocols

Pharmaceutical	Both oncologist and PBS suggested did receive pharmaceutical	Both oncologist and PBS suggest did not receive pharmaceutical	Oncologist suggested that received pharmaceutical but not the PBS	PBS suggests the received pharmaceutical but not oncologist review	Overall agreement	Specificity of PBS	Sensitivity of PBS
5-FU	148	66	9	9	92%	88%	94%
Bevacizumab	34	181	15	2	93%	99%	69%
Carboplatin	52	175	2	3	98%	98%	96%
Cetuximab	0	230	2	0	99%	100%	0%
Cisplatin	6	226	0	0	100%	100%	100%
Cyclophosphamide	27	156	39	10	79%	94%	41%
Docetaxel	41	183	6	2	97%	99%	87%
Doxorubicin	24	177	24	7	87%	96%	50%
Epirubicin	12	208	10	2	95%	99%	55%
Erlotinib	26	205	0	1	100%	100%	100%
Etoposide	1	231	0	0	100%	100%	100%
Gemcitabine	53	171	2	6	97%	97%	96%
Irinotecan	43	179	0	10	95%	95%	100%
Lapatinib	10	222	0	0	100%	100%	100%
Mitoxantrone	11	218	1	2	99%	99%	92%
nab-Paclitaxel	11	214	1	6	97%	97%	92%
Oxaliplatin	78	143	5	6	96%	96%	94%
Paclitaxel	54	149	19	10	88%	94%	74%
Liposomal Doxorubicin	7	218	1	6	97%	97%	88%
Panitumumab	0	226	6	0	97%	100%	0%
Pemetrexed	21	208	0	3	99%	99%	100%
Raltitrexed	9	222	0	1	100%	100%	100%
Trastuzumab	9	193	30	0	87%	100%	23%
Vincristine	25	203	2	2	98%	99%	93%

Note: These figures are for the 232 metastatic participants only
Abbreviations: 5-FU: 5-fluorouracil; PBS: Pharmaceutical Benefits Scheme

The review of the protocols by the oncologist involved having access to the PBS data. As a result, they are not completely independent methods of identification. It has been suggested that sensitivity of 80-90% is necessary to identify the true incidence of use in other medical circumstances involving cancer (surgery or recurrence of breast cancer).[177,178] A lower rate of sensitivity (75%) has been suggested to occur in the PBS administrative data for chemotherapy for cyclophosphamide.[160] The EoCC PBS administrative data had an even lower rate of sensitivity for cyclophosphamide.

Six pharmaceuticals were not successfully identified in the PBS administrative data: trastuzumab, cyclophosphamide (in multiple different protocols) paclitaxel, cetuximab, panitumumab and bevacizumab.

For the trastuzumab protocol, 19 of the 25 patients for whom trastuzumab was not noted in the PBS administrative had metastatic cancer at the time of recruitment into the EoCC study. The difference in the staging between those participants who were recorded as having or not having trastuzumab in the PBS data was statistically significant ($p<0.01$ chi^2 test). This issue is important because trastuzumab is expensive and a substantial percentage of breast cancer patients in the EoCC cohort received trastuzumab.

Cyclophosphamide is an older pharmaceutical. The reason for its potential omission is discussed below, but it appears to be missing from the PBS administrative data because its cost is below the co-payment threshold.[172]

The third pharmaceutical identified by the review of protocols for which there was a potential issue is paclitaxel. Only 80% of patients who were assessed by the oncologist as having used paclitaxel had PBS evidence that they were prescribed paclitaxel. The administrative records of the ten patients who did not have PBS evidence of paclitaxel were examined; six included PBS use of nab-Paclitaxel, a form of paclitaxel. Therefore, there may not be a substantial difference between the oncologist's review of the protocols and the recording in the PBS administrative data. Rather it may be that the use of nab-Paclitaxel was recorded as the use of paclitaxel from a clinical perspective.

Three other high cost pharmaceuticals, namely cetuximab, panitumumab and bevacizumab, were not identified using the PBS administrative data. The total number of participants who received these pharmaceuticals was relatively small. However, they are expensive pharmaceuticals. Accordingly, their exclusion from the PBS administrative data is potentially concerning for the purposes of calculating costs.

Cetuximab and panitumumab are anti-EGFR antibodies whose cost-effectiveness has been questioned in Australia and internationally (see Section 3.2 for a more detailed discussion). Cetuximab for metastatic CRC was accepted by the PBAC at its July 2010 meeting for treatment in the second line of therapy but it was not listed in the schedule until September 2011. The gap between acceptance and listing meant there was a gap between the time that the pharmaceutical was accepted as effective and cost-effective by the PBAC, and its subsequent subsidisation through the PBS. Cetuximab was listed on the EViQ treatment website in November 2010, again suggesting that it was acknowledged to be an effective treatment before its listing on the PBS. An interim access program for cetuximab operated between 2005 and 2009 in Australia[179] and it was estimated that up to 50% of eligible colorectal patients in Australia may have received treatment through this access scheme.[179] The scheme ceased in November 2009.[179]

Panitumumab was listed on the EViQ website in 2009. It was considered and rejected by the PBAC in 2008, was reconsidered in March 2013 and rejected for first line treatment but accepted for later line treatment. It was included in the April 2014 Efficient Funding of Chemotherapy Program schedule.

Bevacizumab is an antiangiogenesis treatment. It has been assessed for use in several types of cancer as angiogenesis is a common feature of various cancers. The breakdown between the cancer sites that were noted by the oncologist's review as receiving a protocol including bevacizumab is clear. The split is approximately 50:50 between CRC and breast cancer. Bevacizumab was listed on EViQ in 2008 in combination with FOLFIRI for the treatment of metastatic CRC. It was accepted at the July 2008 PBAC meeting for listing in the first line of therapy. According to the oncologist's review, EoCC participants received bevacizumab in a later line of therapy for CRC. This use was not recorded in the PBS administrative data. The use of bevacizumab for breast cancer has been controversial.[180] It was initially granted approval by the Food and Drug Administration (FDA) on the basis of an improvement in progression free survival (PFS) but no overall survival benefit was subsequently demonstrated.[180]

These three high cost pharmaceuticals demonstrate some of the issues discussed in Chapter 2. For bevacizumab, evidence of benefit in one line of therapy (the first line) resulted in its use in a later line of therapy for CRC. It also highlights another potential problem associated with the period prior to listing (or expected listing) on the PBS. At this stage the evidence may be available, and facilities will be under pressure to provide the treatment. In some cases, this treatment will be provided through alternative mechanisms.

There are also potential problems with lower cost pharmaceuticals, such as doxorubicin and epirubicin, used to treat breast cancer. Half the participants for whom doxorubicin was present in the oncologist's review of protocols did not receive it according to the PBS data, but received trastuzumab. Given the potential for the combination of doxorubicin and trastuzumab to cause cardiac dysfunction, a decision may have been made to not give doxorubicin despite initially considering it. Those participants whose PBS data indicated no use of epirubicin and doxorubicin all received multiple pharmaceuticals administered in a protocol.

In summary, several high cost pharmaceuticals are observed more frequently in the oncologist's review than in the PBS data. There are several explanations for this. Trastuzumab is missing because of the administrative arrangements that occurred for the subsidisation of that pharmaceutical. Bevacizumab was used for CRC in a line of therapy for which it was not subsidised by the PBS. Cetuximab and panitumumab were used after listing on EViQ but prior to subsidisation on the PBS.

The PBS administrative data appears to be more accurate in describing the use of older pharmaceuticals whose prices exceed the co-payment threshold. The use of newer, more expensive pharmaceuticals is higher than that observed in the PBS administrative data.

4.4.3 Explanation of missing pharmaceuticals from PBS data

The lack of information about pharmaceuticals which fall below the co-payment threshold has been discussed in the literature on the use of the PBS dataset.[172] As of April 2012, under co-payment scripts are recorded.[172] However, they were not recorded before that date, which encompasses the timeframe for the dataset used in this analysis.

The potential for cyclophosphamide to be below the co-payment threshold could explain its lack of identification in the PBS administrative data.[172] Cyclophosphamide is available both as an oral preparation and an intravenous preparation. For the oral preparation, the cost is relatively low compared to other chemotherapy agents. In the December 2009 PBS Schedule, the DPMQ (Dispensed Price for Maximum Quantity) was less than the maximum co-payment for the oral form of cyclophosphamide. The DPMQ is not under the maximum co-payment for the intravenous form. This allows an analysis of cyclophosphamide to be conducted according to whether the formulation is under the co-payment.

The various PBS items for cyclophosphamide were tabulated according to whether the DPMQ was above or below the co-payment threshold for the calendar year 2009. Each prescription

was allocated to one of 13 four-week periods. A linear regression was conducted for each type including time as an explanatory variable with robust standard errors.

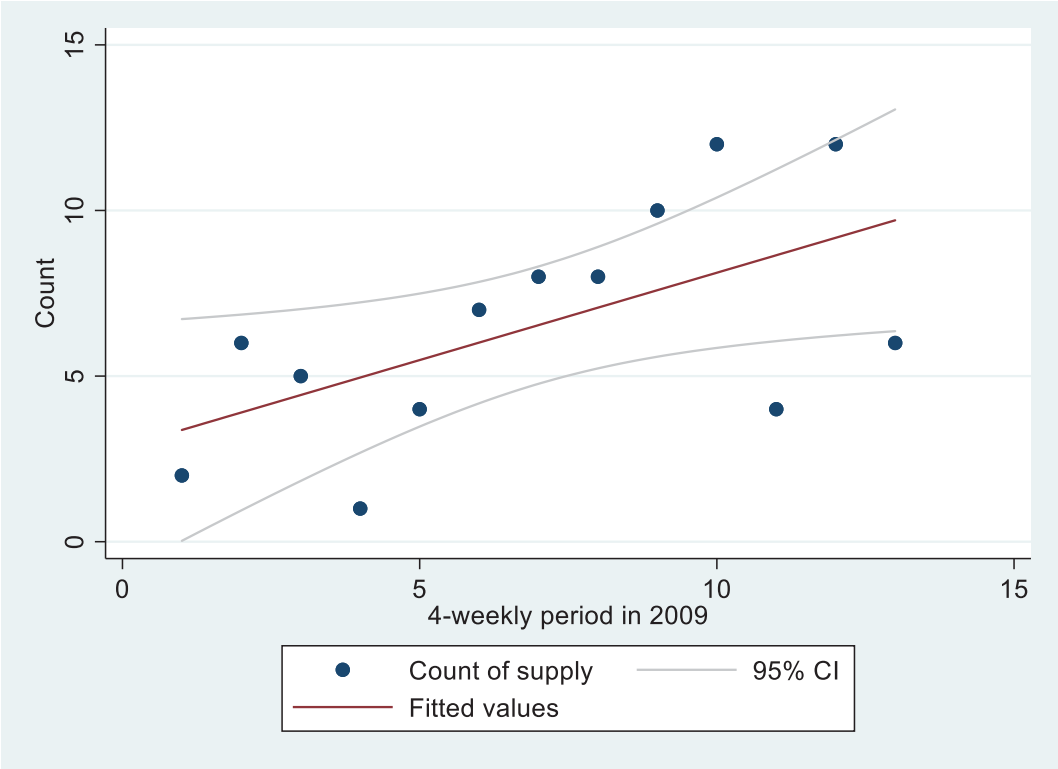
The months of the year and the number of cyclophosphamide scripts supplied is shown below in Table 30. It is divided into the various PBS codes for cyclophosphamide.

Table 30: Cyclophosphamide supply in the EoCC cohort

	PBS item					Total
PBS description	**01031G IV formulation**	**01079T IV formulation**	**01080W IV formulation**	**01266P Oral formulation**	**07055H**	
	Under co-payment	**Not under co-payment**	**Potentially under co-payment**	**Potentially under co-payment**	**Potentially under co-payment**	**Not under co-payment**	
Jan	20	0	8	1	0	**29**
Feb	22	0	9	0	0	**31**
March	16	0	7	0	0	**23**
April	23	0	2	0	0	**25**
May	29	0	13	1	0	**43**
June	33	0	8	0	0	**41**
July	49	0	13	1	0	**63**
August	43	0	10	3	2	**58**
September	39	0	14	5	1	**59**
October	26	0	8	6	0	**40**
November	20	1	10	7	0	**38**
December	15	0	6	8	0	**29**
Total	**335**	**1**	**108**	**32**	**3**	**479**

Note: This analysis was conducted on the whole EoCC cohort.
Abbreviations: IV: intravenous; PBS: Pharmaceutical Benefits Scheme

The regression analysis showed no impact of time for the always over co-payment group but a significant positive impact on the potentially under co-payment group ($p<0.05$). This is demonstrated graphically in Figure 16, which shows an increasing number of cyclophosphamide scripts recorded throughout the year.



Note: This analysis was conducted on the whole EoCC cohort.
Abbreviation: CI: confidence interval

Figure 16: Cyclophosphamide scripts in 2009 by four-week months

This result is consistent with the assumption that whether a participant reached the PBS safety net threshold had a significant impact on the presence of cyclophosphamide in the data. As participants exceeded the threshold for the PBS safety net, their prescriptions for cyclophosphamide are recorded in the administrative data. Cyclophosphamide is not listed in the EViQ protocols as a solitary agent for the treatment of breast, colorectal and lung cancer. Therefore, the lack of cyclophosphamide information is unlikely to have a major impact in determining whether participants received chemotherapy. It should also not make a difference to an estimate of the number of lines of therapy.

This is demonstrated by comparing the oncologist reviewed protocols and the PBS administrative data. The results show that the recording of cyclophosphamide is lower than the other pharmaceuticals involved in the protocol. However, it does suggest that using PBS data only will underestimate the number of pharmaceuticals used and thus the cost to the patient. This is because the patient will bear the full cost of the below co-payment pharmaceuticals.

A review of the other chemotherapy agents suggests that at least two other cancer pharmaceuticals were potentially under the co-payment threshold. Technically, methotrexate is an anticancer agent and falls below the threshold co-payment. Additionally, some

formulations of cisplatin (50mg in 50ml or 10mg in 10ml) are below the co-payment. Several of the supportive therapies associated with cancer care, such as dexamethasone and the 5-HT3 (5-hydroxytryptamine 3) receptor antagonists, would also be below the co-payment. This suggests that the pharmaceutical costs for oncology treatment are incomplete for some participants.

Methotrexate is not used in many chemotherapy protocols and is also used to treat other conditions, such as rheumatoid arthritis. Therefore, its exclusion may be appropriate because its use cannot be attributed solely to oncology treatment. The dosage of cisplatin is 75-80mg/m^2 in metastatic treatment of NSCLC. Therefore, the use of a 100mg vial could be considered as an appropriate vial size for most patients as most participants have greater than a metre surface area. Alternatively, it would require the manipulation of two to eight vials by the pharmacist to achieve a dose of 75mg of cisplatin. When the same comparison undertaken for cyclophosphamide was applied to cisplatin, no relationship was found between time and the recording of the 50mg vial use.

However, there is one protocol listed for metastatic breast cancer that consists solely of the oral use of methotrexate and cyclophosphamide.[181] Potentially, this protocol might not be included in the PBS administrative data because all the components are below the co-payment. Moreover, it would not appear in the MBS administrative data because neither treatment is administered intravenously. Methotrexate and cyclophosphamide was not a protocol that was recorded by the oncologist clinical review. Therefore, it may not be relevant for this verification process and analysis.

There are three major issues identified for the completeness of the PBS data: the lack of trastuzumab in the metastatic breast cancer cohort, the lack of below co-payment chemotherapy treatments (as exemplified by cyclophosphamide) and the potential for similar chemotherapy agents to be coded differently (as exemplified by paclitaxel and nab-Paclitaxel). These issues necessitate the examination below of whether other administrative data can provide a fuller picture of chemotherapy use among the EoCC participants.

4.4.4 Examination of the potential for other administrative data to provide the missing information

Having concluded that the PBS administrative data does not represent a complete record of chemotherapy use, alternative means of detecting the use of chemotherapy in administrative data available in the EoCC dataset were assessed. Three specific methods of detection were

explored: using the MBS chemotherapy infusion items in the MBS administrative data, using information about supportive medications for chemotherapy in the PBS administrative data, and using the chemotherapy AR-DRG (Australian Refined Diagnosis Related Groups) codes in the hospital administrative data.

MBS infusion items as a method of identifying chemotherapy treatment

The administration of intravenous chemotherapy requires specialised care and services.[48,164] They are potentially dangerous medicines and are often administered in hospitals or other facilities.[164] A series of reimbursements are provided by the MBS for the administration of cytotoxic therapy.[182]

Table 31 below shows the mixture of PBS and MBS administrative data that are observed with different forms of chemotherapy agents depending on their mode of administration and reimbursement, assuming the patient is not an inpatient of a public hospital.

As is evident from Table 31, chemotherapy that is administered intravenously could be identified by the presence of an MBS item for chemotherapy administration. This could potentially identify chemotherapy use for those EoCC participants who were treated with trastuzumab, bevacizumab or other intravenous pharmaceutical treatments in the oncology review. There could be MBS infusion items in the administrative data without any associated PBS supply.

Table 31: Potential scenarios of MBS and PBS chemotherapy identification

Scenario	IV or oral	On the PBS	Above or below the co-payment	Observable in PBS	Observable in MBS/admission data	Real-world example
1	IV	Yes	Above	Yes	Yes	Paclitaxel
2	IV	Yes	Below	No	Yes	Cisplatin
3	IV	No	N/A	No	Yes	Trastuzumab for metastatic disease
4	Oral	Yes	Above	Yes	No	Erlotinib
5	Oral	Yes	Below	No	No	Cyclophosphamide
6	Oral	No	N/A	No	No	Regorafenib- prior to listing on the PBS

Abbreviations: IV: intravenous; MBS: Medical Benefits Schedule; N/A: not applicable; PBS: Pharmaceutical Benefits Scheme

One method to check for this is to examine the differences and similarities between the PBS scripts for chemotherapy treatment and the MBS items for chemotherapy. There should be a

relationship between the supply of an intravenous chemotherapy agent and the use of an MBS chemotherapy administration item.

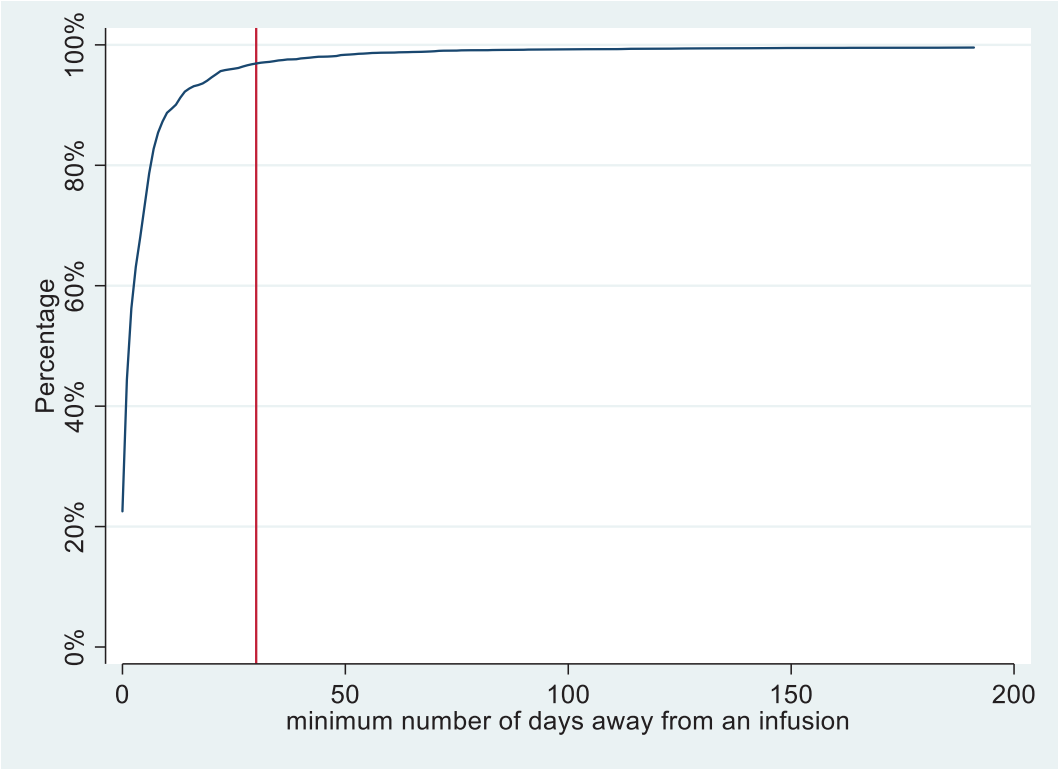
The total EoCC dataset (adjuvant and metastatic) was used for this analysis. The date of supply recorded in the PBS data was assumed to represent the presumed supply of chemotherapy.

Only PBS items for intravenous chemotherapy agents were used. These were identified using the ATC prefix “L01”. Oral treatments were removed. This involved excluding chemotherapy treatments such as oral cyclophosphamide, methotrexate, erlotinib and capecitabine based on their PBS codes.

The date of service of MBS items associated with cytotoxic infusion was used to represent the use of chemotherapy. The MBS codes used to identify the use of cytotoxic infusions were 13915, 13918, 13921, 13924, 13927, 12930, 13933, 13936, 13939, 13945 and 13948.

The number of days difference between the infusion and the closest supply of chemotherapy (either forward or backwards temporally) was calculated.

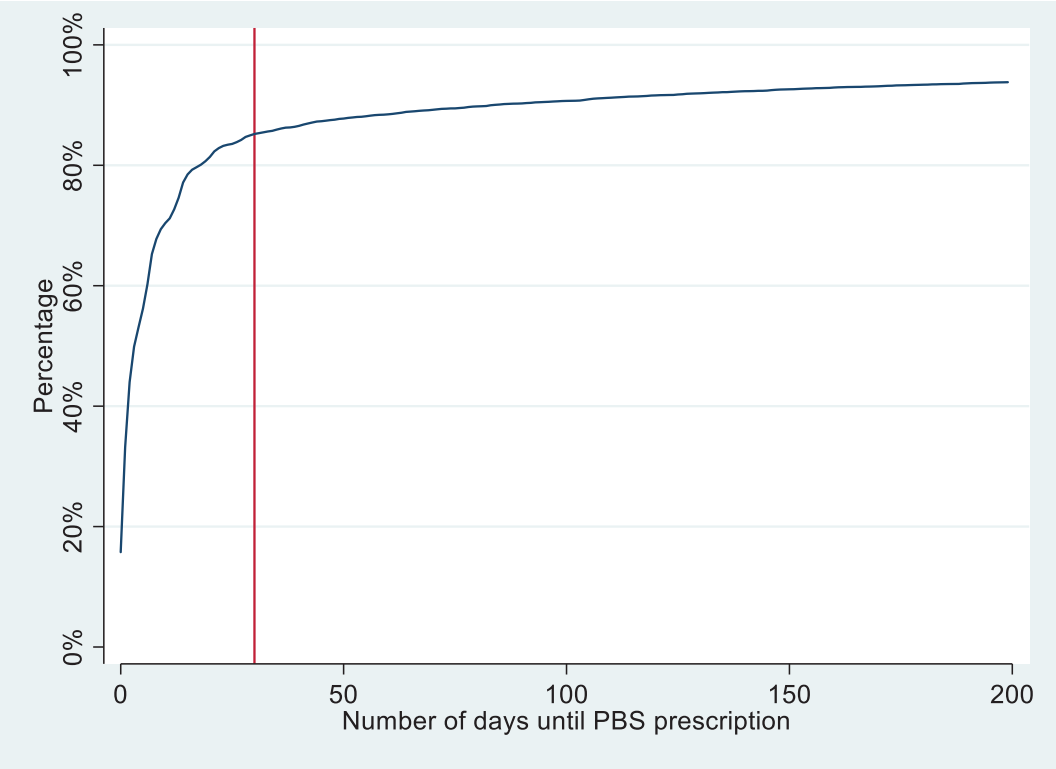
The temporal relationship between the supply of a pharmaceutical and the MBS infusion is shown below in Figure 17. The absolute number of days’ difference between the date of supply of the intravenous prescription and the closest MBS chemotherapy infusion is shown on the x-axis. The y-axis illustrates the percentage of the total number of chemotherapy treatments that occurred below that number of days. As can be seen, most pharmaceutical dispensing items were associated with an infusion item recorded within seven days (79%). 97% of intravenous prescriptions had an associated infusion recorded within 30 days and 99% within 60 days. There is a strong relationship between the date of dispensing an intravenous pharmaceutical and an administrative recording for an MBS item for infusion. This gives confidence that the pharmaceuticals that are prescribed were associated with the delivery of a chemotherapy treatment.



Note: This analysis was conducted on the whole EoCC cohort.
Abbreviations: MBS: medical Benefits schedule; PBS: Pharmaceutical Benefits Scheme

Figure 17: Time interval between PBS date of supply and the closest temporal MBS infusion reimbursement

The converse relationship between the PBS and MBS is from infusions to prescriptions. That is, given an infusion item is identified in the MBS data, what is the relationship between such an item and PBS prescriptions for intravenous chemotherapy agents? This is shown in Figure 18 below. The closest PBS date of supply is generated for each infusion. The situation here is different to the mapping from PBS to MBS. There is a larger proportion of the chemotherapy MBS items for which there is not a corresponding supply of an intravenous pharmaceutical sufficiently close, in terms of time. Infusion items were associated with the supply of a pharmaceutical recorded within seven days (65%). Eighty-five per cent of infusions had an associated pharmaceutical recorded within 30 days and 88% within 60 days.



Note: This analysis was conducted on the whole EoCC cohort
Abbreviations: MBS: Medical Benefits Schedule; PBS: Pharmaceutical Benefits Scheme

Figure 18: Time interval between MBS infusion and closest temporal PBS date of supply

Table 32 below shows the numbers of infusions that were recorded at least 30, 60 and 100 days from a prescription for intravenous chemotherapy. It shows that the "excess" infusions are concentrated in metastatic cancer with regards to stage and breast cancer with regards to site. There are very few "excess" infusions in the NSCLC group.

Table 32: Number of infusions without a PBS prescription by stage and site within 30, 60 and 100 days

	30 days			60 days			100 days		
	Not Met	**Met**	**Total**	**Not Met**	**Met**	**Total**	**Not Met**	**Met**	**Total**
Breast	223	1 192	1 415	181	1 053	1 234	142	930	**1 072**
CRC	36	403	439	24	284	308	18	223	**241**
NSCLC	9	31	40	1	9	10	1	4	**5**
Total	**268**	**1 626**	**1 894**	**206**	**1 346**	**1 552**	**161**	**1 157**	**1 318**

Abbreviations: CRC: colorectal cancer; Met: metastatic; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

Trastuzumab could be one source of the "excess" infusions relative to prescriptions. Trastuzumab is prescribed in either a 21-day cycle or a 7-day cycle when used for metastatic treatment of breast cancer.[183,184]

Table 34 below shows, for metastatic disease, the breakdown of infusions that are more than 60 days distant from a prescription for an intravenous infusion, by the type of cancer and the

presence or absence of trastuzumab according to the oncologist's review. Most of the "excess" infusions are associated with metastatic breast cancer and within breast cancer are more likely to occur with the use of trastuzumab. It appears that the group of patients who received trastuzumab as identified by the oncologist's review were responsible for approximately half of the "excess" infusions.

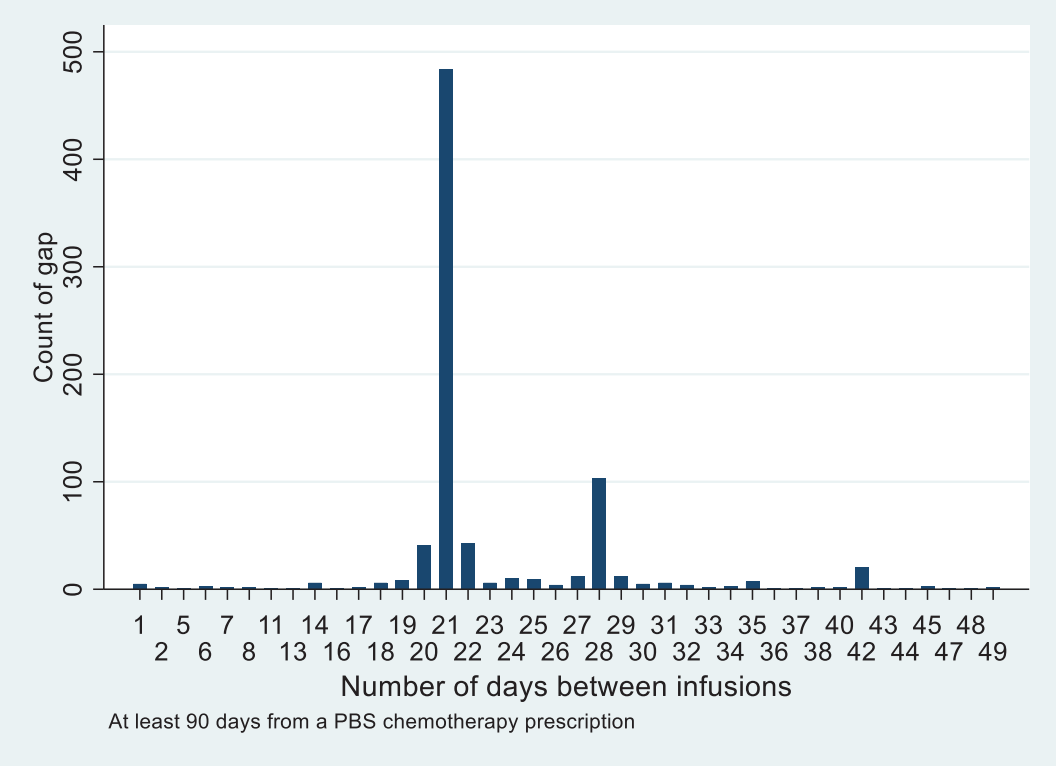
Table 33: Metastatic cancer "excess" infusions by site and history of trastuzumab use

Site	No history of trastuzumab	History of trastuzumab	Total
Breast	382	618	**1,000**
CRC	284	0	**284**
NSCLC	9	0	**9**
Total	**675**	**618**	**1 293**

Note: This analysis was only conducted on the 232 participants with metastatic disease in the EoCC cohort
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

There was a total of 7 201 infusions for the metastatic subgroup of EoCC participants; approximately one-sixth of infusions were delivered some distance from a corresponding PBS script. Accordingly, the use of PBS administrative data may underestimate the use of chemotherapy by at least one-sixth.

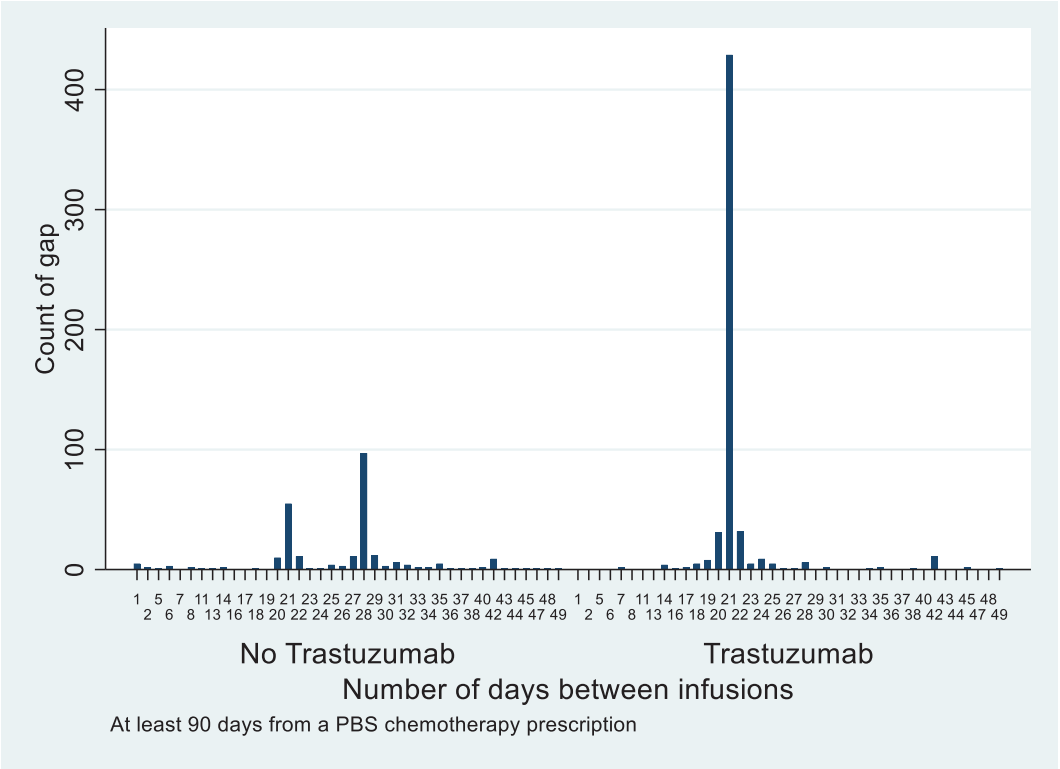
The gap between sequential administrations gives some indication of the character of the "excess" infusions. For a protocol, administration usually occurs in a regular sequence. Table 34 shows the frequency of the gaps between the recording of MBS infusion items for chemotherapy for metastatic breast cancer when the administrations are greater than 90 days distant from a PBS supply of an intravenous chemotherapy agent. There is a peak at 21 days and a much smaller peak at 28 days. This may indicate that the infusions are associated with the administration of treatments and are not random.



Abbreviation: PBS: Pharmaceutical Benefits Scheme

Table 34: Count of gap between successive "excess" infusions for metastatic breast cancer

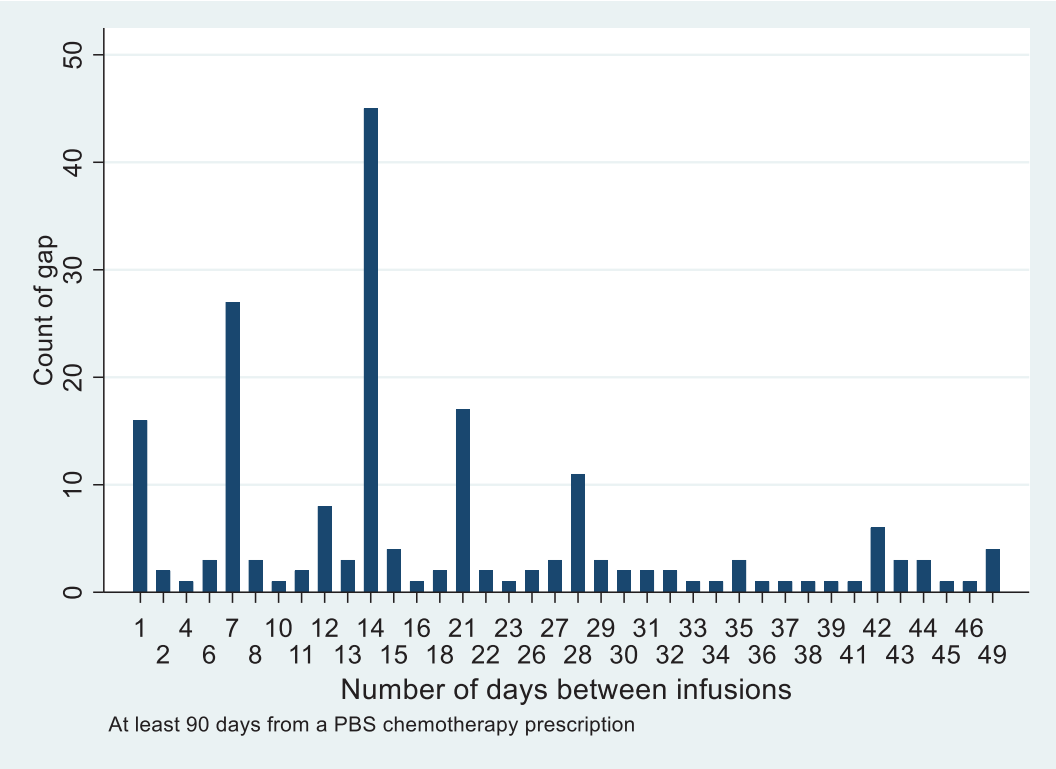
This information is divided into those with an identified history of trastuzumab use and those who had not received it according to the oncologist's review. As is evident, the presence of infusions outside the 90-day period is heavily influenced by the genetic status of the tumour. Those participants with previously identified trastuzumab use had significantly more infusions and were more likely to have a 21-day gap between infusions. Those without an identified history of trastuzumab use had fewer "excess" infusions identified and were more likely to be on a 28-day than a 21-day cycle.



Abbreviation: PBS: Pharmaceutical Benefits Scheme

Table 35: Gap between successive "excess" infusions for metastatic breast cancer by recorded use of trastuzumab

A similar pattern is not seen for metastatic CRC. For this disease several different multiples of 7 days are seen, namely 7, 14, 21, 28, 35, 42, 49. Unlike breast cancer, is it difficult to be confident about what pharmaceuticals are provided in the CRC setting. However, the "excess" infusions are not random but rather in a pattern that is consistent with a treatment sequence.

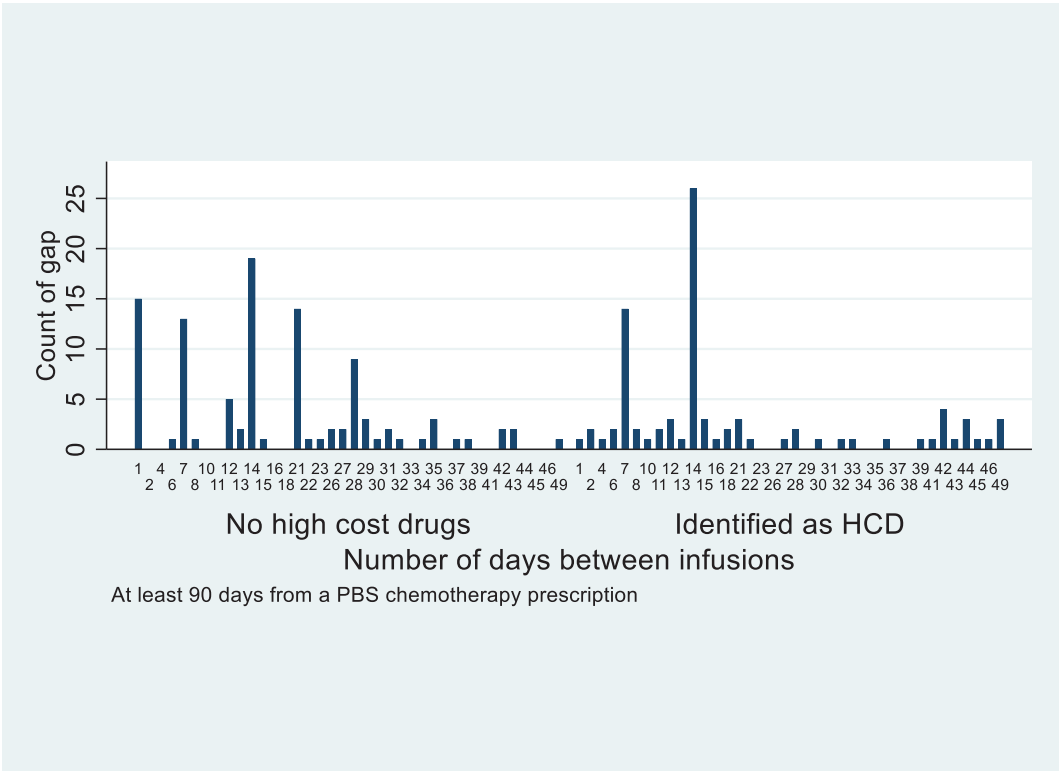


Abbreviation: CRC: colorectal cancer; PBS: Pharmaceutical Benefits Scheme

Table 36: Gap between successive "excess" infusions for metastatic CRC

It is difficult to be confident about the actual chemotherapy that might be received in this case. While oxaliplatin and irinotecan are often given in a 14-day cycle, 5-FU, bevacizumab, cetuximab and panitumumab might be given in a shorter time frame. Different patterns are observed in the number of days between infusions if the EoCC participants are divided into those identified as having received non-PBS bevacizumab, cetuximab and panitumumab and those who did not.

Figure 19 below shows the breakdown between the "excess" infusions that are associated with participants with and without the high cost pharmaceuticals identified in the oncologist's review. The average number of "excess" infusions in the high cost drug group was 7.2 infusions, whereas in the group identified by the oncologist's review as not having used high cost pharmaceutical the average number of "excess" infusions was 1.6. This difference was statistically significant. The pattern of administration was also different between the two groups. The high cost pharmaceutical group was more likely to have a 7 or 14-day gap between infusions while infusions in the no high cost pharmaceutical group were spread over a greater number of multiples of seven.



Abbreviations: CRC: colorectal cancer; HCD: high cost drug

Figure 19: Gap between successive "excess" infusions for metastatic CRC by history of use of high cost pharmaceuticals (HCD)

The main reason for considering the issue of "excess" infusions is that their presence implies the use of chemotherapy not captured by the PBS data. This has impacts for both the costs and the consideration of the lines of therapy.

There are many alternative explanations for the chemotherapy associated with "excess" infusions not appearing in the PBS. One plausible explanation is that this chemotherapy was supplied using funding from another source such as the Herceptin Program, private funding from the patient or charitable organisation, public hospitals, potentially trials or compassionate programs funded by pharmaceutical companies or health insurance companies.[185] Other explanations could include miscoding or errors in the dates of provision of chemotherapy services or infusion. However, the consistency of the results would argue against these latter explanations. Most of the "excess" infusions were supplied to participants that received a high cost pharmaceutical, such as trastuzumab, cetuximab, panitumumab or bevacizumab.

Use of chemotherapy in hospital admission data

As discussed previously, the EoCC linked dataset included hospital admission data, including DRG (Diagnostic Related Groups) information. One of the day admissions recorded is a chemotherapy admission. This is coded by the AR-DRG R63Z. Two key issues were investigated

below: i) is there a relationship between the AR-DRG and the PBS administrative data for chemotherapy and ii) is there a relationship between the AR-DRG and the MBS administrative data for infusions. That is, does the addition of the AR-DRG for chemotherapy add to the information that has been generated using both MBS and PBS items?

The admission data included the month and year of both admission and separation in which the AR-DRG occurred but not the actual dates. However, the date of the procedure component of the data included year, month and date. It is assumed that the date of procedure accurately captured the date of the chemotherapy infusion associated with the AR-DRG R63Z code. The dates of the AR-DRG for chemotherapy (R63Z) were compared to the dates of MBS chemotherapy infusion items.

The length of stay for all the recorded AR-DRG R63Z was 1 day, providing some reassurance that the use of the date of procedure is appropriate. For the full dataset, only 215 participants had an AR-DRG R63Z. When the centres who recruited EoCC participants were compared, five centres had a record of a participant with the AR-DRG R63Z and seven centres did not have a record of an AR-DRG R63Z code. The private hospitals were all included in the centres that had AR-DRGs for chemotherapy available. This pattern was repeated for the 232 participants for whom full information was available. This suggests that the chemotherapy AR-DRG is not consistently recorded in a similar way across institutions.

As expected in New South Wales (which has privatised out of hospital chemotherapy facilities), 97% of the chemotherapy AR-DRG instances were classified as referring to private patients regarding payment status. As expected, a majority (93%) had as their recorded principal procedure “administering an anti-neoplastic agent.” The next most common principal procedure was “loading of an implantable device with an anti-neoplastic agent.” The relationship between the AR-DRG items for chemotherapy and the MBS items for cytotoxic infusions was explored. Over 80% of the AR-DRGs for chemotherapy occurred on the same day as an MBS chemotherapy infusion. There were 317 incidences of chemotherapy AR-DRGs for 13 patients for which there were no MBS data for infusions.

However, the AR-DRG does indicate when and where certain events are occurring; if the AR-DRG code and the infusion code for the MBS occurred on the same day, it implies that they occurred in the same place and potentially for the same activity. There was a corresponding AR-DRG admission where a combination of MBS, non-chemotherapy PBS and admitted data linked data were observed and when the MBS infusions were greater than 100 days distant

from the PBS chemotherapy script dispensed. This confirms that these occurrences represent chemotherapy use that is not present in the PBS administrative data.

The MBS administrative data for the EoCC cohort do not provide information about which hospital was used to deliver chemotherapy. However, approximately two-thirds of the MBS infusion items that were 100 days from the dispensing of a PBS chemotherapy script and had a corresponding AR-DRG occurred at a private facility. Most participants recruited from private hospitals had breast cancer and were treated with trastuzumab. Almost all the CRC treatments for which there were no corresponding treatments observed in the PBS data were also provided by private facilities.

The procedure codes were also used to search the non-chemotherapy admissions to see if chemotherapy was administered in other situations. There were 489 admissions for which the procedure codes included either (96199-00) or (96207-00). Of these admissions, 435 (89%) admitted patients had a length of stay of one day. All the one day admissions where MBS data were available received an infusion on the same day but only 15% had a PBS chemotherapy script dispensed on the same day. However, 90% had a PBS prescription dispensed within 30 days. 90% of the activity that was not attributed to the chemotherapy AR-DRG but had a procedure code consistent with the administration of chemotherapy can be attributed to one centre.

Therefore, the AR-DRG codes did not add any more information than that provided by the MBS items about the use of chemotherapy to treat the EoCC cohort. However, the AR-DRG information provides an indication of where some of chemotherapy treatment occurred. This information supports the notion that different unidentified treatments may have been given to patients recruited at private and public facilities. Patients with CRC and AR-DRG information were more likely to be treated in a private facility. Overall, in relation to the EoCC data, MBS and PBS items provide a good indication of the use of intravenous chemotherapy whereas the addition of AR-DRG information is of limited value. It is, however, worth noting that the use of AR-DRGs and the choice of code appeared to be institution specific. This may have some impact on costs.

PBS treatments associated with chemotherapy

Another potential method of identifying the administration of chemotherapy treatment is to look for other treatments that are potentially given alongside chemotherapy. To examine this

issue, the top ten protocols (listed above in Figure 15) were examined in the EViQ database and other therapies that may be used alongside tabulated.

Many items that are prescribed alongside chemotherapy are non-specific and fall below the co-payment threshold. These items include ranitidine, dexamethasone, metoclopramide and chlorpromazine. These supportive therapies were not examined as an indicator of chemotherapy use because of their non-specific nature.

Pharmaceuticals that fall above the co-payment threshold included the 5-HT receptor antagonists and aprepitant prescribed for nausea, and G-CSF prescribed for prevention or treatment of neutropenia. Most of these have specific indications in support of the use of chemotherapy.

Table 37 shows the relationship between these supportive indicators of chemotherapy use and PBS chemotherapy identification. As can be seen, the use of PBS supportive therapy temporally distant from the use of chemotherapy is relatively rare.

Table 37: Use of supportive treatment and relationship to use of PBS chemotherapy

Indicator	Number of participants recording use without chemotherapy	Number occurring with 30 days of chemotherapy	Number occurring greater than 30 days from chemotherapy	Number occurring in 100 or more days
Aprepitant	1 (6 episodes)	682	38	12
5-HT3 antagonist	4 (9 episodes)	2 903	138	46
G-CSF	0	8	0	0

Note: This analysis was conducted on the whole EoCC cohort.
Abbreviations: 5-HT3: 5-hydroxytryptamine 3 (receptor antagonist); G-CSF: granulocyte-colony stimulating factor

Most of the use of chemotherapy supportive treatments occurred temporally adjacent to the use of an MBS chemotherapy infusion. Less than 3% of the aprepitant prescriptions occurred greater than 30 days away from an MBS chemotherapy infusion item (the corresponding figure for a PBS chemotherapy item was 5%). 3% of prescriptions for 5-HT3 receptor antagonists also occurred greater than 30 days distant from an MBS chemotherapy infusion item (again the corresponding figure for a PBS chemotherapy item was 5%). The percentage of aprepitant prescribing that occurred greater than 30 days from either an MBS item or a chemotherapy PBS item was less than 1% for both aprepitant and 5-HT3 receptor antagonists. The raw figures are shown in Table 38 and Table 39.

Table 38: Time from PBS chemotherapy items and MBS chemotherapy infusion item to the prescribing of aprepitant

Time to closest PBS chemotherapy record	Time to closest MBS chemotherapy infusion				
	30 days or less	31-99 days	100+ days	Missing MBS	Total
30 days or less	617	10	5	12	**644**
31-99 days	18	0	4	4	**26**
100+ days	12	0	0	0	**12**
Missing PBS	6	0	0	0	**6**
Total	**653**	**10**	**9**	**16**	**688**

Note: This analysis was conducted on the whole EoCC cohort
Abbreviations: MBS: Medical Benefits Schedule; PBS: Pharmaceutical Benefits Scheme

Table 39: Time from PBS chemotherapy items and MBS chemotherapy infusion items to the prescribing of 5-HT3 receptor antagonists

Time to closest chemotherapy record	Time to closest MBS chemotherapy infusion				
	30 days or less	31-99 days	100+ days	Missing MBS	Total
30 days or less	2 680	31	19	35	**2 765**
31-99 days	69	11	7	5	**92**
100+ days	34	2	9	1	**45**
Missing PBS	8	0	0	1	**9**
Total	**2 791**	**44**	**35**	**42**	**2 912**

Note: This analysis was conducted on the whole EoCC cohort.
Abbreviations: 5-HT3: 5-hydroxytryptamine 3 (receptor antagonist); MBS: Medical Benefits Schedule; PBS: Pharmaceutical Benefits Scheme

This suggests that there is limited value in using the supportive PBS therapies in addition to the combination of MBS and PBS items to identify the administration of chemotherapy. Less than a one per cent increase in the number of chemotherapy treatments is inferred by the supportive treatments compared to the combination of PBS and MBS data.

4.4.5 Discussion and conclusion

Pharmaceuticals that would be relevant to the determination of the number of lines of therapy a patient has had (including high cost pharmaceuticals) were missing from the PBS administrative data. The oncologist's review, the Herceptin Program and the comparison of MBS and PBS items all confirmed that the PBS data was incomplete regarding anticancer pharmaceutical treatments.

There was also substantial heterogeneity between types of cancer and potentially missing treatments. NSCLC and non-metastatic cancer were less likely to be identified as missing treatments. Breast cancer, CRC and metastatic cancer were more likely to be identified as

missing treatments from the PBS administrative data. One possibility is that alternative methods were used to fund these chemotherapy treatments.

Several alternative means of funding cancer treatment were - and remain - available. These include private financing, compassionate programs funded by pharmaceutical companies or health insurers and funding from the State (mainly but not exclusively hospitals). The presence or absence of these alternative methods of funding care have significant implications for the accuracy of the conclusions that can be drawn from the use of the PBS administration data.

Previous funding decisions such as the implementation of the Herceptin Program have resulted in missing PBS data. The lack of recording of use of pharmaceuticals that fall below the co-payment over the period of the study is another source of missing PBS data. Both mechanisms which resulted in missing data have been corrected for contemporary data.[172,175]

Obviously, the use of pharmaceuticals not subsidised by the PBS will also be missing. There is some suggestion that high cost pharmaceuticals fall into this category, especially during the time close to their consideration and acceptance by the PBAC. Non-subsidisation will continue to be a potential reason for information to be missing about treatments.

A review of the timing of the MBS chemotherapy items in relation to the PBS chemotherapy supply strongly suggested that a substantial amount of chemotherapy treatment was missing from the PBS chemotherapy records. It is assumed that this is partly explained by the three weekly treatments associated with trastuzumab for metastatic breast cancer. However, there are also additional four weekly treatments for breast cancer and extra treatments for CRC that are unaccounted for in the PBS records. Up to one-sixth of the infusions identified by the MBS administrative data did not have had the corresponding chemotherapy treatment identified from the PBS data.

The use of the AR-DRG codes corresponding to chemotherapy use did not add to the information provided by the combination of PBS and MBS administrative data. However, the use of these codes reinforced the presence of chemotherapy administration not captured in the PBS data. Institutions were found to be inconsistent as to whether they recorded AR-DRG information and the type of code they used, with some potential implications for assessing costs. The consideration of the use of supportive treatments for chemotherapy did not add any information to the combination of the PBS and MBS administrative data.

The strong relationship between the coding of chemotherapy administration within the EoCC MBS administrative dataset and the AR-DRG strongly suggests these two datasets are counting the same activity. Care should be taken not to double count this activity when costs are attributed to the activities (see Section 5.2).

The comparison between the PBS and MBS items was a useful way of checking for completeness of anticancer treatments. It may be an appropriate method to demonstrate the completeness (or otherwise) of data on anticancer treatments for future costing or cost-effectiveness studies in Australia.

The approach taken in this Section is translatable to other datasets in Australia. Nonetheless, it is not clear that this would produce similar results because of the differences in the administration of the PBS section 100 schemes. The wide variety of models used for the funding of chemotherapy means that the external validity of the analysis of the EoCC administrative data is open to question in other jurisdictions.

4.5 Use of the PBS to estimate the number of lines of therapy

This Section aims to:

1. establish an algorithm for estimating the number of lines of therapy using the PBS administrative data; and
2. apply the algorithm to the second data extraction of the EoCC cohort.

The number of lines of therapy was estimated using the PBS administrative data as part of the EoCC study. This was undertaken using a similar method to the estimation of new pharmaceutical use (oncologist's review), where the addition of each new pharmaceutical was assumed to comprise a new line of therapy (see Section 4.3). However, in the assessment below, all pharmaceuticals that were initiated within a specified period were considered part of one protocol and therefore one line of therapy.

The reason for including a period is that some protocols consist of multiple pharmaceuticals. These pharmaceuticals could also be used to treat the cancer as individual therapies. The importance of considering multiple pharmaceuticals as a single protocol and line of therapy was demonstrated in Section 4.3 in the discussion of the oncologist's review of the lines of therapy.

The period of time approach was used to group pharmaceuticals that were considered likely to be part of the same protocol. A similar approach was used to calculate lines of therapy from

administrative databases in the United States.[186] Seal et al. (2014)[186] used 36 days as the timeframe to determine a new line of therapy in CRC patients. That is all new pharmaceuticals used with a 36-day span were considered to be part of the same protocol and line of therapy. Other studies have used 28 days.[187] Previous Australian research using the EoCC dataset suggested that 42 days was the most appropriate length.[161]

Table 40 illustrates how the calculation of the number of lines of therapy was operationalised for a pair of hypothetical patients. Both patients were commenced on 5-FU: one received oxaliplatin within a week of starting treatment with 5-FU, the other commenced the new treatment over 3 months later (100 days). Both patients then received irinotecan 200 days after starting 5-FU.

In this example, the period for considering all new pharmaceuticals as part of the same protocol or line of therapy was 30 days. So patient A and patient B both received the same pharmaceuticals, but patient A received two lines of therapy (FOLFOX and FOLFIRI) while patient B received three lines of therapy (5-FU, FOLFOX and FOLFIRI).

Table 40: Hypothetical generation of lines of therapy in CRC

Day	Patient A		Patient B	
	New Pharmaceutical	**Decision**	**New Pharmaceutical**	**Decision**
1	5-FU	New line of therapy	5-FU	New line of therapy
7	Oxaliplatin	Within 30 days so not a new line of therapy		
100			Oxaliplatin	New line of therapy as given over 30 days later
200	Irinotecan	Over 30 days since oxaliplatin so a new line of therapy	Irinotecan	Over 30 days since oxaliplatin so a new line of therapy

Abbreviation: 5-FU: 5-fluorouracil

This approach had two weaknesses. First it excluded non-PBS therapies, so new and experimental lines of therapy were not captured. It has been demonstrated that pharmaceutical use is missing from the administrative data (see Section 4.4). Second, the method of determining the lines of therapy was sensitive to the timing used to determine a single line of therapy when multiple pharmaceuticals are used in a protocol. This latter scenario was more likely to be an issue in the case of non-small cell lung cancer, given the

potential for treatment with two agents (e.g. cisplatin and gemcitabine) to be followed by the use of planned maintenance therapy with a third agent (e.g. pemetrexed). In this case, because there was no failure of treatment, the third pharmaceutical introduced 90 days after the first two agents was not a new line of therapy. However, if progression or unacceptable toxicity had occurred, pemetrexed would have been another line of therapy. It cannot be determined with certainty which scenario occurred.

4.5.1 Methods

The method used to enumerate the lines of therapy using PBS administrative data was to consider only the 232 participants with metastatic disease whose hospitalisation and registry data were also available via the CHeReL. Only the PBS administrative data available prior to the oncologist's review (the first EoCC data extraction, see Figure 14) was included to facilitate comparison. The steps taken for the assessment are detailed below.

1. Pharmaceuticals with an ATC classification beginning with "L01", which correspond to the anti-neoplastic subgroup, were included. Pharmaceuticals without an ATC classification beginning with "L01" were discarded.
2. Methotrexate, chlorambucil, mercaptopurine, fotemustine and hydroxyurea were excluded. Methotrexate was excluded because it is used to treat patients with several conditions other than cancer, such as rheumatoid arthritis and inflammatory bowel disease. When it is used in the treatment of breast cancer, it is in combination with other treatments; thus, its exclusion should result in a lack of false positives but not create false negatives. Hydroxyurea was excluded because it was associated with participants who had a previous diagnosis of lymphoma and was not listed as usual treatment for the cancers of interest according to the linked central cancer registry. Fotemustine, chlorambucil and hydroxyurea were excluded for the same reason.
3. Pharmaceuticals were grouped together if one was a pro-drug for another, for example, 5-FU and capecitabine were grouped together. Capecitabine is converted to 5-FU after ingestion and therefore is considered a pro-drug.
4. The date of supply in the PBS administrative data was used to order all the pharmaceuticals received by each participant. Then the gap between the supply dates was calculated retrospectively from the recruitment date. If that gap was greater than 270 days, then the preceding pharmaceuticals were discarded. This was on the assumption that treatment prior to this point was treatment for adjuvant or early cancer and not metastatic disease.

5. From the assumed point of use of the first pharmaceutical with an ATC classification of L 01 (the first retained date of service) all new pharmaceuticals in the next 38 days were considered part of the same protocol and the same line of therapy.
6. A new pharmaceutical outside the first 38 days was considered the start of a new line of therapy.
7. All new pharmaceuticals used within 38 days of the start of the new line of therapy (step 6) were considered part of the same protocol and the same line of therapy.
8. In the absence of any information about the use of pharmaceuticals, that is no ATC classification of "L 01", it was assumed that all patients were undergoing their first line of therapy. This is because all recruited participants were already receiving chemotherapy. This ensured the number of participants remained 232.

Several sensitivity analyses were undertaken.

1. The number of days required for a new protocol to commence was varied from 20 to 60 (substituted into step 5 and step 7 above).
2. Trastuzumab, cetuximab and cyclophosphamide were removed from both the oncologist review and the PBS data.
3. Step 4 was removed.
4. Only prospective data were included in the analysis, that is, the line of therapy at the point of recruitment and onward.
5. Only prospective data excluding trastuzumab were included in the analysis.

The number of lines of therapy calculated using the PBS administrative data were compared to the number of lines of therapy calculated using the new pharmaceutical use (oncologist's review) method detailed in Section 4.3. Agreement and correlation were calculated. Kappa statistics were calculated as was agreement and weighted agreement. The most appropriate length of time for a protocol was chosen by the length with the highest z-score for unweighted agreement.

The first and second extraction of the EoCC PBS data including the extraction after the oncologist's review (see Figure 14) was also used to estimate the total number of lines of therapy. This was estimated in the EoCC metastatic cohort using the most appropriate length of time as estimated above.

4.5.2 Results

Table 41 presents the number of lines of therapy calculated using the PBS method using different numbers of days to classify new pharmaceuticals as part of the same protocol. Most patients received more than one line of therapy. Approximately 13% received four or more lines of therapy. The average number of lines of therapy across all patients was 2.21 (for 46 days), compared to 2.5 estimated using the new pharmaceutical use (oncologist's review) method as outlined in Section 4.3. Decreasing or increasing the number of days for which all new pharmaceuticals were included in the same line of therapy did not make a substantial difference. The number of days with the highest weighted agreement was 46.

Table 41: Number of lines of therapy using the PBS method

Number of days for new pharmaceuticals to be included in protocol	Mean number of lines of therapy	Mean number of lines of therapy for breast cancer	Mean number of lines of therapy for colorectal cancer	Mean number of lines of therapy for NSCLC	Percentage of cohort with four or more lines of therapy
20	2.45	2.53	2.16	3.00	19.0%
22	2.41	2.51	2.13	2.89	17.7%
24	2.40	2.50	2.10	2.87	17.2%
26	2.38	2.49	2.06	2.87	15.9%
28	2.37	2.48	2.06	2.87	15.5%
30	2.32	2.46	1.99	2.82	15.5%
32	2.30	2.46	1.93	2.82	15.1%
34	2.29	2.45	1.93	2.82	14.7%
36	2.28	2.45	1.90	2.79	14.7%
38	2.25	2.43	1.89	2.74	13.8%
40	2.25	2.43	1.88	2.74	13.8%
42	2.23	2.43	1.83	2.71	13.4%
44	2.22	2.42	1.83	2.68	13.4%
46	2.21	2.41	1.82	2.68	13.4%
48	2.21	2.41	1.82	2.68	13.4%
50	2.19	2.38	1.80	2.66	13.4%
52	2.16	2.38	1.78	2.55	12.9%
54	2.16	2.38	1.78	2.53	12.9%
56	2.14	2.37	1.75	2.53	12.9%
58	2.12	2.36	1.73	2.47	12.5%
60	2.11	2.35	1.73	2.47	12.5%

Abbreviation: NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

The number of lines of therapy received differed depending on which of the two methods was used. The PBS method resulted in a lower mean number of lines of therapy than the new pharmaceutical use (oncologist's review). This difference was most pronounced for breast

cancer where the difference in the mean number of estimated lines of therapy was 0.6. The differences were smaller for CRC and NSCLC (Table 42). Thus, the two methods of estimating the lines of therapy do not agree and there appears to be a systematic difference.

Table 42: Differences in estimated number of lines of therapy between the PBS method and the oncologist's review method

Cancer site	Mean using PBS method	Mean using oncologist review	Agreement	Expected agreement	Mean difference (standard deviation)	Spearman coefficient
All	2.21	2.50	49%	24%	-0.28 (1.07)	0.60 (p<0.01)
Breast	2.41	3.0	39%	19%	-0.63 (1.23)	0.58 (p<0.01)
CRC	1.82	1.94	56%	31%	-0.13 (0.86)	0.57 (p<0.01)
NSCLC	2.68	2.48	55%	26%	0.21 (0.81)	0.74 (p<0.1)

Note: Oncologist's review is the new pharmaceutical use (oncologist's review) as described in Section 4.3
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

This difference was potentially explained by variations in protocols and some of the issues described above concerning the PBS data. Trastuzumab was systematically missing from the PBS data, as was cetuximab. Cyclophosphamide's first identification in the EoCC PBS data might be associated with the financial co-payment threshold being reached rather than because a new line of therapy was commenced (see Section 4.4).

Each of these pharmaceuticals were individually removed from both the PBS data and the new pharmaceutical use (oncologist's review) to determine whether there was a change in the level of agreement (Table 43). The results were sensitive to the exclusion of trastuzumab and the assumptions about adjuvant treatment. Excluding trastuzumab and the assumption around adjuvant treatment improved the agreement between the two methods of estimating the lines of therapy.

Table 43: Differences in estimated number of lines of therapy between PBS method and the new oncologist's review with removal of specific pharmaceuticals and assumptions

Cancer site	Removal (Best kappa z-score)	Mean using PBS method	Mean using oncologist review	Agreement	Expected agreement	Mean difference (standard deviation)
All	Trastuzumab	2.21	2.4	48%	24%	-0.19 (1)
Breast	(46 days)	2.41	2.84	38%	20%	-0.42 (1.2)
CRC		1.82	1.94	56%	31%	-0.13 (0.86)
NSCLC		2.68	2.48	55%	26%	0.21 (0.81)
All	Cetuximab	2.21	2.5	49%	24%	-0.28 (1.1)
Breast	(46 days)	2.41	3.0	39%	19%	-0.63 (1.23)
CRC		1.82	1.93	56%	32%	-0.11 (0.84)
NSCLC		2.68	2.48	55%	26%	0.21 (0.81)
All	Cyclophosphamide	2.17	2.49	48%	24%	-0.32 (1.0)
Breast	(44 days)	2.32	3.0	37%	19%	-0.7 (1.2)
CRC		1.83	1.95	57%	31%	-0.11 (0.86)
NSCLC		2.66	2.47	55%	26%	0.18 (0.77)
All	Assumption of	2.44	2.5	50%	24%	-.04 (1)
Breast	adjuvant	2.84	3	40%	20%	-0.2 (1.2)
CRC	treatment	1.94	1.94	58%	31%	0 (0.83)
NSCLC	(46 days)	2.73	2.47	55%	27%	0.26 (0.79)
All	Trastuzumab and	2.43	2.4	50%	24%	0.02 (1)
Breast	assumption of	2.8	2.8	41%	20%	0 (1.1)
CRC	adjuvant	1.94	1.94	57%	31%	0 (0.83)
NSCLC	treatment (46 days)	2.74	2.47	55%	27%	0.26 (0.79)

Note: Oncologist's review is the new pharmaceutical use (oncologist's review) as described in Section 4.3
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

The level of agreement in results between the two methods of estimating number of lines of therapy also improved when only prospective information was considered (Table 44). Agreement remained weakest for breast cancer. Marginal improvements in agreement occurred when trastuzumab was excluded (Table 45). The time span for including all new pharmaceuticals in a single protocol maximised agreement at 50 days, slightly higher than when the retrospective data were included.

Table 44: Differences in estimated number of prospective lines of therapy between the PBS method and the oncologist's review

Cancer site	Mean using PBS method	Mean using oncologist review	Agreement	Expected agreement	Mean difference (standard deviation)	Spearman coefficient
All	1.53	1.69	66%	42%	-0.20 (1.07)	0.54 (p<0.01)
Breast	1.54	1.82	62%	39%	-0.27 (0.74)	0.6 (p<0.01)
CRC	1.31	1.46	68%	52%	0.16 (0.7)	0.35 (p<0.01)
NSCLC	1.84	1.95	71%	32%	-0.1 (0.7)	0.67 (p<0.01)

Note: Oncologist's review is the new pharmaceutical use (oncologist's review) as described in Section 4.3

Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

Table 45: Differences in estimated number of prospective lines of therapy between the PBS method and the oncologist's review excluding trastuzumab

Cancer site	Mean using PBS method	Mean using oncologist review	Agreement	Expected agreement	Mean difference (standard deviation)	Spearman coefficient
All	1.49	1.68	66%	42%	-0.18 (0.7)	0.54 (p<0.01)
Breast	1.54	1.79	64%	39%	-0.24 (0.71)	0.6 (p<0.01)
CRC	1.31	1.46	68%	52%	0.16 (0.7)	0.35 (p<0.01)
NSCLC	1.84	1.95	71%	32%	-0.1 (0.7)	0.67 (p<0.01)

Note: Oncologist's review is the new pharmaceutical use (oncologist's review) as described in Section 4.3
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer; PBS: Pharmaceutical Benefits Scheme

The analysis thus far has been restricted to the EoCC PBS administrative data for which the oncologist's review was available following the first data extraction. The number of lines of therapy was estimated using the first and second EoCC PBS data extractions (see Figure 14). The length of time in which new pharmaceuticals were allocated to the protocol and thus the same line of therapy was 46 days.

The mean lines of therapy in the first data extraction was 2.21 and the mean number of lines of therapy for both data extractions was 2.36. Table 46 shows that tabulation of the lines of therapy. The combination of the two data extractions demonstrates a larger proportion of the

EoCC metastatic cohort received four or more lines of therapy. The difference between the two estimates was the greater amount of censoring in the first data extraction.

Table 46: Breakdown of lines of therapy by data extraction

Number of lines of therapy	PBS data to June 2010 (first data extraction)	Percentage of participants with greater than three lines of therapy	PBS data to June 2014 (second data extraction for the 2010 cohort)	Percentage of participants with greater than three lines of therapy
1	82		70	
2	68		68	
3	51		53	
4	18	13%	26	18%
5	9		11	
6	3		3	
7	1		1	

Abbreviation: PBS: Pharmaceutical Benefits Scheme

4.5.3 Discussion and conclusions

For breast cancer, the differences between the methods in terms of estimates of the mean lines of therapy can be partially explained by the absence of trastuzumab in the PBS data. This absence produced a systematic bias. The performance of the PBS data for estimating the lines of therapy improved when trastuzumab was not excluded from consideration.

For CRC and NSCLC, comparison between the new pharmaceutical use (oncologist's review) method and the PBS method suggested that the PBS method excluded newer pharmaceuticals that alter the estimated number of lines of therapy. Conversely, the oncologist's review did not include older pharmaceuticals, also altering the estimated number of lines of therapy. It is possible that both methods slightly underestimated the number of lines of therapy.

A retrospective review of the lines of therapy for patients receiving metastatic treatment requires assumptions about whether treatments are given for metastatic disease or adjuvant treatments (which subsequently failed). The estimation of the number of lines of therapy is sensitive to these assumptions. For this purpose, prospective data collections are superior to retrospective data collections in correctly assessing the number of lines of therapy.

The number of days within which new treatments should be assigned to the same protocol and line of therapy was higher in this analysis than observed in previous assessments.[161,186]

The first data extraction was used for the comparison with the oncologist's review because the data were common to both methods. Extending the algorithm to the combination of the first

and second EoCC PBS extractions increased the estimated number of lines of therapy received by the cohort. This difference is due to censoring.

4.6 Conclusions

One aim of this Chapter was to estimate the number of lines of therapy received by the EoCC cohort. It was found that, in clinical practice, receiving multiple lines of therapy was common, with the majority of participants (70%) receiving two or more lines of therapy. All methods for estimating the number of lines of therapy found that a minority of patients received four or more lines of therapy. However, the proportion varied significantly between the methods, with estimates ranging from 13% to 46%. Therefore, a substantial minority of participants received a greater number of lines of therapy than in the economic evaluations discussed in Chapter 3. This information is also used in Chapter 6 to conclude that the potential for displacement exists in Australia.

The external validity of these estimates is limited because of the use of retrospective data, the selection of participants who were actively receiving treatment in New South Wales and the censored nature of the data. The internal validity is limited by the fact that not all treatments, and therefore potentially not all lines of therapy, were captured in the data.

The results described in this Chapter may not be generalisable to the population of patients with metastatic cancer who are treated with chemotherapy. This is because the majority of participants in the EoCC study had already received chemotherapy prior to recruitment. Thus, the numbers of lines of chemotherapy may be biased upwards compared to participants recruited prior to receiving any treatment.

The other aim of this Chapter was to establish the validity of administrative data in estimating the number of lines of therapy. Several methods of examining the data demonstrated conclusively that not all treatments received were recorded in the administrative data. Comparison between the oncologist's review and the PBS data demonstrated that several treatments were missing from the PBS records, including several high cost pharmaceuticals. In turn, examination of PBS data suggested that several older pharmaceuticals were missing from the oncologist's review.

The presence of missing records of treatments was confirmed by an examination of the MBS infusion items which demonstrated that a minority of recorded infusions did not have PBS chemotherapy items associated with them. In this data collection, there were extra treatments for CRC and breast cancer, as evidenced by the MBS infusion items. The existence of extra

treatments was not shown for NSCLC using the same method of identification. Other methods of assessing the presence of extra treatments using the administrative data did not add to this conclusion.

The PBS method of estimating the number of lines of therapy predicted a similar number of lines of therapy compared to the new pharmaceutical use (oncologist's review), provided only prospective data was used and trastuzumab was removed from the data.

Additionally, treatments for metastatic disease were difficult to distinguish from treatments for early stage cancer which subsequently failed. This makes it difficult to assess the number of lines of therapy given for advanced disease and the length of time within each line of therapy.

The downward bias in identifying treatments using PBS administrative data impacted the estimation of the number of lines of therapy and the costs of chemotherapy. Not identifying treatments resulted in an under-estimation in the number of new protocols and new lines of therapy. The outcomes from treatments received but not recorded could mistakenly be attributed to treatment with the pharmaceuticals that are present in the PBS administrative data. Importantly, more expensive treatments such as cetuximab, bevacizumab and trastuzumab were missing from the administrative data and could have a strong effect on cost estimates.

Due to this uncertainty, it is concluded that administrative data available in Australia in 2010 was not appropriate to calculate the price changes required to account for displacement without significant caveats. One of the significant risks to the use of observational data for cost-effectiveness analysis - missing data - is prevalent in the PBS administrative data for the EoCC cohort.

However, since the period covered by the EoCC study there have been changes in the collection of administrative data, such as the inclusion of under co-payment pharmaceuticals and trastuzumab. Subsequently, some missing treatments may appear in a contemporary analysis of the PBS data, thus reducing the level of uncertainty. These changes, however, will not improve the identification of treatments not administered through the PBS.

Comparing the infusions in the MBS and the presence of oncology pharmaceuticals in the PBS is one method of demonstrating that additional treatments are used that are not included in the administrative data. This assessment should be conducted in future studies where the completeness of data about oncology treatments is important.

Chapter 5 Assessing the costs of lines of therapy

This Chapter uses administrative data to generate information about the time in each line of therapy, and the distribution of costs within and between lines of therapy. The Elements of Cancer Care (EoCC) cohort is used to estimate the costs and length of time for each line of therapy. This Chapter builds upon the estimation in Chapter 4 by including the costs of cancer care by line of therapy.

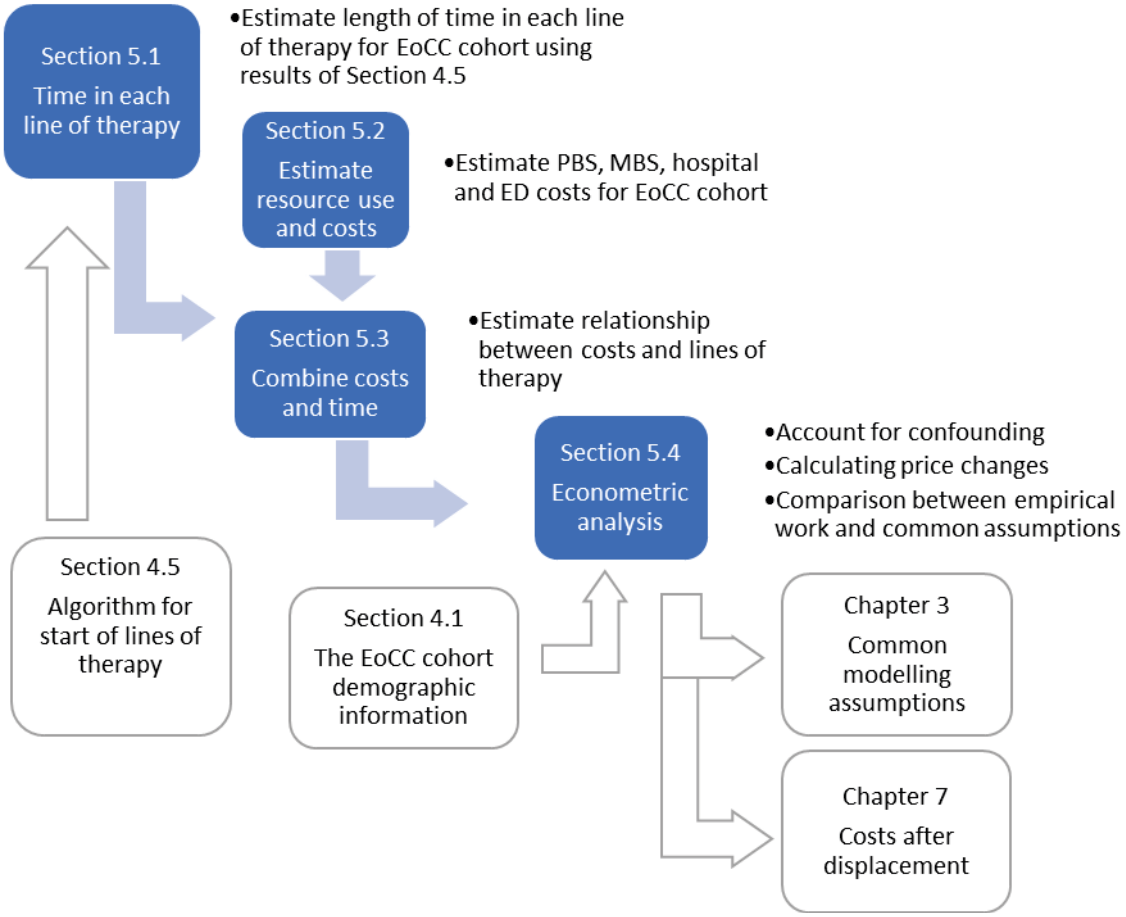
The motivation is to assess the relationship between increasing line of therapy and monthly cost. This assessment is required to ensure that the modelling conducted in Chapter 7 is based on realistic assumptions. This Chapter also provides empirical evidence to test some of the common modelling assumptions made in the literature reviewed in Chapter 3 (for example, constant cost per month).

This Chapter aims to:

1. estimate the length of time associated with each line of therapy;
2. estimate the costs by broad cost category and total costs for the participants; and
3. assess the relationship between the monthly cost within a line of therapy and between lines of therapy.

This Chapter also discusses the challenges and limitations associated with the use of observational data in assessing the cost of treatment of the three cancer types that are the focus of this thesis. The three main risks are missing data, confounding factors and insufficient numbers of comparable patients.[158] Missing data was previously identified and its implications explored in Chapter 4. Any use of administrative and registry data requires consideration of its weaknesses and the bias that may result in measuring treatment effect and costs. In order to conduct a valid investigation of costs or a cost-effectiveness analysis, the important costs and outcomes need to be identified, measured and valued.[158]

Confounding or bias in the selection of treatments means that simple comparisons between observed alternatives may be inappropriate. A range of econometric techniques can be used to assess the impact of one alternative compared to another while controlling for the potential biases. This Chapter used multivariate regression and panel data techniques to adjust for potential confounding of omitted variables on the relationship between monthly cost and increasing lines of therapy.



Note: Filled boxes are contained in this Chapter, unfilled boxes from other Chapters
Abbreviations: ED: emergency department; EoCC: Elements of Cancer Care; MBS: Medical Benefits Schedule; PBS: Pharmaceutical Benefits Scheme

Figure 20: Scheme of Chapter 5

Figure 20 outlines the structure of Chapter 5 and links to the other Chapters. Section 5.1 estimated the mean and median time spent by patients in the EoCC cohort in each line of therapy adjusting for the censored nature of the data. The methods developed in Chapter 4 are employed to determine the start and end of each line of therapy. Section 5.2 estimated the Pharmaceutical Benefits Scheme (PBS), Medical Benefits Schedule (MBS), hospital and emergency department (ED) costs from the available administrative data. There is the potential for the estimation of total costs to be subject to bias because of the censored nature of the observational cohort. Non-parametric methods that adjust for censoring were employed to control for this bias. Section 5.3 combined the costs and length of time to calculate mean cost per month in each line of therapy. The temporal relationship between the costs and the length of time within a line of therapy was estimated. These estimates could be subject to confounding because of increasing morbidity and mortality associated with later lines of therapy. In Section 5.4 an econometric analysis utilising multivariate regression and a panel

data structure to adjust for potential confounding and bias was conducted. Extra output from the econometric analysis has been included in Appendix D.

The data derived from the EoCC project was approved by the Human Research Ethics Committee (University of New South Wales, approval number 07014).[63]

5.1 Length of time for each line of therapy

The length of time attributed to each time of therapy is an important component in estimating the potential impact of displacement.

An additive model over progression free survival was the most common model structure used in the literature for the economic evaluation of multiple lines of therapy as discussed in Section 3.1. This model divides the total overall survival into lines of therapy. It equates the average benefit of a treatment to the length of time prior to the next treatment, that is, to the period over which the treatment was estimated to work. This model framework is used in this Section to divide the total survival into lines of therapy.

The algorithm developed in Chapter 4 was used to estimate the start of each new line of therapy when a new line of therapy commences. This is the time to the next treatment. The start date of the treatment in each line of therapy and therefore the start date of the line of therapy is described in Section 4.5. When another line of therapy was commenced, the initial line of therapy was assumed to have terminated the day prior. The last line of therapy for an individual is either censored because of the end of the observation period or the line of therapy ceased because of the participant's death. Censoring because of the end of observation is right censoring and the event of interest was not observed.

As discussed in Chapter 4 there was the potential for censoring of several participants because of the end of the observation period, which differed for the 2009 and 2010 cohorts. Additionally, the administrative data gathered can predate the recruitment of the participant to the study. For the period prior to recruitment the participant was not at risk. This is referred to as left truncation or late entry in survival analysis. Not adjusting for left truncation may result in bias, with higher estimates of survival occurring. Only those who survived long enough to be in recruited are included in the analysis. There is also left censoring with some of the lines of therapy having occurred entirely prior to recruitment.

Given the results of Section 4.5, the level of agreement between the PBS administrative data and the new pharmaceutical use (oncologist's review) occurred when trastuzumab was

excluded and current and prospective lines of therapy only were used. The impact of left censoring is controlled for by only using current and prospective lines of therapy. Right censoring is adjusted for by a survival analysis using the non-parametric Kaplan-Meier approach. An adjustment for left truncation was undertaken by calculating of risk from the recruitment date when prospective observation and risk occurred.

5.1.1 Methods

The method of identifying the first day of a line of therapy was detailed in Section 4.5. In summary, the protocol used at the recruitment date was the first protocol for which stop and start dates were calculated. A 50-day span was used to determine the inclusion of new treatments within the same protocol for a line of therapy (see Section 4.5). The stop date was the day before the commencement of the next line of therapy or death. Participants without any chemotherapy (and therefore for whom it was not possible to calculate the stop and start dates) were discarded from this analysis.

A participant with a start date of the line of therapy prior to the recruitment date, was assumed to have delayed entry into observation for the first prospective line of therapy, thereby adjusting for left truncation

Trastuzumab was removed from the EoCC PBS data (see Section 4.5). The number of lines of therapy was calculated as described in Section 4.5 with the exclusion of trastuzumab and with the assumption of no adjuvant therapy.

The line of therapy was either censored (if there was no death or new line of therapy), or complete (because of a new line of therapy or death).

The censored and end dates were calculated using three assumptions.

1. A recorded death date was assumed to be the exit date. This was available for the initial data collection from the Registry of Births, Deaths and Marriages as month and year only. It was assumed to be the fifteenth day of each month. The date was shifted to later in the month if there was activity in the EoCC PBS, EoCC MBS or procedure dates beyond the fifteenth.
2. If there was a lack of administrative data for 90 days prior to the censoring date this was assumed to be due to death in the absence of a recorded death in the Registry data. Death was estimated as the last recorded activity in EoCC MBS or procedure dates or 90 days beyond the last EoCC PBS date of service,[188] whichever was later. This

was for participants who did not die in the prior initial data collection. The Registry of Births, Deaths and Marriages data was not available as part of the second data collection.

3. Patients with administrative data in the 90 days prior to the censoring date and no recorded death were assumed to be censored at the censoring date. This differed according to the recruitment cohort: 30/06/2010 for the 2009 cohort and 30/06/2014 for the 2010 cohort.

The total and average number of lines of therapy were calculated for each participant. The mean and median survival was calculated for each line of therapy with and without adjustment for left censoring around the recruitment date for the first prospective line of therapy. Kaplan-Meier estimates were produced for total survival and by line of therapy. The analysis was conducted in Stata 15.[173]

5.1.2 Results

Of the 232 participants, four did not have any oncology pharmaceuticals in the EoCC PBS data - these were excluded from further analysis. Of the remaining 228 participants, there was an estimated 402 separate lines of therapy, of which 80 lines of therapy (and 80 participants) were censored. One hundred and six participants (47%) had only one prospective line of therapy, while 122 (53%) had at least two prospective lines of therapy.

The calculated line of therapy at recruitment is shown in Table 47, as is the number of prospective lines of therapy that were included in the EoCC PBS data. The mean number of prospective lines of therapy (not adjusting for censoring) was 1.76 per participant. The mean time in the fourth and fifth lines of therapy are based on very small numbers and a 95% confidence interval was not calculated because of a lack of variation. Adjusting for the left truncation present in the first line of therapy reduced the calculated mean time before the next treatment started.

Table 47: Breakdown of retrospective and prospective lines of therapy

Number of lines of therapy at recruitment	Total number of prospective lines of therapy					
	1	**2**	**3**	**4**	**5**	**Total**
0	5	2	2	1	0	10
1	43	43	12	4	1	103
2	30	28	8	1	2	69
3	20	4	6	0	0	30
4	4	4	1	1	0	10
5	4	2	0	0	0	6
Total	106	83	29	7	3	228
Mean survival	478 days	362 days	131 days	43 days	62 days	
Mean survival adjusting for left truncation (95% CI)	314 days (269 to 360)	362 days (296 to 428)	131 days (58 to 204)	43 days (*)	62 days (*)	

Note: The 95% confidence interval was not calculated in the 4th and 5th lines of therapy because of the small sample size
Abbreviation: CI; confidence interval

5.1.3 Discussion

The estimate of the length of the first prospective line of therapy was impacted by the left side truncation. The internal validity of the results - that the estimates represent the actual length of time in each line of therapy - was limited by the lack of data for trastuzumab and the small number of observations, especially in the later lines of therapy. There was a decrease in mean survival with increasing lines of therapy (greater than two).

The impact of the left truncation was to increase the estimated length of time in the first line of therapy. This was consistent with expectations.

As previously discussed, the time within a line of therapy is not the time to progression (Section 3.1.9) but rather the time to commencement of the next treatment, or to death. Time to next treatment and progression free survival time are positively correlated.[161] It is also commonly assumed in economic evaluations of treatment sequences that time on treatment and progression free survival are equivalent (see Section 3.1.9 and Section 3.2).

However, there are several reasons why the time to next therapy may not be the same as the time to progression. First, the new treatment may not be introduced because of progression but rather because of the previous treatment's unacceptable adverse events. There may be a period of time between the recognition of progression and the introduction of the new treatment. This may occur because of the time taken for informed clinical decision-making in recognising progression, because stabilisation of the participant is required or to ensure that

the prior treatment is not active in the participant before the subsequent treatment begins. Finally, progression may occur sometime prior to its recognition, depending on monitoring and the availability of investigations able to establish its presence.

The results are consistent with expectations, namely that increased lines of therapy are associated with decreased survival. Adjusting for censoring and truncation eliminated the difference between the first prospective line of therapy and the second. The strength of this conclusion is limited by the small number of participants in the later lines of therapy and the limitations of the data.

5.2 Resource use and costs

Costs from four sources were included in the EoCC administrative database: emergency department presentations, hospital admissions, the PBS and the MBS.

The perspective taken in the costing is that of the health system. This included the costs to the State and Australian Federal Government health systems, private health insurance and out of pocket costs for the purchases of pharmaceuticals and medical services only. Transport costs, other patient costs and productivity costs were excluded.

One potential issue with these calculations was the attribution of costs from private hospital admissions which contain a mix of out of pocket costs, private insurance payments (with a potential subsidy from the Australian Federal Government), PBS and MBS. Previous approaches to address this potential issue have included reducing the cost associated with private admissions[162] or using different cost schedules for public and private admissions.[63] A sensitivity analysis was undertaken where patient costs were excluded, as estimated in the PBS and MBS data. Another potential complication is the cost of ED attendances for patients who were subsequently admitted. These may be included in both the ED administrative data collection and the admitted patients' administrative data collection. This could result in a bias towards increased costs. The potential impact of double counting was estimated using different decision rules.

A second potential issue was censoring. As with the time, costs will also be censored because the observations are censored. This may result in bias if the costs for censored individuals are different from uncensored individuals. The assumptions that the cost at time of censoring and total cost are independent, required for the use of a Kaplan-Meier estimator, is not reasonable.[189] The impact of censoring was adjusted for using an alternative non-parametric estimator, using the Bang and Tsiatis method.

A third issue is changes in costs that occur over time. A base year was used for the admitted data and the emergency department to eliminate inflation (2011-2012). The pharmaceuticals and medical services were adjusted by medical inflation to the same year.

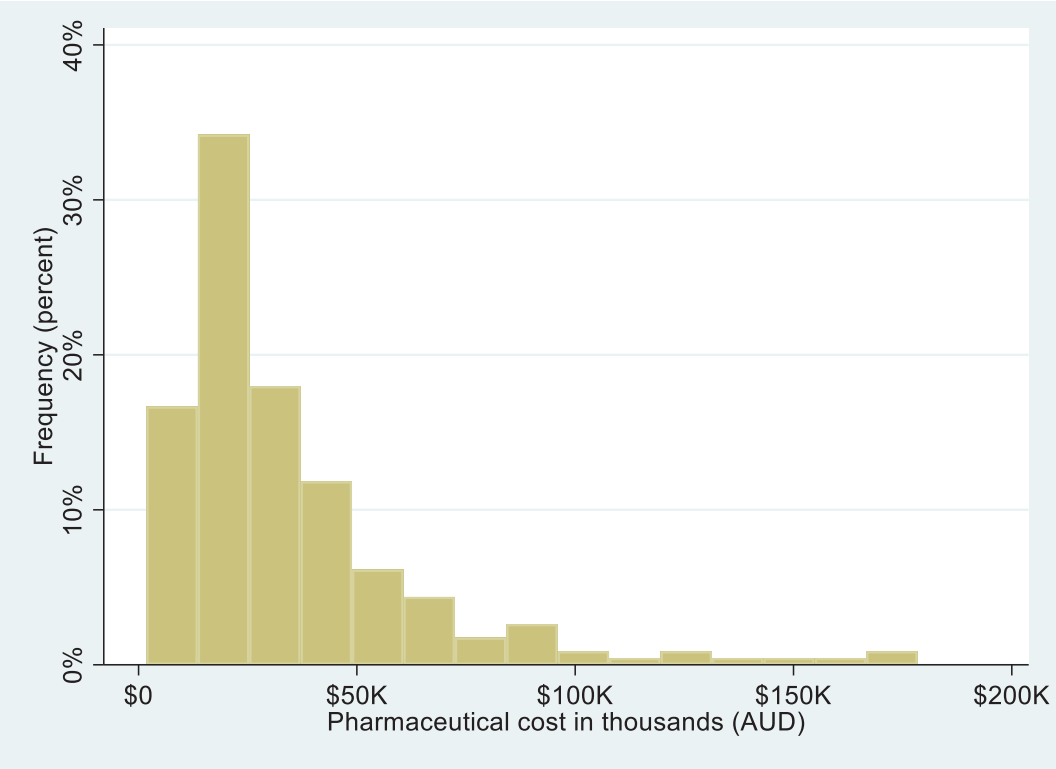
5.2.1 Pharmaceutical Benefits Scheme

The costs for the PBS were calculated by summing the net benefit recorded as being provided by the Australian Federal Government as a subsidy using the EoCC PBS data with the patient out of pocket payment. The figures were measured in 2011-2012 prices by deflating or inflating by the AIHW inflation measure.[190] The total pharmaceutical cost and the total number of supplied prescriptions per participant was calculated.

Additionally, the total cost per participant was tabulated by Anatomical Therapeutic Classification (ATC) code. The cost per 28-day month was calculated by dividing the total pharmaceutical cost by the total number of months of survival. The mean, median, 10% and 90% percentiles were calculated. These calculations were undertaken from the start of the line of therapy occurring at recruitment to exit from the study (either death or censoring). These calculations were repeated for each line of therapy with the 28-day month starting from the first day of each line of therapy. Sensitivity analyses included restricting the time from recruitment onwards and excluding the patient co-payment in the cost calculations.

All 228 participants had PBS costs. The total cost was $7.8 million for the 228 participants, with a mean (median) cost of $34 407 ($25 308) per participant. A substantial majority of the PBS cost was spent on anti-neoplastic agents (89% of the total PBS costs). The next most expensive cost were pharmaceuticals for the musculo-skeletal system (3%). The distribution of pharmaceutical costs was skewed to the right, with the mean being greater than the median. (Figure 21). Excluding patient co-payments decreased the estimate of expenditure to $7.7 million.

The mean monthly cost was $1 750 for pharmaceuticals.



Symbols: $: dollar; K: thousands
Abbreviation: AUD: Australian dollar

Figure 21: Histogram of total pharmaceutical cost

Most of the PBS costs of the EoCC cohort were associated with the treatment of cancer. As discussed previously, the lack of information about below co-payment products, trastuzumab and other high cost pharmaceuticals suggests that the costs for cancer treatment have been underestimated. These estimates excluded any special pricing arrangements that may exist for the high cost pharmaceuticals, which would reduce the total amount of the PBS cost.

These figures are higher than reported in previously published work on the EoCC cohort ($1 636 per month) which did not include the 2015 data extraction.[63] This difference reflects the inclusion of high cost pharmaceuticals, such as cetuximab, since the 2011 data extraction.

5.2.2 Medicare Benefits Schedule

The costs of MBS for the EoCC cohort were calculated by summing the net benefit recorded by the Australian Federal Government as a subsidy using the EoCC MBS data and the recorded out of pocket payment. The figures were expressed in 2011-2012 prices by deflating or inflating by the AIHW inflation measure.[190] The total number of services and the cost were calculated. The cost per 28-day month was also calculated by dividing the total pharmaceutical cost by the total number of months of survival. The mean, median, 10th and 90th percentiles were calculated from the start of the line of therapy when recruitment occurred.

These calculations were repeated for each line with the 28-day month starting from the first day of each line of therapy. Sensitivity analyses included restricting the time to the date of recruitment onwards, excluding the patient co-payment and excluding the hospital derived costs by removing those items with a hospital indicator.

All 228 participants had MBS expenditure. A total of $2.4 million for the 228 participants, was spent on the MBS items by the Australian Federal Government and when patient co-payments were included the cost increased to $2.9 million. The mean (median) cost was $12 801 ($10 233) per participant. This was skewed to the right. The monthly mean cost was $747.

Imaging, specifically computerised tomography, was the largest area of expenditure (13%) and the next largest cost was the administration of cytotoxic chemotherapy (11%). MBS expenditures within hospital constituted approximately 27% of the total expenditure.

5.2.3Admitted patient data collection

The Australian Refined Diagnostic Related Group (AR-DRG) categories were extracted from the data and costed according to the Hospital Casemix Annual report from 2011-2012, if it was a private admission. This included both the medical and hospital charges.[191] The public admissions were costed according to the relevant national hospital cost data collections for 2011-2012.

As the AR-DRG system changed in 2010 to Version 6. Missing private costs were replaced by the public hospital weights. Admissions without an AR-DRG code were excluded. The AR-DRG code J06Z (major procedures for breast conditions) was altered to the AR-DRG code J06A (major procedures for malignant breast conditions).[192] Similarly, J07Z was altered to J07A. The cost weights for J06A and J07A were used. These changes were made because of differences in the coding system prior to Version 6 of the AR-DRG.

As sensitivity analyses, application of the public rates and the rate of 82% of the public weight was applied to the private admissions (used in prior publications).[162] Additionally, a sensitivity analysis including only the hospital charges for private admissions was conducted to estimate the potential impact of double counting the cost of medical services in the admitted patient data collection and the MBS.

Two participants did not have any recorded admissions. One admission was discarded because it did not have an AR-DRG associated with it. The remainder (226 participants-99%) had at least one admission recorded in the data. However, only 211 participants (93%) had hospital

admissions in the period from the start of the line of therapy at recruitment to exit from the study. There was a total of 4 143 admissions in this period amounting to 8 543 days in hospital. The average length of stay was less than 2 days.

The majority of admissions were for the AR-DRG chemotherapy (62%), with the next most common cost for "other factors influencing health condition for ages less than 80." The total cost for admitted services was over $11 million. Only including the hospital charges component of private admissions reduced the costs by $2 million.

Table 48: Total cost of admissions under different assumptions

Costing	Public and private costed separately	All admissions as public AR-DRG	Private admissions costed as 82% of public	Only hospital component for private
Number of participants	211	211	211	211
Mean	$55 091	$61 108	$53 887	$45 128
Median	$36 220	$44 350	$39 642	$33 257
10% centile	$10 377	$10 998	$10 998	$8 180
90% centile	$115 681	$137 740	$120 992	$91 288
Total	**$11 624 250**	**$12 893 722**	**$11 370 114**	**$9 521 985**
Average cost per month (for 211 participants)	$2 898	$3 163	$2 847	$2 474

Abbreviation: AR-DRG: Australian Refined Diagnosis Related Groups

The top ten most costly AR-DRGs are presented in Table 49. Chemotherapy was the costliest AR-DRG followed by malignant breast disorders. The administration of chemotherapy represented 15% of the total costs attributed to admissions.

Table 49: Most costly AR-DRG in the EoCC admitted data

AR-DRG description	DRG	Admitted cost	Percentage of total cost
Chemotherapy	R63Z	$1 399 936	14.7%
Malignant Breast Disorders +Cc	J62A	$639 944	6.7%
Digestive Malignancy - Ccc	G60B	$396 136	4.2%
Oth Fctr Infl Health Status,Sd	Z64B	$385 287	4.0%
Pancreas, Liver &Shunt Pr-Ccc	H01B	$341 628	3.6%
Digestive Malignancy + Ccc	G60A	$296 638	3.1%
Muscskel Malig Neo -Ccc	I65B	$274 168	2.9%
Oth Heptobilry &Pancrs Pr-Ccc	H06B	$269 176	2.8%
Nervous System Neoplasm+Cscc	B66A	$268 204	2.8%
Respiratory Neoplasms -Ccc	E71B	$188 838	2.0%
Sum		**$4 459 955**	**46.8%**

Note: Costs based on the public and private costed separately assumptions as in Table 48

Abbreviation: AR-DRG: Australian Refined Diagnosis Related Groups

Admitted services were costly. The majority of costs were for AR-DRGs associated with the treatment of cancer, complications of cancer disease or complications of treatment. The majority of private admissions were single day admissions in private hospitals for either the administration of chemotherapy or other factors influencing health status. The assumptions made about the costs of private admissions, excluding medical services, had an impact on the calculated costs. The potential for double counting medical services needs to be considered when calculating total costs for hospital and MBS data.

5.2.4 Emergency department data collection

The emergency department (ED) attendances were calculated using the NSW Emergency Department Data collection. These were calculated in total and from the start of the first prospective line of therapy.

The number of emergency department presentations discharged from the emergency department to hospital and to the community were estimated using the mode of separation data field. Participants categorised as "Dead on arrival" were considered a separate category. This separated ED attendances with no admitted hospital component from those attendances where the patient was subsequently hospitalised.

Costs were calculated by using the cost weights in the Independent Hospital Pricing Authority (IHPA) Round 16 National Hospital Costs Data Collection (NHCDC)[193] for each triage category, admission or for participants dead on arrival.

Twenty-five participants did not have any ED activity. Two-hundred and three had ED activity. From the start of the line of therapy at recruitment to exit from the study, 144 participants had an ED presentation.

The mean number of presentations for participants who had ED activity was 2.6. The majority of presentations resulted in an admission to a non-intensive care unit ward (57%). The majority (70%) were in the urgent categories (triage categories 3 or below). Only 3% were in the less urgent category (triage category 5).

The average cost per participant with an ED presentation was $1 452 with a total cost for all participants $179 000. For unadmitted ED presentations, 68 participants had an ED attendance with an average cost of $630 per participant. The majority of participants with ED treatment were subsequently admitted into the hospital. ED costs were a minor component of total cost.

5.2.5 Total costs

There is the potential for double counting the costs when different categories are combined. For example, the MBS items for hospital services are present in both the MBS items and the medical services component of a private hospital admission. This was seen in the comparison of EoCC AR-DRGs with the EoCC MBS items in Section 4.4. To avoid double counting, only the MBS items were included, that is, the medical costs associated with the Casemix for private hospital patients have been excluded. These MBS costs are the actual costs and not an average cost associated with all patients, including non-cancer patients.

Similarly, participants with ED presentations who are subsequently admitted may have their costs included in two activity counts, the ED and the admitted patients.[194] The costs for patients who presented to ED and were subsequently admitted were excluded. This excluded the majority of ED presentations.

The total costs were estimated by summing for each individual the PBS costs (Australian Federal Government and patient out of pocket payments), MBS costs (Australian Federal Government costs and patient out of pocket payments), unadmitted ED presentations, public hospital costs (AR-DRG costs) and private hospital admissions (only hospital costs-excluding the medical costs).

Censoring is likely to be an issue when estimating the costs associated with the EoCC cohort. Censoring may be informative about costs. If participants are heterogenous with regard to cost, then a high cost at the point of censoring is positively correlated with a high cost at the endpoint.[195] Therefore, without adjustment for censoring inappropriately low total costs may be calculated.

Non-parametric and parametric estimators have been developed to address this issue. How the costs are weighted and the use of either total cost or more detailed cost history differ between the methods. For example, the Lin method uses survival probability.[196] The Bang and Tsiatis method uses the inverse probability of not being censored to weight the censored and uncensored observations.[197] The Zhou and Tian estimator is shown to be more efficient when a detailed cost history is available.[197] The use of non-parametric methods avoids the requirement to make assumptions about the distributions of costs because the costs are estimated over a fixed period of time, that is, one year etc. A simulation study suggested that the Bang and Tsiatis estimator might be preferred.[196]

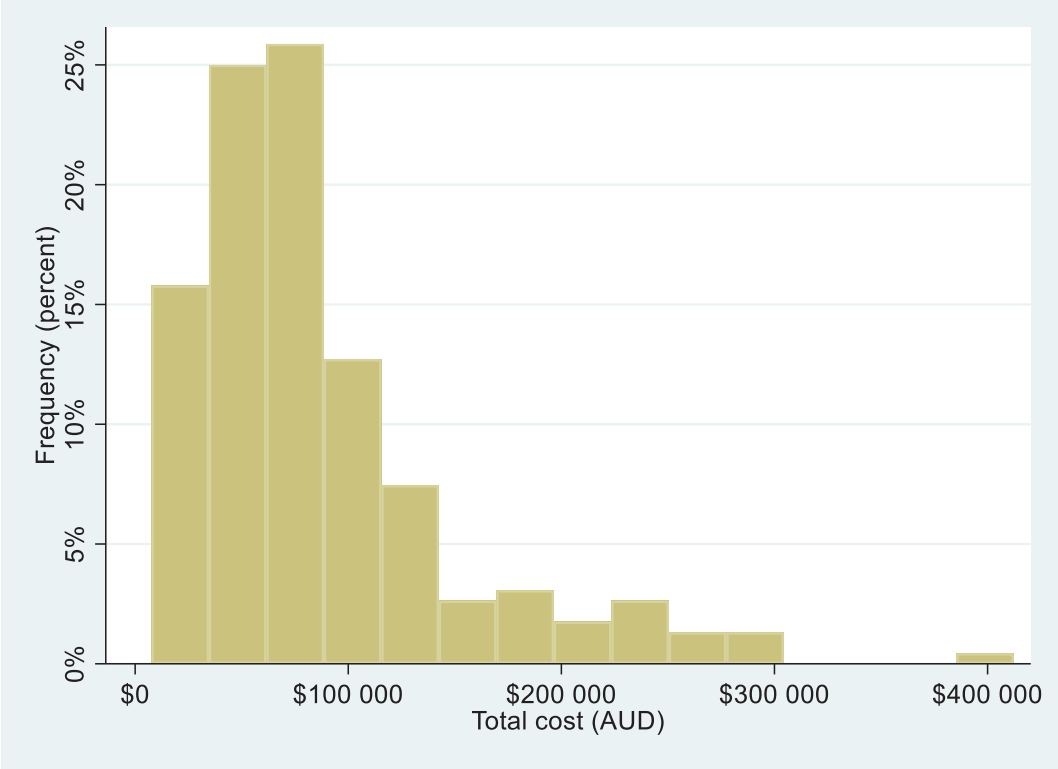
Censoring was taken into account by calculating a mean total cost for survival lengths of one to four years (with each year consisting of thirteen 28-day months [364 days]), using the Bang and Tsiatis method with inverse probability weighting using length of survival and total costs.[197] Adjustment for censoring was also undertaken stratified by type of cancer and several demographic criteria. As a sensitivity analysis, mean costs were also estimated using the mean monthly cost for all participants and the mean monthly cost of the uncensored participants only.

The results unadjusted for censoring are shown in Table 50. The cost of medical care was over $20 million for the 228 participants as identified in the administrative data. The cost per participant was almost $90 000 without adjustment for censoring. The mean cost per month of survival time was $4 534 (unadjusted for censoring). The distribution of costs is shown in Figure 22. There were no participants with a zero cost and the distribution was skewed to the right.

Table 50: Total costs for EoCC participants with metastatic carcinoma of interest

Type of cost	Total cost	Number of participants with activity	Cost per participant	Percentage	Cost divided by total months of survival
Pharmaceuticals	$7 844 765	228	$34 407	38.6%	$1 750
Medical services	$2 918 583	228	$12 801	14.4%	$651
Admissions	$9 521 985	211	$45 128	46.8%	$2 124
Emergency Departments services	$42 814	68	$630	0.2%	$10
Total	**$20 328 147**	**228**	**$89 159**	**100.0%**	**$4 534**

Abbreviation: EoCC: Elements of Cancer Care



Abbreviation: AUD: Australian dollar

Figure 22: Histogram of total costs by participant

The costs of the cancer pharmaceuticals and their administration (either MBS or admission) are shown in Table 51. The largest cost component was the chemotherapy pharmaceuticals. Approximately 42% of all expenditure recorded in the EoCC cohort was related to chemotherapy pharmaceuticals or their administration.

Table 51: Costs of chemotherapy pharmaceutical and administration

Type of cost	Total cost	Cost per participant	Cost divided by total months of survival
Chemotherapy pharmaceuticals	$6 777 430	$29 726	$1 512
Chemotherapy admissions	$1 399 936	$6 140	$312
Chemotherapy administrations (MBS)	$261 992	$1 149	$58
Total of administration	**$8 439 357**	**$37 015**	**$1 882**
Percentage of all cost	42%		

Abbreviation: MBS: Medical Benefits Schedule

The figures adjusting for censoring are shown in Table 52 using the Bang and Tsiatis estimator. Sensitivity analysis using unadjusted figures are also presented, both for all participants and the uncensored participants only. The costs are similar for one year but for longer time periods the costs are larger adjusted for censoring. The total costs adjusted for censoring are shown for several demographic subgroups in Table 53.

Table 52: Total costs adjusting for censoring using inverse probability weighting

Number of years	Total cost from start of first line of therapy (95% CI) using Bang and Tsiatis estimator	Total cost – mean cost (95% CI)	Total cost – removal of censored observations (95% CI)
1	$57 021 ($52 719 to $61 324)	$58 869 ($54 499 to $63 240)	$57 899 ($49 503 to $66 295)
2	$88 122 ($79 529 to $96 528)	$75 342 ($69 172 to $81 513)	$74 806 $66 017 to $83 596)
3	$103 081 ($92 353 to $113 808)	$80 728 ($73 561 to $87 895)	$85 496 ($75 318 to $95 673)
4	$115 245 ($101 455 to $129 036)	$84 789 ($76 804)	$92 167 ($81 239 to $103 094)

Abbreviation: CI: confidence interval

Table 53: Total costs adjusting for censoring using inverse probability weighting for the first two years in subgroups (Bang and Tsiatis estimator)

Subgroup	Total cost from start of line of first prospective line of therapy- one year (95% CI)	Total cost from start of line of first prospective line of therapy- two years (95% CI)
Breast cancer	$49 377 ($42 822 to $55 932)	$75 525 ($62 653 to $88 397)
Breast cancer without trastuzumab	$52 161 ($43 714 to $60 608)	$81 567 ($64 020 to $99 114)
Breast cancer with trastuzumab	$43 541 ($33 907 to $53 174)	$62 284 ($51 253 to $75 315)
Colorectal cancer	$63 364 ($56 523 to $70 205)	$101 626 ($87 615 to $115 638)
NSCLC	$58 726 ($50 322 to $67 130)	$77 144 ($66 084 to $88 205)
No private health insurance	$50 433 ($43 348 to $57 518)	$74 323 ($60 422 to $88 224)
Private health insurance	$58 488 ($52 720 to $64 255)	$90 270 ($79 560 to $100 981)
2009 cohort	$56 245 ($50 697 to $61 792)	$75 387 ($65 056 to $85 719)
2010 cohort	$58 174 ($51 338 to $65 010)	$105 654 ($91 398 to $119 911)

Abbreviation: CI: confidence interval; NSCLC: non-small cell lung cancer

5.2.6 Discussion

Anticancer pharmaceuticals and their administration represented the largest single cost in the provision of medical care to the EoCC cancer cohort. This is consistent with previous research both within this cohort[63] and elsewhere in Australia.[162]

This research estimated a lower cost for ED attendances than prior research because ED costs for admitted patients were excluded to avoid double counting. The excluded charges for medical services in private admissions - again to avoid double counting - decreased the cost of admissions compared to alternative methods of estimation.[162] These changes were justified by the data. As discussed in Section 4.4, AR-DRGs for chemotherapy and MBS items for infusion of chemotherapy occurred on the same day for private patients and therefore were included in both data collections.

The estimation of the mean cost per month may be biased downwards slightly because of a potential over-estimation of survival. This is because the estimation of death was based on the absence of administrative data (point 2 of the methods detailed in section 5.1.1 required 90 days without activity as a marker of mortality). This may overestimate survival in several cases as mortality may have occurred prior to that time.

The lack of trastuzumab in the dataset may have contributed to the treatment of breast cancer appearing to be the least costly of all cancer types over one year. Therefore, the conclusions of Chapter 4 appear justified, namely, that the missing treatments are potentially important in attaining an accurate calculation of total cost. Other costs were excluded from the four data

collections, for example allied health, dental services and non-admitted hospital services such as community nursing.

Censoring was important for estimating total costs. The estimation was lower without adjustment for censoring for periods greater than one year. The estimate of the costs associated with the 2010 cohort were higher. This was expected, given the censoring of the 2009 cohort occurred prior to the introduction of several high cost pharmaceuticals (as discussed in Section 4.4). The possession of private health insurance appeared to be associated with higher costs and the use of trastuzumab appeared to be associated with lower costs.

One disadvantage of non-parametric estimators is that adjustment for covariates cannot be undertaken. Therefore, when combining the costs and lines of therapy a multivariate regression approach is taken in Section 5.4.

5.3 Combining costs and lines of therapy

The timing of the costs within a line of therapy, that is, the distribution of the costs within a line of therapy is important to ensure accurate modelling. It was commonly assumed that the cost was constant over time within a line of therapy, as discussed in Section 3.1. Altering this assumption may alter the conclusions of the resultant economic evaluations. The distribution of costs for the EoCC cohort within a line of therapy was explored to confirm or reject the assumption of constant costs. The pharmaceutical costs alone (PBS and patient out of pockets payments) and the total costs were considered, given the importance of cancer pharmaceuticals in the modelling explored in Section 3.1 and in the empirical costs of the EoCC cohort (Section 5.2).

5.3.1 Methods

The costs (pharmaceutical and total) were allocated to a specific month and line of therapy. The line of therapy was determined as described in Section 5.1. The months were defined in 28-day periods after the start of the line of therapy at recruitment. The total costs were as described in Section 4.5. The costs of the numerically highest line of therapy experienced during each month was assigned to that month. For example, if the line of therapy increased from the first line of therapy to the second line of therapy in the fourth month, the first three months would be assigned to the first line of therapy and the fourth month onward to the second line of therapy.

The costs of pharmaceuticals included the Australian Federal Government component and the out of pocket payments as described in Table 50. The mean monthly cost across participants

within each line of therapy was calculated. The trend was estimated using linear regression on the log of total costs within each month clustered on the participant. Months for uncensored patients (i.e. those who died) were truncated when expenditure ceased. Total costs for six months were calculated adjusting for censoring using the Bang and Tsiatis estimators.

5.3.2Results

There were 4 685 months identified; 243 months had no medical expenditure (5.2%). The mean monthly costs for each line of therapy are shown in Table 54. The mean monthly costs increase with increasing lines of therapy; however, the estimated total costs for six months are similar.

The total cost across all participants for each line of therapy decreases as the number of lines of therapy increases. This is because the number of participants who receive a line of therapy decreases with increasing lines of therapy. Additionally, the length of time spent in the line of therapy, for a participant, decreases as the number of lines of therapy increased.

Table 54: Mean monthly costs and six-monthly total costs for each line of therapy

Line of therapy	Mean monthly cost (95% CI)	Total cost for the first six months - adjusted for censoring (95% CI)	Total cost within cohort
1	$4 199 ($3 975 to $4 422)	$25 802 ($26 627 to $27 978)	$13 381 791
2	$5 090 ($4 713 to $5 468)	$26 658 ($23 653 to $29 664)	$4 498 491
3	$5 404 ($4 510 to $6 299)	$22 726 ($18 286 to $27 166)	$913 314
4	$6 542 ($4 016 to $9 068)	$23 012 ($16 253 to $31 570)	$215 896
5	$8 756 (-$3 133 to $20 646)	Not able to be calculated	$52 539

Note: Total cost for the first six months using Bang and Tsiatis estimator for censoring
Abbreviation: CI: confidence interval

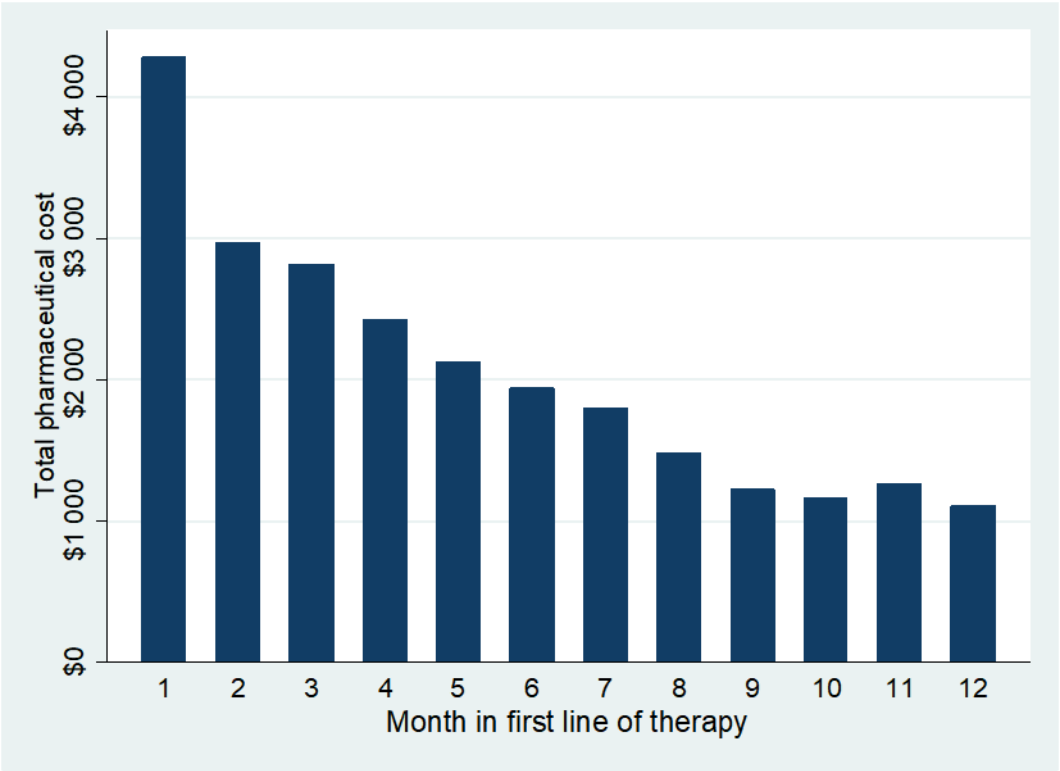
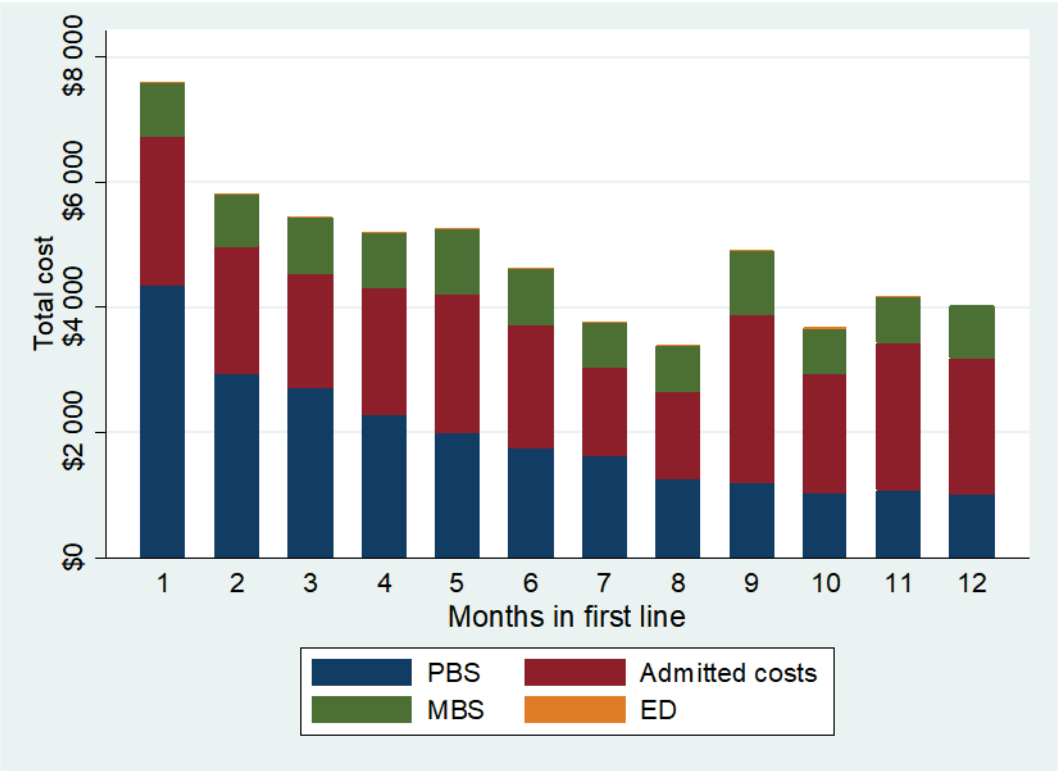


Figure 23: Mean pharmaceutical cost per month in the first line of therapy (for the first 12 months)

The mean costs of the pharmaceuticals for each 28-day month within the first line of therapy are shown in Figure 23. Pharmaceutical costs decreased over time. This decrease was statistically significant ($p<0.01$). A similar scenario was seen for mean total costs ($p<0.01$), shown in Figure 24 for the first line of therapy.



Abbreviations: ED: emergency department; MBS: Medical Benefits Schedule; PBS: Pharmaceutical Benefits Scheme

Figure 24: Mean total cost per month in the first line of therapy (for the first 12 months)

Figure 25 shows the mean cost for the first 12 months of treatment for the first three prospective lines of therapy. As can be seen the costs were higher for the later lines of therapy. The mean costs were higher for the first months of treatment within each line of therapy.

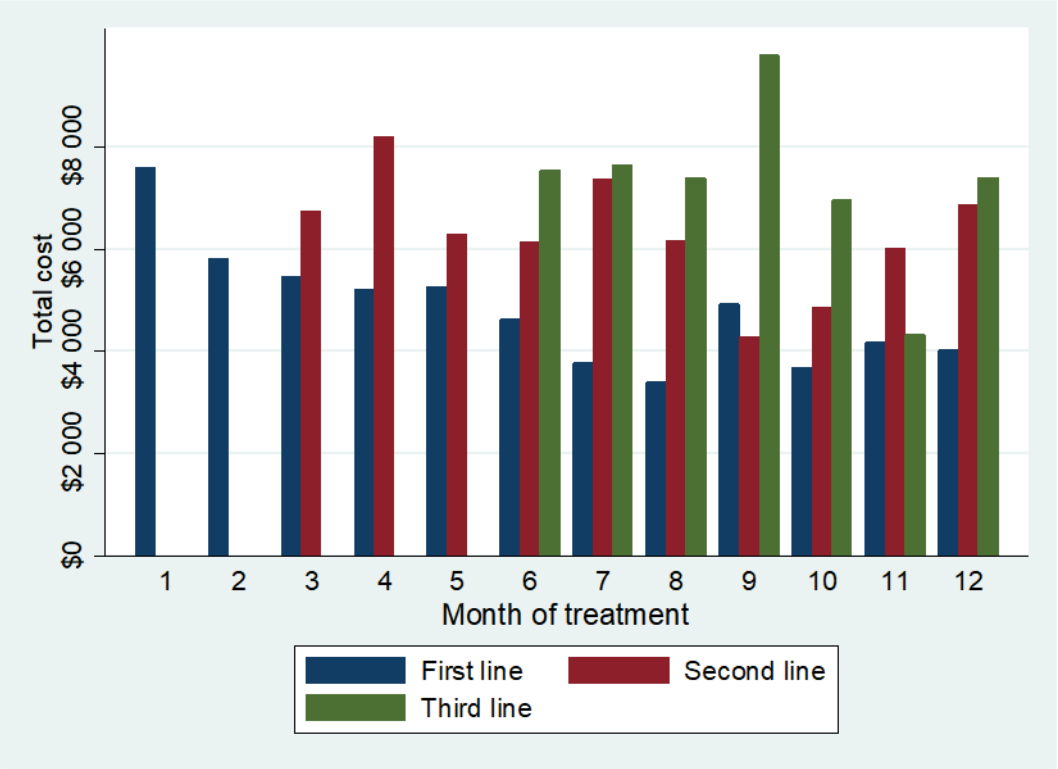


Figure 25: Mean cost per month for first three lines of therapy

5.3.3 Discussion

The mean monthly cost associated with a month of survival appeared to increase with increasing lines of therapy. The mean monthly cost doubled between the first prospective line of therapy and the fifth.

Over time, within the first line of therapy, the monthly cost of pharmaceuticals decreased. This also occurred for the total monthly cost. The decreasing mean cost of treatment associated with increasing lines of therapy could potentially be explained by a decreasing marginal cost of the additional month of survival. Earlier lines of therapy were associated with increased time within a line of therapy (see Section 5.1). The censored cost for the first six months of treatment was similar for all lines of therapy. Suggesting a similar initial cost for each lines of therapy and that the decreased mean cost may be a consequence of a decreasing marginal cost within a line of therapy.

This result contradicts the assumptions made in literature reported in Section 3.1 and 3.2 when modelling economic evaluations of multiple lines of therapy. A common assumption in the literature modelling multiple lines of therapy was that the cost per month of therapy is constant, both within a line of therapy and between lines of therapy. Relaxing this assumption of a constant cost is explored in Chapter 7. Prior Australian work has shown that costs were

higher in the month after diagnosis and declined thereafter which is consistent with the findings in this thesis.[162]

5.4 Econometric analysis of the monthly costs in lines of therapy

A more complete examination of the monthly cost was undertaken adjusting for several of the biases that may exist in the data. This econometric analysis aimed to estimate the relationship of monthly costs within a line of therapy and between the lines of therapy while holding other factors fixed.

5.4.1 Modelling considerations

The dependent variable was monthly cost. The relationship between costs and each line of therapy was examined by exploiting the longitudinal nature of the data.

A panel data approach was used to determine the relationship between total costs and the line of therapy. The descriptive review of total cost and lines of therapy suggested that the total cost may be related to the number of months after treatment had been initiated and the line of therapy. This is biologically plausible with treatment reduced or having ceased some time prior to the next line of therapy (see Chapter 6).

Several other features of the data led to potential complications in examining the data and estimating the impact of increasing lines of therapy. These included:

- the right skew of the data;
- determining the variable for the second dimension in the panel;
- the potential for correlation and endogeneity between cost, lines of therapy, comorbidities and death;
- increasing availability of technology;
- increasing cost of new pharmaceuticals over time;
- other omitted variables;
- the clustering of costs within institutions and individuals; and
- attrition within the panel structure.

Medical expenditure occurred in 95% of the months during the study period, unlike the usual consideration of medical costs.[198] Therefore, an excess of zero costs need not be considered in this thesis.

The right skew of the data can be addressed by transforming the dependent variable (cost) to achieve a more normal distribution. This may improve the efficiency of estimation.[198]

However, the transformation can produce difficulty in interpreting the incremental or marginal impact of changes in the dependent variables in dollar terms.[198] Taking the log of costs is a common approach. This has the benefit that when the dependent variable is logged but the independent variables are not, then coefficients can be interpreted as percentage changes (for small changes- the log-linear model).[199] The use of a generalised linear model (GLM) is one method of transforming the costs but allowing the recovery of the incremental impact of changes in a dependent variable.[198] The appropriateness of transforming the dependent variable can be assessed using a Box-Cox model for the log transformation, or other transformations such as the square root transformation.

The first dimension within the panel is the participant (denoted by i=1….N for N=228). The second dimension is time, but there is a choice of time dimension. It could time on treatment (first month of treatment being month 1, second month of treatment being month 2 etc.) or date (e.g. June 2010 being month 1, July 2010 being month 2 etc.). Time of treatment was selected because of the interest in the distribution of costs within a line of therapy and the differing dates of recruitment and starting treatment. Therefore, the first period is the first month of treatment of the first prospective line of therapy (denoted by t=1) and so on. This initial period occurred different dates between participants. The choice of time on treatment as the time dimension means that technology development or the listing on new pharmaceuticals could have occurred at a different time period for each participant.

The relationship between comorbidities, death and costs may also be important.[153] Previous research has suggested that the costs of care are higher closer to death.[200] It was assumed that death, comorbidities and later lines of therapy were all correlated with cost (see Chapter 6). Without controlling for this form of endogeneity estimating the impact of an increasing line of therapy may be biased upwards because death is potentially more likely with increasing lines of therapy. This is a form of omitted variable bias. To control for this bias, death and comorbidity need to be included in the multivariate analysis.

A similar logic is applied to the increasing availability of technology and the increasing availability of expensive pharmaceuticals over time, even accounting for medical inflation. Without considering the increasing availability of technology the estimate of the costs of lines of therapy may be biased upwards. Because of the choice of the time dimension is time on treatment the time dimension does not control for this potential bias (for example nine months of time on treatment could occur in 2009, 2010 or 2011 for different participants). This

is another form of omitted variable bias. To control for this bias, dummies for each year were included.

As seen in Section 4.4, there were differences between centres in the use of pharmaceuticals and charging practices. This also needs to be controlled for, by the inclusion of a dummy variable for centre.

Panel data contain multiple observations on the same individuals. There may be other omitted variables that vary between individuals but not time, which are correlated with the cost and the line of therapy. For example, characteristics of the cancer or the patient and/or clinician preferences around aggressiveness of treatment that may not change or change very slowly. The use of panel data methods can potentially control for those omitted variables.[199] Two commonly used panel data methods are the fixed effects and random effects models.[201] These methods allow variation between units (participants) by varying the intercept in the regression but not the slope (coefficient on the independent variables). A random effects model is a more efficient estimator but requires an additional assumption, that individual level effect is independent of the explanatory variables included in the specification. This assumption can be tested and whether the fixed effects or random effects model is appropriate can be determined. Fixed effects models have the disadvantage of only using the differences that occur within a participant to estimate the coefficients. Therefore, the estimated variables require variation within individuals and cannot be used to estimate a coefficient on unchanging characteristics within an individual (such as sex, income status at recruitment or type of cancer).

It is a reasonable assumption that the residuals for an individual participants monthly cost will be correlated with each other (autoregressive), given that medical treatment for cancer involves the regular repeated applications of treatments (see Chapter 6). Therefore heteroskedasticity and autocorrelation consistent standard errors will be used in the panel data.[199]

Attrition of individuals within the panel data is a potential problem. Those who leave may differ from those who remain and therefore the estimates may be biased.[198] The observed data used in the econometric analysis derives from administrative data and is not dependent on participant response once consent is given. Therefore, attrition due to participant non-response is not an issue. Participants in the EoCC cohort left the panel in one of two ways, either because they were censored or due to their death. Leaving the panel because of death

will be correlated with the inclusion of a variable indicating death occurred in the same period. This variable has already been included to adjust for potential omitted bias. Censoring is dependent on when the participants were recruited. It is expected that the panel will be unbalanced with participants having left after different treatment lengths (either because of death or censoring). The impact of censoring is also tested for by including a balanced panel in the sensitivity analyses.

Other confounding and endogeneity might not be able to controlled for using a panel data approach, for example, simultaneous determination of the total cost and the line of therapy.[201] This could occur because increased cost (in investigations etc.) identifies progression and therefore causes an increase in the line of therapy. An increase in the line of therapy induces the use of more treatment (and increases cost). The use of an instrumental variable could eliminate this form of endogeneity.[201] Unfortunately, a useful instrumental variable was not located in the available data.

5.4.2 Methods

Total costs (and logged total costs) were regressed using ordinary least squares (OLS) and panel data methods. The explanatory variables included dummies for demographic details (age, sex, private health insurance, income, concession card status- missing data was treated as a separate category for each variable), cancer type, number of prior treatments, recruitment year, recruitment centre, year of administration and health status (comorbidities). Comorbidities were included by comparison of ATC codes to the comorbidities as described in Halfon et al. (2013)[202] and a running total of comorbidities produced over time. A dummy variable for death was included for the last three months before death.

A stepwise backwards and then forward approach to model selection was used. The model selection was undertaken for unaltered costs and logged costs. The combination of line of therapy (five lines of therapy), age (three age categories), type of cancer (three types of cancer), number of months of treatment since the start of the line of therapy at recruitment, death, comorbidities, year (from 2006 to 2014) and centre (12 centres) was considered the minimal grouping of explanatory variables. This group was selected because it was considered that it would minimise the biases discussed in Section 5.4.1.

Six steps were undertaken in the model selection.

1. Each variable in the minimal grouping was removed, and the change in Bayesian Information Criterion (BIC) and Akaike information criterion (AIC) reviewed. If the BIC

and AIC decreased and the coefficient was not significant when included the variable was permanently removed.

2. Two-way interactions between the remaining terms were entered and kept if the combination was significant and the AIC and BIC decreased.
3. Additional demographic and treatment variables were introduced in the following prespecified order (based on expectation of altering cost): prior chemotherapy, sex, trastuzumab use, private health insurance, income, concession card status and recruitment year. The variables were retained if they were significant and the AIC decreased.
4. The following interactions were considered in the prespecified order: female sex and colorectal cancer (CRC), trastuzumab and lines of therapy. The prespecified order was based on clinical expectation of increased costs. If the interactions were statistically significant and the AIC reduced, the interactions were retained.
5. Logged or unlogged costs were selected on the lowest AIC and BIC.
6. Polynomials on the continuous variables (months and comorbidities) were then included if the coefficient for the new polynomial was significant and the AIC and BIC reduced with the inclusion of the polynomial.

A choice was then made to use either fixed effects or random effects using the Mundlak test at a 5% level of significance. The Hausman test was not used because of the expectation that error would be heteroskedastic. Robust standard errors were used for both heteroskedasticity and within panel serial correlation for the panel data estimates. The root mean square error (RMSE), mean absolute prediction error (MAPE), crossfolded validation (using RMSE) were used to test the predictive power of the models.

The Pregibon link test were also considered as a specification test. The choice of a logged dependent variable was checked by using a Box-Cox transformation.

The appropriateness of the use of panel data was tested using a F-test for fixed effects or the Breusch-Pagan test for random effects.

The estimated fixed effects equation (for model 12 in Table 56 with time invariant characteristics removed) is shown in Equation 14.

$$y_{it} = \delta_1 t + \delta_2 t^2 + + \delta_3 t^3 + \delta_4 t^4 + \delta_5 t^5 + \beta_1 Com_{it} + \beta_2 Year_{it} + \beta_3 LoT_{it} + \beta_4 Com_{it} * t + \beta_5 Death_{it} + \beta_6 Deathmonth_{it} + \alpha_i + e_{it} \quad (14)$$

Where y_{it} is the total cost (or logged total cost) in the cumulative month *t* of participant *i*;
α_i is the individual time invariant fixed effects of participant *i*;
t is the number of cumulative months of treatment since the start of treatment for the first prospective line of therapy;
t^2 is the squared cumulative months of treatment (polynomial) etc.;
Com_{it} is the cumulative number of comorbidities in month of treatment t;
$Year_{it}$ is a dummy for the year that cumulative month occurred in and zero otherwise;
Com_{it} *t is the interaction between comorbidities and number of months of treatment;
LoT_{it} is a dummy variable for the number of prospective lines of therapy in month *t* of participant *i*, and zero otherwise (this is the variable of interest);
$Death_{it}$ is a dummy variable for the last three months prior to death and zero otherwise;
$Deathmonth_{it}$ is a dummy variable for the last month when death occurs and zero otherwise; and
e_{it} is the error term

The null hypothesis was that the coefficients for the later lines of therapy (β_3) are zero. The statistical significance of the lines of therapy for costs was determined by a joint F-test on the coefficients of the dummies on lines of therapy. The Bonferroni correction was used to estimate which lines of therapy were significantly different from the others. The significance level was 5%. The alternative hypothesis was that the later lines of therapy have a different cost than the initial line of therapy.

In the sensitivity analysis a balanced panel was used to estimate the coefficients without attrition. A strictly prospective group where only months from recruitment were included in the analysis was also used, to see the impact of the use of retrospective data on the estimation. Dummies for each month for the first 20 months was used in a sensitivity analysis as an alternative specification. Additional sensitivity analyses included using only uncensored participants, including only the 2010 cohort, removing the trastuzumab participants and excluding the last month observed. As well, each of the cancer types and years was modelled individually. Diagnostics comprised reviewing the residual plots, including residual versus predicted, as well as added variable plots to determine the specification was appropriate.

The results of the logged costs were approximated back to a linear scale by using a GLM. This was formally checked by use of a Box-Cox regression. The choice of link was made using a Box-

Cox approach, and the choice of family by the modified Park test. The *margins* command in Stata was used to estimate the impact of a new line of therapy.

The analysis was conducted in Stata 15.[173]

5.4.3 Results

The demographic details were previously reported in Section 4.2. The costs and lines of therapy were reported earlier in this Chapter. The panel was unbalanced (as expected), the mean number of the periods in the panel was 18.4, and the range varied from 1 to 64. The sample was heterogenous and therefore robust standard errors were appropriate.

Table 55 shows the impact on the results of alternative specifications of the OLS models. The logged total costs had a higher R^2, lower AIC and BIC. The estimates for the coefficients are listed in Appendix D. In all specifications, the joint F-test for the coefficient of the lines of therapy dummies was significant, for both unaltered and logged costs. The coefficient of the dummy for the second line of therapy was always significant and positive. A value of greater than zero for the both unaltered and logged costs indicates costs increased.

The residual plots confirmed that logged cost had an improved specification compared to the unaltered costs regarding the normality of the residuals. However, the specifications with unaltered costs were more likely to pass the Pregibon link test for correct model specification. The model performed poorly for prediction.

When the dependent variable was logged a polynomial to the fifth power was preferred for the months' term. The components of the initial model specification were accepted, as was an interaction term between comorbidity and months. The recruitment year was the only other independent variable accepted into the specification for the non-fixed effects models. Private health insurance and income were excluded (and were correlated with centre) as the coefficients were not statistically significant. Model 12 was selected as the specification for analysis (logged costs, to the fifth power, interaction between month and comorbidity, year of recruitment and the minimum grouping) using the prespecified sequential steps for model selection outlined in the methods.

Table 56 shows the results for the panel data specifications. The Mundlak test rejected random effects in most model specifications (and all model specifications using the full dataset). Accordingly, the fixed effects model was the preferred specification when the panel data was used. The dummies for time invariant characteristics (such as cancer centre, year of

recruitment and type of cancer) were, therefore, excluded in the results of the fixed effects estimators.

The F-test that the intercepts were different was significant for all specifications of fixed effects, suggesting that the panel data structure was appropriate.

The Box-Cox model suggested that the logging the dependent variable was the most appropriate transformation (theta=0.16), having the lowest restricted log likelihood, and that the most appropriate GLM was a log link function. The modified Park test returned a value of 1.6 and the gamma family was used.

Table 55: Model selection without panel effects

Model specification			OLS Unaltered costs							OLS Logged costs				
Model number	Independent variables	Lines of therapy significant	Coefficient on second line of therapy (95% CI)	R^2	AIC	BIC	Link test t value.	RMSE	N	Crossfold RMSE	R^2	AIC	BIC	Link test t value.	N
1	Lines of therapy, death, year, centre, month, comorbidity, age, cancer	Yes	$1 432 ($957 to $1 907)	0.096	88 280	88 478	*0.681*	5 833	4 373	5 743	0.199	14 769	14 965	-6.281	4 201
2	Model 1 with interaction between month and comorbidity	Yes	$1 456 ($983 to $1 930)	0.098	88 271	88 476	1.971	5 827	4 373	5 791	0.204	14 742	14 945	-4.776	4 201
3	Model 1 with year of recruitment	Yes	$1 539 ($1 065 to $2013)	0.098	88 269	88 474	*1.324*	5 825	4 373	5 830	0.202	14 755	14 958	-5.899	4 201
4	Model 2 with year of recruitment	Yes	$1 558 ($1 085 to $2 031)	0.100	88 262	88 472	2.519	5 819	4 373	5 808	0.207	14 729	14 939	-4.406	4 201
5	Model 1 with months to fourth power	Yes	$1 634 ($1 164 to $2 103)	0.120	88 169	*88 386*	2.288	5 757	4 373	5 765	0.261	14 437	14 653	-6.605	4 201
6	Model 1 with months to fifth power	Yes	$1 634 ($1 165 to $2 104)	0.120	88 170	88 393	2.132	5 757	4 373	5 772	0.262	14 431	*14 646*	-7.069	4 201

Model specification			OLS Unaltered costs								OLS Logged costs				
Model number	**Independent variables**	**Lines of therapy significant**	**Coefficient on second line of therapy (95% CI)**	**R^2**	**AIC**	**BIC**	**Link test t value.**	**RMSE**	**N**	**Crossfold RMSE**	**R^2**	**AIC**	**BIC**	**Link test t value.**	**N**
7	Model 3 with month to fourth power	Yes	$1 696 ($1 227 to $2 165)	0.121	*88 165*	88 389	2.550	*5 754*	4 373	*5 743*	0.261	14 435	14 657	-6.371	4 201
8	Model 2 with month to fourth power	Yes	$1 634 ($1 164 to $2 104)	0.120	88 171	88 394	2.349	5 758	4 373	5 772	0.261	14 439	14 661	-6.541	4 201
9	Model 4 with month to fourth power	Yes	$1 696 ($1 227 to $2 165)	0.121	88 167	88 397	2.604	5 755	4 373	5 760	0.261	14 437	14 665	-6.308	4 201
10	Model 3 with month to fifth power	Yes	$1 697 ($1 228 to $2 166)	0.121	88 167	88 396	2.395	5 755	4 373	5 763	0.263	*14 428*	14 650	-6.818	4 201
11	Model 2 with month to fifth power	Yes	$1 635 ($1 165 to $2 104)	0.120	88 172	88 402	2.177	5 758	4 373	5 766	0.262	14 433	14 655	-7.049	4 201
12	Model 4 with month to fifth power	Yes	$1 697 ($1 228 to $2 166)	0.121	88 168	88 405	2.429	5 755	4 373	5 761	0.263	14 430	14 658	-6.801	4 201

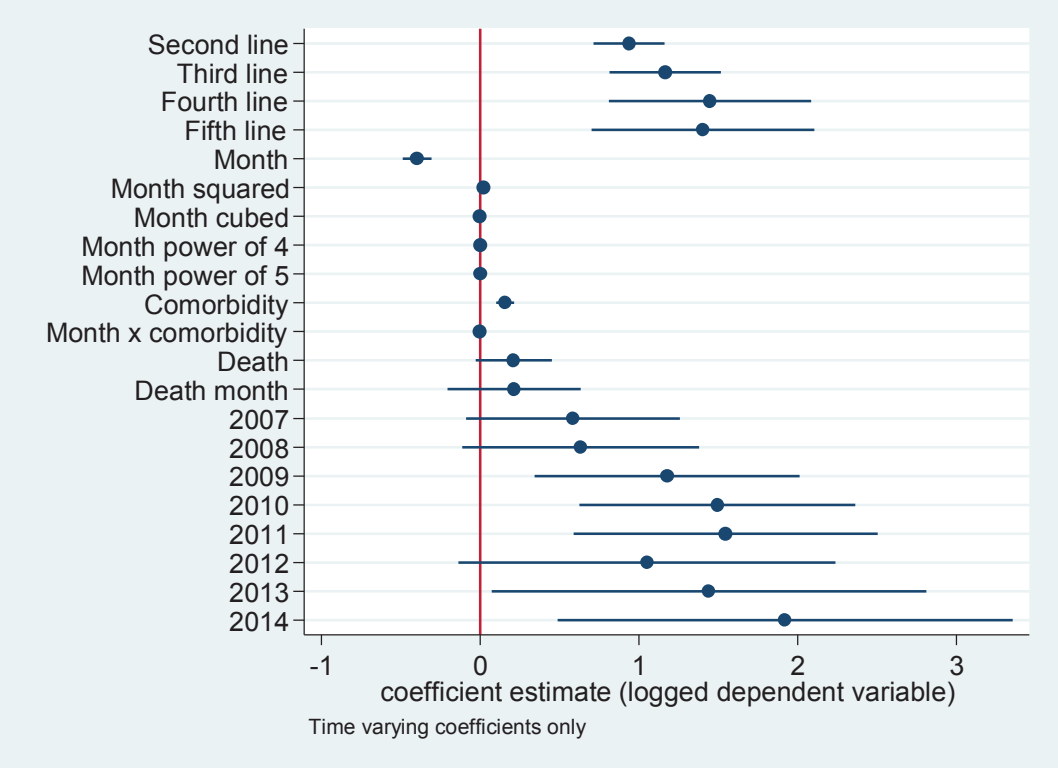
Abbreviation: AIC: Akaike information criterion; BIC: Bayesian information criterion; CI: confidence interval; N: number of observations; RMSE: root mean square error
Note: Standard errors used: red italicised text demonstrate superior performance on that metric
Note: The tables of coefficients are available in Table 123, Table 124, Table 125 and Table 126

Table 56: Model selection with panel effects

Model specification		Random effects – logged costs			Fixed effects – logged costs							
Model number	**Independent variables**	**Lines of therapy significant**	**Breusch and Pagan test appropriate for panel data**	**RMSE**	**Failed Mundlak**	**Lines of therapy significant**	**F-test appropriate for panel data**	**AIC**	**BIC**	**Within R^2**	**RMSE**	**N**
1	Lines of therapy, death, year, centre, month, comorbidity, age, cancer	Yes	Yes	1.3236552	Yes	Yes	Yes	13 993	14 088	0.09	1.2774532	4 201
5	Model 1 with months to fourth power	Yes	Yes	1.2705142	Yes	Yes	Yes	13 662	13 776	0.16	1.2276489	4 201
7	Model 3 with month to fourth power	Yes	Yes	1.2715056	Yes	Yes	Yes	13 662	13 776	0.16	1.2276489	4 201
12	Model 4 with month to fifth power	Yes	Yes	1.2704436	Yes	Yes	Yes	13 655	13 782	0.17	1.2263427	4 201

Note: The individual coefficients for all of the independent variables are shown in Table 127 and Table 128
Abbreviation: AIC: Akaike information criterion; BIC: Bayesian information criterion; N: Number of observations; RMSE: root mean square error

Figure 26 shows the coefficients values and 95 per cent confidence interval for the time varying independent variables for model 12. The time invariant variables are not shown, being excluded in the fixed effects panel data. The dummies for the second to fourth lines of therapy are all statistically significantly different from zero. They are all greater than zero and this implies that later lines of therapy are associated with higher costs per month.

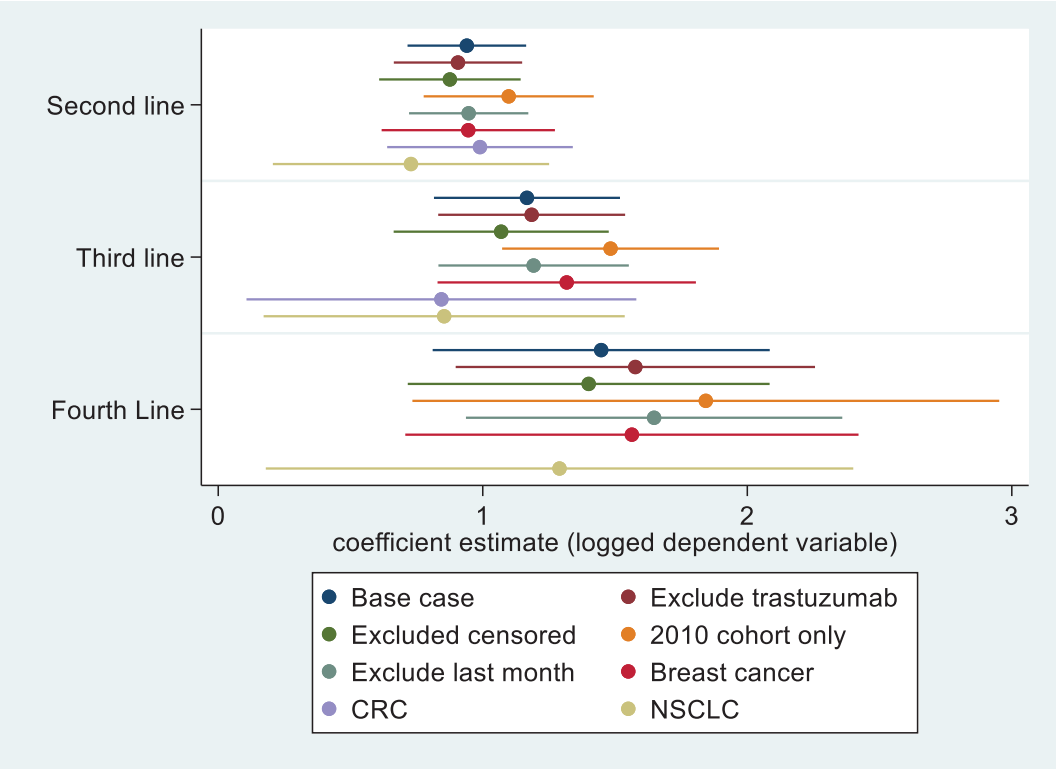


Abbreviations: OLS: ordinary least squares

Figure 26: Coefficient plots for the time varying variables (logged costs- model 12)

Figure 27 shows the differences in the coefficients for the lines of therapy of the prespecified alternative subgroups. Fixed effects on logged total cost was used for all analysis.

For all the alternative subgroups the coefficients were greater than zero and significant. This implies that costs increase in later lines of therapy. The confidence intervals for some lines of therapy are wider because of the small number of observations. This shows that the main results are consistent across the subgroups.



Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Figure 27: Lines of therapy coefficients for subgroups of the EoCC (logged cost model 12)

Figure 28 shows the coefficients for the lines of therapy when the data was restricted to a balanced panel or for prospective data only. This is important because it shows that one method of adjusting for censoring does not alter the results. The conclusion that costs increase with an increased line of therapy was robust to extensive sensitivity analysis.

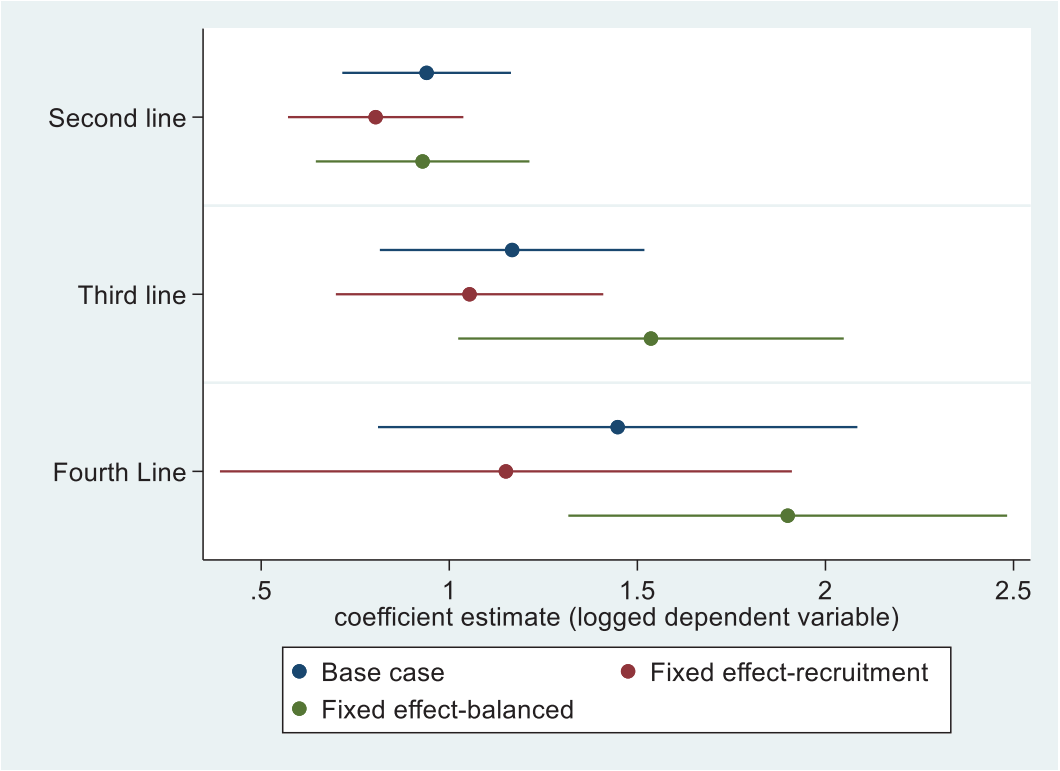


Figure 28: Lines of therapy coefficients for balanced and prospective only (logged cost model 12)

Figure 29 demonstrates the predicted monthly cost in each of the first 18 months of prospective treatment using the logged costs as the dependent variable. A GLM model was used with separate intercepts for each participant (equivalent to the fixed effects assumptions) to recover the same scale as unadjusted costs. No time invariant variables were included as per the fixed effects assumptions. The later line therapies did not start until sometime after the first line therapy was given. The other independent variables were assumed to be the conditional mean for the observed month and line of therapy, and so vary between the lines of therapy and month as for the participants.

As can be seen, the second and third line therapies had a substantially higher average cost than the first line therapy given the month of treatment. There was an increase in the mean cost of the third line after the end of the first year. The difference in means for the months seven to twelve was $3 343 between the first and second line of therapy and $4 829 for the difference between the first and third line of therapy.

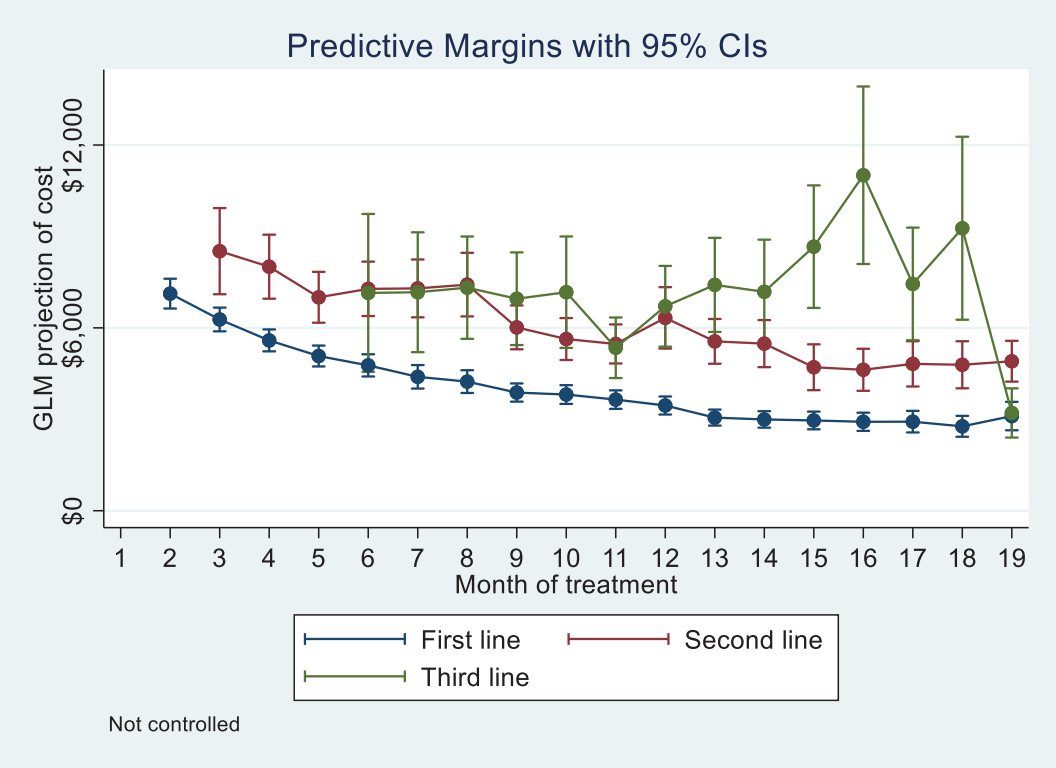


Figure 29: Estimation of uncontrolled monthly cost in each line of therapy over first 18 months

Figure 30 shows the same information but instead of using the conditional mean, the variables for death, comorbidity and year were assumed to be the same for all months and lines of therapy. This reduced substantially the differences between the lines of therapy for the estimated monthly cost. The second and third line of therapy were still more costly as point estimates. A large proportion of the difference in mean monthly costs between the lines of therapy was driven by changes in mortality and morbidity as well as increasing technology (time). The large increase in costs in the third line after 12 months was substantially less pronounced. The conditioning to the year 2010 increased the cost of the first months of treatment in the first line of therapy (which occurred prior to 2010). The cost of the first month of third line treatment (occurring in the sixth) is lower than the subsequent months of treatment. This was an individual participant (i.e. a solitary result).

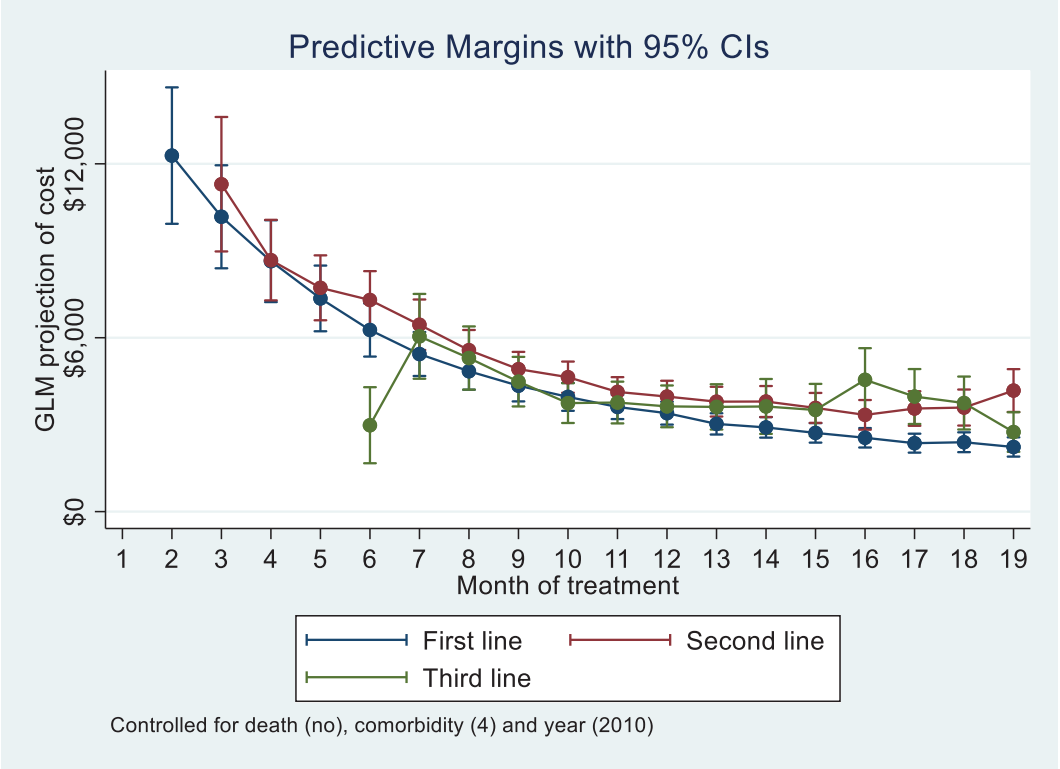


Figure 30: Monthly cost in each line of therapy for first 18 months controlled for death, comorbidities and year

Figure 31 shows the predicted monthly costs in the first three lines of therapy if the same participants who received three lines of therapy were in the first, second and third lines of therapy simultaneously. That is, Figure 31, adjusts for all differences except for the line of therapy (for those who received up to three lines of therapy).

The second and third line of therapy were estimated to be costlier relative to the first line of therapy, and costlier than when participant characteristics were not considered. However, it can be clearly seen that there was a diminishing marginal cost within a line of therapy for all lines and the differences decreased as the treatment length increased. The use of the third line of therapy in the initial months (which is a physical impossibility) is associated with a very high cost.

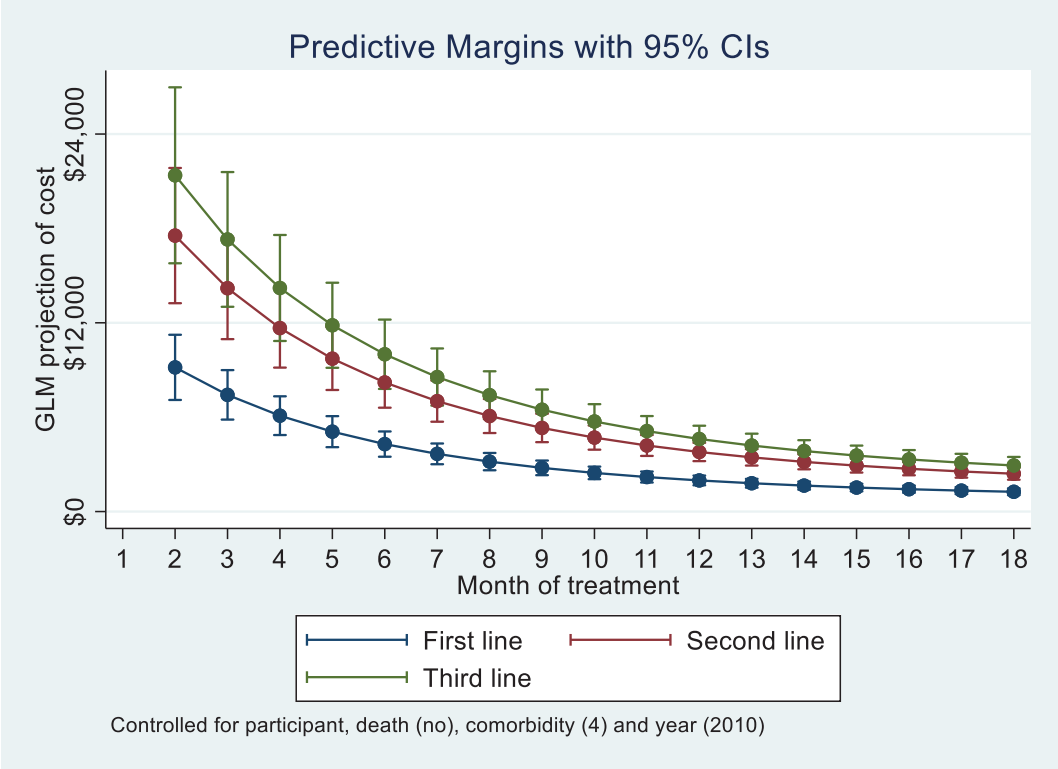


Figure 31: Predicted monthly cost in each line of therapy for first 18 months controlled for participant, death, comorbidities and year

A sensitivity analysis was undertaken treating each month of treatment as a separate variable, that is, not assuming any functional form associated with the number of months on treatment. The results for the logged specification fixed effects are shown in Figure 32. Despite not using a functional form for the number of months on treatment there is still a decreasing cost with increasing months for all lines of therapy after controlling for death, comorbidity and year.

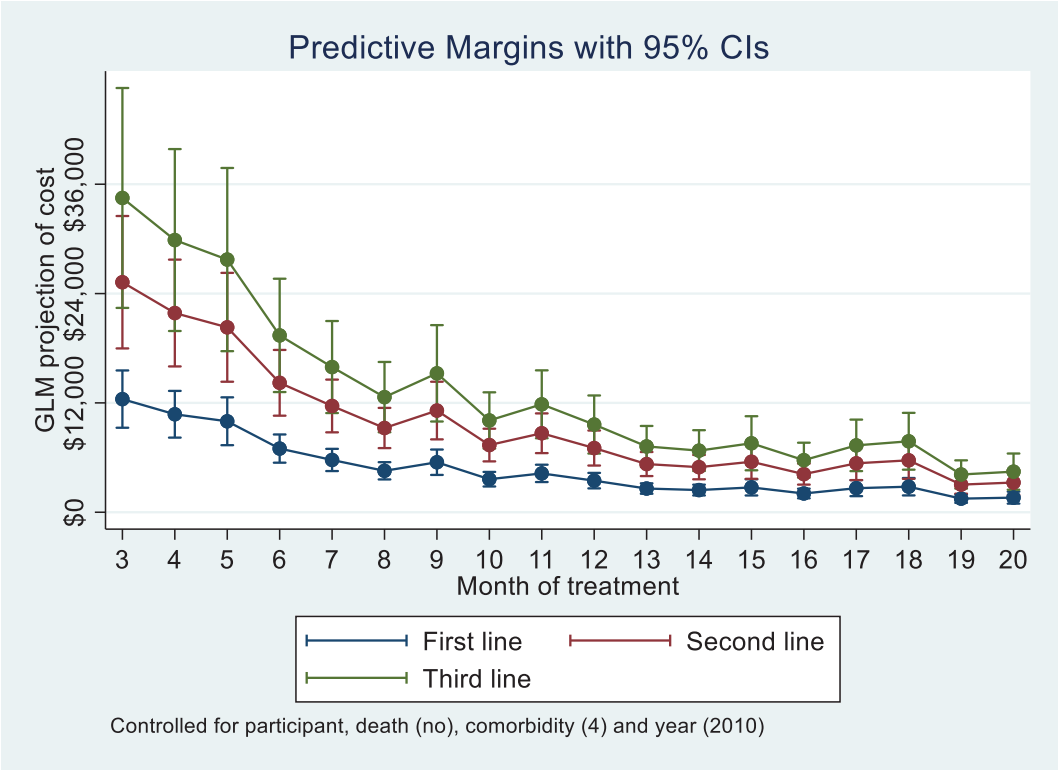


Figure 32: Cost per month assuming no functional form over the months

Comparing the results from the econometric analysis to the results of naïve estimation performed in Section 5.3 suggested that the naïve estimation may have underestimated the monthly impact of an additional line of therapy in the second line of therapy. This was because the increased time in the first line of therapy was associated with decreasing cost, that is there was a survivor effect. Therefore, when comparing the months for which second or third line therapy was provided with what would have happened if first line therapy had continued to be been given, the first line of therapy would have continued to become less expensive and observed difference between the lines of therapy would have increased. The impact of death and comorbidities may have increased the point estimates of later lines of therapy in the naïve comparisons compared to the multivariate analysis.

Table 57: Comparison of the coefficients across specifications

Metric	Naïve combination of costs and survival	OLS using unaltered costs	Fixed effects panel data unaltered costs	Fixed effects panel data using logged costs
Mean monthly cost difference between first and second line of therapy	$891 ($437 to $1 346)	$1 737 ($1 253 to $2 221)	$2 068 ($1 199 to $2 937)	$1 975 ($1 416 to $2 535)
Mean monthly cost difference between first and third line of therapy	$1 205 ($224 to $2 186)	$2 126 ($1 157 to $3 095)	$2 685 ($1 456 to $3 915)	$2 884 ($1 823 to $3 947)
Mean monthly cost difference between first and fourth line of therapy	$2 343 (-$168 to $4 518)	$1 894 (-$569 to $4 356)	$3 443 ($1 038 to $5 847)	$4 302 ($469 to $8 134)
Mean monthly cost difference between first and fifth line of therapy	$4 557 (-$520 to $9,636)	$2 713 (-$5 473 to $10 900)	$4 944 ($2 661 to $7 227)	$3 912 (-$2 347 to $10 172)
Method of calculation	Naïve comparison of means, difference using mean and variance	Coefficient on the relevant term of model 12	Coefficient on the relevant term of model 12 using panel data	Margins calculation using GLM of model 12 for months 13 to 24, no death, comorbidity (4) year (2010)- only included time varying variables
Location and source in thesis	Table 54	Table 124	Table 127	Figure 31

Abbreviations: OLS: ordinary least squares

5.4.4 Reduction in costs

As discussed in Chapter 2, altering the cost of treatments can be used to correct for a change in the cost-effectiveness that may occur with displacement.

The required reduction in cost for latter lines of therapy to have the same cost per month as earlier lines of therapy was estimated in four different ways.

1. The percentage decrease required from the first prospective line of therapy to the second to equalise total cost per month.
2. The percentage decrease required from the second prospective line of therapy to the third to equalise total cost per month.
3. The percentage decrease required from the combined first and second prospective lines of therapy to the remaining lines of therapy to equalise total cost per month.
4. The percentage decrease required in the first retrospective line of therapy and the second line of therapy to equalised oncology pharmaceutical costs per month.

The first three estimates were calculated using the results of the GLM with dummies for participants (to approximate the fixed effects) and robust standard errors. The difference between the coefficients was calculated using the STATA *margins* command and the percentage decrease required. For the third estimate dummies for the lines of therapy were calculated for the combined first and second line of therapy and for the combined third, fourth and fifth lines of therapy. The fourth estimate was calculated by comparing the per day cost, calculated by dividing the cost of oncology pharmaceuticals by the number of days in the line of therapy.

Different methods of calculating the reduction in costs required for latter lines of therapy to have the same cost per time as earlier lines of therapy produced different results. The required reduction in costs or prices ranged from 17% to 48%. The low number of participants in the later lines of therapy impacted on the confidence interval surrounding the point estimates.

Table 58: Reduction in cost required

Method	Point estimate	Lower bound of 95% CI	Upper bound of 95% CI
Comparison of first line of therapy to second line of therapy- total costs	48%	40%	55%
Comparison of the second line of therapy to the third line of therapy- total costs	17%	2%	31%
Comparison of the first two lines of therapy to later lines of therapy- total costs	28%	14%	40%
Comparison of first retrospective line of therapy to second line of therapy-pharmaceutical costs only	27%	10%	50%

Abbreviation: CI: confidence interval

5.4.5 Discussion

Understanding the relationship between the cost of treatment, lines of therapy and time within a line of therapy is important for modelling displacement. The motivation of this work was to estimate the impact of an increase in the line of therapy to evaluate the correct approach to modelling in Chapter 7.

Using simple regression without considering the panel data structure or the potential omitted variables suggested a high cost was associated with increasing lines of therapy, almost doubling in the fifth line of therapy. This conclusion was supported after adjusting for several potential biases.

The panel data structure and multivariate analysis were used to control for several confounding factors that might have otherwise biased the results. The rejection of a random effects model for the panel data resulted in an inability to confidently produce estimates for time invariant characteristics such as sex, type of cancer and private health insurance status.

Adjusting for increases in medical technology availability and usage resulted in a reduced cost estimate associated with increasing lines of therapy. However, without these adjustments, the correlation between later lines of therapy and temporal proximity to death would have resulted in a biased estimate of the impact of additional lines of therapy. There is the potential for imperfect multicollinearity between the line of therapy and year but the potential for omitted variable bias requires year should be added to the model.[199] Transformation of costs to logged costs resulted in improved diagnostics.

This analysis identified three main drivers of mean costs. The first driver - more important for third and later lines of therapy - was the cost associated with death and comorbidities. The second driver was that the modelled costs were higher for the initial months of treatment and

then decreased over time. The third driver was the increased cost associated with increasing lines of therapy.

For each line of therapy, costs decreased with additional time in that line of therapy. As shown in Figure 30 the mean cost of treatment for different lines of therapy was similar when patient death, technology development and comorbidity status (but not the patient fixed effects) were controlled for. As Figure 31 shows when the patient fixed effects were also controlled for, there is a decreasing marginal cost within the line of therapy. Therefore, one explanation of the difference in mean costs between lines of therapy is the differences in the time spent in each line of therapy. On average the time spent in the first line of therapy exceeded the time spent in the third line of therapy. That is, there is a survivor effect with costs, the mean costs decreasing with increasing survival - a decreasing marginal monthly cost within a line of therapy. This is also consistent with the costs in the first six months for all lines of therapy being similar when censoring was considered (Table 54).

These results were robust to extensive sensitivity analyses. The required reduction in costs for the later lines of therapy to have the same cost per month was estimated between 17% and 48%. These results were impacted by the low number of participants in later lines of therapy.

This examination of costs and lines of therapy did not prove causality. It did not prove that an increase in the lines of therapy caused higher costs, rather it demonstrated a continued association after controlling for several potential biases and forms of endogeneity. The results found in this dataset need to be confirmed in other datasets with different cancers and different cancer pharmaceuticals. The external validity of this econometric analysis is limited because of the select nature of the population studied and the use of a fixed effects panel model, which does not assume that the study sample is drawn from a larger population – unlike the random effects panel model.[199]

This Chapter also demonstrated the complexities of estimating the incremental impact of an additional lines of therapy using administrative data. This should be considered with evaluating potential price changes based on administrative data.

5.5 Conclusions

The two cost categories that contributed most to the total costs for the EoCC cohort were pharmaceuticals and hospital admissions. Within each of these categories, the largest costs were for pharmaceuticals used to treat cancer and the administration of chemotherapy. The uncensored mean cost per participant was approximately $90 000 and the cost per month was

over $4 000. The mean cost increased to more than $110 000 over four years when adjusting for censoring. This is consistent with previous research suggesting a mean monthly cost of $4 500 for the treatment of metastatic cancer patients in Australia.

An econometric analysis demonstrated that the mean cost per month of a later line of therapy is higher compared to earlier lines of therapy in the EoCC cohort. This result was consistent over a robust sensitivity analysis and multiple different specifications. One potential explanation for this finding is that the monthly cost decreases as the time increases within a line of therapy. That is, there is a decreasing marginal cost with respect to time. This is not consistent with the modelling assumptions used in Chapter 3 that used a constant marginal cost.

The interpretation of the results must also take account of the fact that displacement - the movement of a protocol from one line of therapy to a later line of therapy - was not the subject of the analysis. Rather, the subject of the analysis was the change in cost with an increase in a line of therapy for an individual.

These results must be tempered by the results of Chapter 4, which found that not all cancer pharmaceuticals or lines of therapies were included in the administrative data. Participants with breast cancer who were treated with trastuzumab had a lower estimated cost than those with breast cancer not treated with trastuzumab. This result lacked face validity and represented the lack of inclusion of these costs in the EoCC PBS dataset. The existence of extra treatments, including the use of high cost pharmaceuticals, has an obvious impact on the assessment of costs. The number of participants in the EoCC who had usable information for the assessment of survival and costs was modest as so the results are based a relatively small sample.

Relaxing the assumption of a constant marginal cost has a potentially significant impact on the change in cost-effectiveness due to displacement. This is explored in Chapter 7. The modelling undertaken in Chapter 7 assumes that there is not a linear association between the length of benefit associated with a treatment and its cost using information generated from RCTs.

Chapter 6 Displacement of protocols and the resulting clinical consequences

One of the issues that may occur with displacement is that existing treatments or protocols may move into a later line of therapy for which there is no evidence about their relative cost and effectiveness. This was discussed in Chapter 2 and the potential consequences outlined.

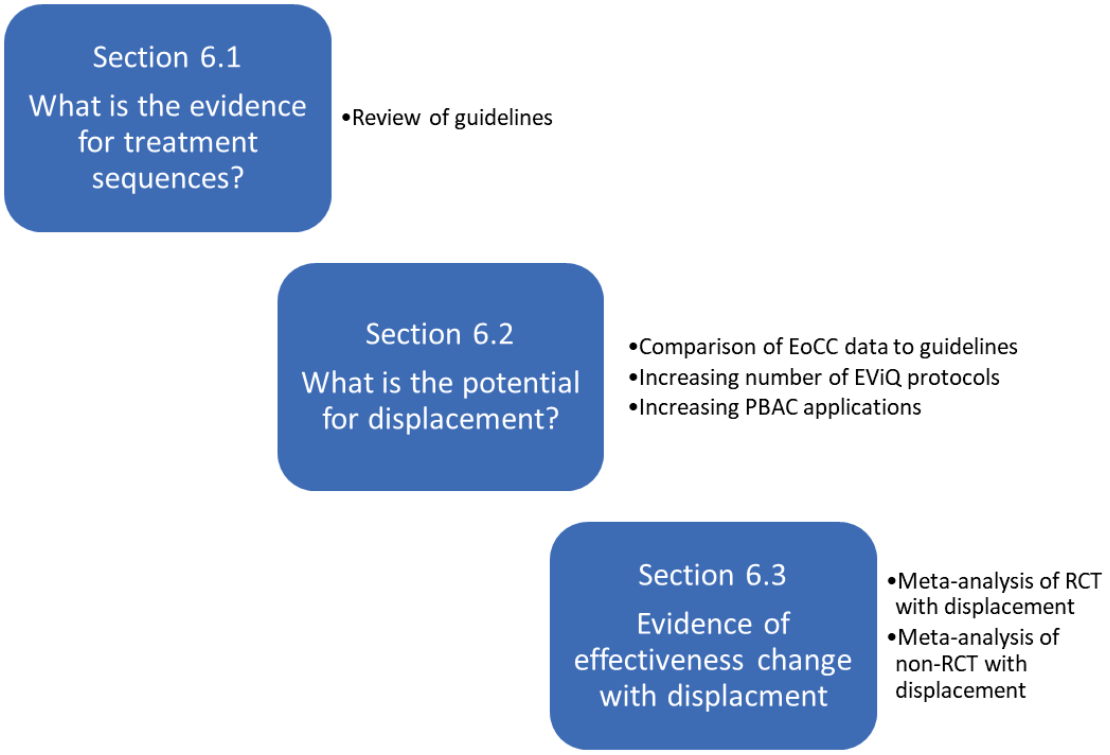
Chapter 3 demonstrated that published economic evaluations only consider a treatment sequence of three lines of therapy or less. Chapter 4 established that a substantial minority of participants in the Elements of Cancer Care (EoCC) cohort received four or more lines of therapy. Chapter 5 demonstrated that the monthly cost of treatment for the EoCC cohort increased with increasing lines of therapy, after adjusting for multiple sources of bias.

For displacement to be an important economic concern there must be:

- increasing number of treatments;
- increasing lines of therapy for which there is limited evidence; and
- evidence that a change in the line of therapy produces a change in the relationship between benefit and cost for a protocol.

The motivation for this Chapter is to assess whether the prerequisites for displacement to be an important economic concern exist in the clinical literature for Australia. This Chapter reports on the potential clinical consequences for displacement of a treatment from one line to therapy to a later line of therapy. This Chapter aims to:

1. establish the number of lines of therapy for which there is high quality evidence;
2. establish whether there are increasing therapeutic options in Australia; and
3. estimate the change in clinical effectiveness that occurs with displacement.



Abbreviations: EoCC: Elements of Cancer Care; EViQ: Cancer Treatments Online; PBAC: Pharmaceutical Benefits Advisory Committee; RCT: randomised controlled trial

Figure 33: Scheme of Chapter 6

The Sections in this Chapter are shown in Figure 33. Section 6.1 reviewed guidelines to assess the level of evidence for longer treatment sequences at the time of the EoCC cohort data collection. Section 6.2 assessed whether there are increasing treatment options in Australia. Section 6.3 conducted a meta-analysis of trials that estimated the change in effectiveness with the displacement of a protocol. Additional information about the searches, quality of the recovered studies and data extraction are presented in the Appendices E and F. No ethics approval was sought for this Chapter, as it involved the use of publicly available literature.

6.1 Available evidence for longer length of treatment sequence

One hypothesis that may explain the difficulty of incorporating an increased length of treatment sequence in economic evaluation is the limited clinical evidence that supports an increased treatment sequence length. The lack of clinical evidence makes it difficult to assess the clinical and economic impact of displacement.[203]

6.1.1 Methods

The existence of clinical evidence supporting multiple lines of therapy was assessed by reviewing Australian national and international guidelines for breast cancer, colorectal cancer (CRC) and non-small cell lung cancer (NSCLC).

Australian national guidelines reviewed were those published by the National Health and Medical Research Council (NHMRC) and those referenced on the Cancer Australia website. The initial search and review occurred on the 19/01/2015. A second review was conducted on the 24/02/2017.

Internationally, the guidelines examined were the National Comprehensive Cancer Network (NCCN) guidelines from the United States of America (US) and the NICE guidelines from the United Kingdom (UK). These were chosen for pragmatic reasons; they are published in English and considered authoritative.[204] The level and grading of evidence as well as any substantive comment related to the number of lines of therapy was extracted. The NCCN guidelines were searched on the 23/9/2014 and then again on the 19/01/2015. This involved accessing the NCCN website[ix] and reviewing the guidelines listed for breast cancer, colon cancer (or colorectal depending on the time of review) and non-small cell lung cancer. A third extraction was undertaken on the 28/02/2017 for the NCCN guidelines.

The UK NICE guidelines were searched on the 19/01/2015. The guidelines on the website[x] were reviewed for each disease (breast cancer, CRC and NSCLC). Where more than one guideline existed, the guidelines for advanced cancer were chosen. A second extraction was undertaken on the 3/03/2017.

6.1.2 Results

Australian guidelines 2015

Australian guidelines produced by the NHMRC involving metastatic colorectal, breast and non-small cell lung cancer were over 5 years old. The note on the NHMRC website suggested they may no longer reflect current practice. Accordingly, these have not been searched for their evidentiary basis for multiple lines of therapy.[205]

The Cancer Australia website[xi] included a collection of clinical guidelines. The topics included breast cancer and lung cancer. For breast cancer, there was a 2011 supplement to the NHMRC 2001 guideline regarding the use of chemotherapy in advanced breast cancer. It offered minimal guidance for later lines of therapy except to note that one of the unanswered questions for the use of chemotherapy in advanced breast cancer was “What

[ix] http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
[x] http://www.nice.org.uk/guidance/published?type=Guidelines
[xi] http://canceraustralia.gov.au/clinical-best-practice

evidence is available from clinical trials for treatment of metastatic breast cancer beyond the first-line setting?"[206]

For NSCLC, new clinical practice guidelines for the treatment of lung cancer were available in the form of a wiki.[207] In the discussion of third line therapy the comment was made that "Few randomised controlled trials (RCTs) have evaluated third line therapy in unselected patients with advanced NSCLC." The grade of evidence for third line therapy was level B which is considered a body of evidence to guide practice in most situations.[208] The level of evidence for third line treatment was considered level II, based on a RCT.[207]

These guidelines suggested that docetaxel, pemetrexed or erlotinib (grade B evidence, level II evidence) may be appropriate.[208]

There were no up to date guidelines available for metastatic CRC.

Australian guidelines 2017

There were no changes to the recovered literature from 2015 for breast cancer or CRC.
The lung cancer wiki (http://wiki.cancer.org.au/australia/Guidelines:Lung_cancer) suggested that erlotinib should be given as treatment, which was consistent with the 2015 recommendations.[209]

NCCN guidelines 2015

In 2014, the NCCN guidelines for NSCLC suggested that three lines of therapy be used. It was acknowledged that while treatment in first line is well supported by clinical evidence the recommendations for second and third line are less well supported. The first line therapy suggestions were supported by category one evidence (high level evidence), the second line by category 2A ("lower level evidence and uniform consensus") and the third line by category 2B ("lower level evidence and consensus the intervention is appropriate").[210] In 2015, three lines of therapy were also suggested and were supported by the same grades of evidence.[211] The discussion on page MS-38 noted that many new active pharmaceuticals were available for lung cancer but the reported response rates were low.

The 2013 version 3 NCCN guidelines for breast cancer included this paragraph on sequential treatment:

"sequential responses are often observed with chemotherapy, supporting the use of sequential single agents and combination chemotherapy regimens. The current guidelines include doses and schedules of these single agents and combination regimens for metastatic breast cancer. Failure to achieve a tumour response to three sequential chemotherapy regimens or ECOG performance status of three or greater is an indication for supportive therapy only."- Page MS-49.[32]

CRC had a more established set of protocols[xii] and a broad sequence algorithm attached to it in the 2013 NCCN recommendations. However, in 2014, no recommendations were made to continue treatment after completion of the first, second and third lines of therapy.[31] There were also several agents identified whose effectiveness when used after one another or in combination was not well understood (page MS-29-30). The use of several of the agents in a non-first line setting was supported by lower level evidence than in the first line setting in terms of number of trials but all the evidence was graded as 2A in the NCCN guidelines.

In 2015, another line of therapy, regorafenib, was added for use after the third progression.[46] It was also noted in these guidelines that choices of therapies in later lines will be altered by the therapies given in earlier lines. The guidelines also suggested not using several agents in later lines of therapy because a lack of evidence of effectiveness after prior use of standard therapies.

NCCN guidelines 2017

There were no changes to the advice offered in the 2016 breast cancer guidelines compared to the 2013 guidelines with regard to the three sequential chemotherapy regimens.[20]

Several new anticancer pharmaceuticals and protocols were discussed in the 2017 NCCN guidelines for colon cancer. These included nivolumab, pembrolizumab and trifluridine with tipiracil. The order in which these protocols (including regorafenib) would ideally be given was still not known with certainty.[212]

Since 2015, evidence has been developed for stratifying initial therapy based on histology (squamous cell carcinoma or not) and the molecular/genetic profile of the tumour (ALK, EGFR,

[xii] Protocol is the clinical term used to describe the treatments given within a line of therapy (defined in Chapter 2) and will be used in this Chapter, as it focuses on clinical evidence.

ROS and PD-L1), the consideration of maintenance therapy and the use of therapy post-progression.[213]

Maintenance therapy, including the use of pemetrexed (among others) after systemic chemotherapy, was considered an option. For patients with a mutation for EGFR therapy it was suggested that treatment continue but potentially include another anticancer agent, as anti-HER2 therapy is managed in breast cancer.[213]

After progression and the use of targeted agents, the options for treatment of patients with a sufficiently good performance status included docetaxel, pemetrexed and gemcitabine if these agents had not been used previously.[213]

There was also a discussion about emerging targeted agents for other mutations, including BRAF V600E, MET amplification, RET rearrangements and HER2 mutations.[213]

NICE guidelines 2015

NICE guidelines for the treatment of advanced breast cancer were released in July 2014.[214] They recommend up to three lines of therapy for patients (without anti HER-2 pharmaceuticals being considered), assuming anthracyclines have been used previously in treatment. The protocols for the three lines of therapy are docetaxel, vinorelbine and capecitabine. Of interest is the rationale for continuing use of RCTs in the evaluation of cost-effectiveness and effectiveness.

"Most patients with advanced breast cancer who receive chemotherapy will be given at least two different regimens and many will receive three. The available evidence to support decisions about the most clinically and cost-effective sequence in which to use these pharmaceuticals is extremely limited. There is also very little good quality evidence about the relative clinical and cost-effectiveness of currently recommended treatments, either in combination or in sequence. Following on from the recommendations in this guideline, it would be important to establish clinical trials to investigate this problem in a more systematic fashion than hitherto." Page 16.[214]

Guidelines for the diagnosis and treatment of lung cancer were released in 2011.[215] They provided evidence for two lines of therapy. According to these guidelines. pharmaceuticals are considered to be appropriate in the first and second line of therapy.

Guidelines for the treatment of metastatic CRC were released in December 2014.[216] They suggested the use of two lines of therapy.

NICE guidelines 2017

There was no change in the clinical practiced suggested from 2015 in the guidelines published in 2017.

Other material

Recent reviews considered the evidence for treatment in CRC after the second line of therapy.[73,203] The authors concluded that the level of evidence was poor with very few RCTs and that it relied mainly on retrospective analysis of previously received treatment. They suggested that phase 3 prospective trials be undertaken.[73,203]

6.1.3 Discussion

The guidelines produced in the UK, USA and Australia in 2015 used similar evidence and came to similar conclusions. There was good clinical evidence for initial lines of therapy but limited evidence for later lines of therapy. The recommendations differed regarding the number of lines of therapy that should be offered. The American and Australian guidelines generally suggested that more lines of therapy should be offered than the UK guidelines.

For non-small cell lung cancer two to three lines of therapy were recommended by all the guidelines. The pharmaceutical recommended for third line therapy in the Australian guidelines is recommended as first or second line therapy in the NICE guidelines. The updated guidelines published in 2017 showed some divergence between jurisdictions. The recent explosion in genetic and molecularly targeted agents were included in the NCCN guidelines in a manner that is not replicated in the UK or Australia.

There was widespread recognition that the evidence base for later lines of therapy was weak. However, different guidelines reached different conclusions about the exact number of lines of therapy supported by the evidence. In two of the three NCCN 2017 guidelines, pragmatic advice was given that after treatment in the initial lines of therapy, clinicians should consider the use of anticancer treatments that have shown to be effective in earlier lines of therapy, but which have subsequently been displaced with newer agents.

The evidence base is consistent with the number of lines of therapy that were included in the economic evaluations of treatment sequences discussed in Chapter 3. The limited evidence base that existed at the time of the EoCC data collection did not limit the number of lines of therapy in cancer treatment to the three lines of therapy for which strong evidence existed (see Chapter 4).

6.2 Therapeutic options available in Australia over time

Pharmaceuticals are licensed for use in Australia by the Therapeutic Goods Administration (TGA). Applications for public subsidy are considered by the Pharmaceutical Benefits Advisory Committee (PBAC) and, if approved for subsidy, the pharmaceutical is provided through the Pharmaceutical Benefits Scheme (PBS). Approval for listing on the PBS represents a substantial increase in access for patients to pharmaceuticals.[74]

One method of establishing whether there are increasing treatment options available is to assess whether the number of pharmaceuticals being subsidised for each disease is increasing. Alternatively, it could be assumed that an increasing number of pharmaceuticals being submitted for consideration for use by the PBAC is evidence of an increase in the number of available options. However, without subsidisation these options may not be readily available to the population.

The availability and potential use of pharmaceuticals could also be assessed via consideration of TGA applications. However, given the expense of treatments, subsidisation by the PBS is a major step in the availability of treatments. Therefore, the focus here is on the subsidisation of treatment through the PBS process.

EViQ is an online service provided by the Cancer Institute NSW and contains a collection of evidence-based chemotherapy protocols or treatments.[217] Protocols are developed by a multidisciplinary team and reviewed periodically.[218] EViQ was established to improve cancer control in New South Wales and its remit is to facilitate evidence-based medicine and reduce treatment variation.[218] EViQ claims widespread use by cancer clinicians in the Asia-Pacific region.[218] An increasing number of protocols also represent an increasing number of choices for cancer control and therefore the potential for increasing lines of therapy.

6.2.1 Methods

A review was undertaken of all applications made to the PBAC for metastatic breast cancer, metastatic CRC and advanced NSCLC. The review included applications whether successful or not. The website of applications[xiii] was searched on the 19/01/2015 and the documented outcomes of all PBAC meetings between the 1/01/2009 to the 31/12/2014 was searched using the keyword “cancer”. A second data extraction was undertaken on the 10/04/2017 for the

[xiii] http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes

outcomes of PBAC meetings held between 01/01/2015 and 01/12/2016. The relevant public summary documents supplied by the PBAC online were then reviewed.[219]

All successful applications for listing on the PBS were searched for pharmaceuticals that had an indication for metastatic non-small cell lung cancer, CRC and breast cancer. They were included if the pharmaceutical was a form of anticancer treatment whereas supportive treatment (such as antiemetics, pain relief and bisphosphonates) was excluded. Treatment restricted to early stage cancer (non-metastatic cancer) was excluded.

The public summary documents from each PBAC meeting were searched to identify all first-time rejections and deferrals. Any pharmaceutical which was the subject of a first-time rejected application and which referred to metastatic cancer was subsequently included. Only the first incidence of a successful submission and the first incidence of an unsuccessful submission were included in the data collection. If an application was initially unsuccessful and subsequently successful, only the successful application was included. The results were tabulated.

The oncology protocols at EViQ were also reviewed[xiv] on the 19/01/2015 and this was repeated on the 15/06/2017. The chemotherapy protocols for breast, colorectal and respiratory subsections were reviewed. For breast and CRC, the metastatic protocols were extracted. For lung cancer, only the protocols for non-small cell lung metastatic or advanced cancer were extracted. For each of the chemotherapy protocols reviewed the name of the protocol, the pharmaceuticals involved and the approval date were extracted. The results were then tabulated.

6.2.2 Results

Table 59 shows the applications received by the PBAC and their outcomes for the period 2009-2016 for the three cancer types of interest. The number of potential treatments subsidised through the PBS by the Federal Government for metastatic disease of each of the cancer types of interest increased over time. By 2016, at least two additional therapies were subsidised for each type of cancer. Additionally, for each cancer type, there was at least one further pharmaceutical available for treatment that was unsubsidised at the time of extraction.

[xiv] https://www.eviq.org.au/Category/tabid/65/categoryid/1/Default.aspx

Table 59: Successful and initial unsuccessful applications for funding through the PBAC process for pharmaceuticals for metastatic cancer

Year	Successful metastatic breast cancer Listings	Unsuccessful metastatic breast cancer Listings	Successful metastatic CRC listings	Unsuccessful metastatic CRC listings	Successful advanced NSCLC listings	Unsuccessful advanced NSCLC listings
2016				Trifluridine with tipiracil[220]	Ceritinib[221]	Nivolumab[222] Pembrolizumab[223]
2015	Lapatinib[224]	NAB-paclitaxel[225]				Nintedanib[226]
2014	Trastuzumab[227] Pertuzumab[228] Trastuzumab emtansine[227]			Regorafenib[229]		
2013	Eribulin[230] Everolimus[231]		Panitumumab[232]	Aflibercept[233]	Afatinib[234]	
2012	Vinorelbine[235]				Gefitinib[236] Erlotinib[237]	
2011			Capecitabine[238]			Bevacizumab[239]
2010						
2009					Pemetrexed[240]	

Abbreviation: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

The results for the new protocols approved by EViQ are displayed in Table 60. Over time there has been a continual increase in the number of protocols considered to have an evidence basis for treatment.

Table 60: Protocols by year of approval via EViQ

Year approved	Metastatic breast cancer	Metastatic CRC	Metastatic NSCLC
2004	1	1	1
2005	7	5	4
2006	3	2	3
2007	1	0	2
2008	4	1	0
2009	2	1	1
2010	0	2	0
2011	0	2	0
2012	4	5	5
2013	0	8	3
2014	4	0	2
2015	1	4	0
2016	2	0	0

Note: the website for the EViQ is **www.eviq.org.au**
Abbreviations: CRC: colorectal cancer; EViQ: Cancer Treatments Online; NSCLC: non-small cell lung cancer

6.2.3 Discussion

This review demonstrated that there were increasing options available for treating CRC, breast cancer and NSCLC in Australia. This was reflected in the increased number of pharmaceuticals both submitted to the PBAC and available for subsidisation by the PBS for each cancer type of interest. The number of protocols considered by experts to have a sufficient degree of evidence to be included in EViQ was also found to be increasing. In turn, this implies that there is real potential for displacement of treatments.

The estimation of available treatments undertaken does not accurately represent the increase in available protocols. There are barriers to entry to both applications to the PBAC and to listing on EViQ. Therefore, the number of new agents may exceed those suggested in this review.

6.3 The effectiveness of displaced protocols

In this Section a systematic review and meta-analysis of the clinical literature of displaced protocols was undertaken. It reports the results of RCTs in which protocols are used in different lines of therapy. The null hypothesis is that the line of therapy in which a protocol is

used does not impact on the clinical outcomes of that protocol. That is, displacement does not alter the effectiveness of a protocol.

This Section's specific aims were to estimate whether:

- the effectiveness of a protocol altered with displacement;
- the toxicity of a protocol altered with displacement; and
- the length of time on treatment and intensity of a protocol altered with displacement.

There is a scarcity of economic evaluations involving multiple lines of therapy, as discussed in Section 3.1. One-third of the economic evaluations assessed were based on a single RCT with multiple lines of therapy. Although the results of these economic evaluations provided limited information about the implications of displacing a protocol from one line of therapy to a subsequent line, the majority modelled a reduction in effectiveness associated with displacement of a protocol (see Chapter 3).

The approach undertaken in this Section was to review the clinical literature to assess whether there was evidence that the effectiveness of a treatment or protocol is independent of its place in a treatment sequence (that is, what line of therapy it is in). In this context, the best evidence available is that from RCTs.[102] Such evidence has been used where possible, supported by lesser grades of evidence.

The clinical evidence was synthesised in a meta-analysis and the results used to accept or reject the hypothesis that the effectiveness of a protocol will not change when it is displaced from one line of therapy to a subsequent line of therapy.

The seven stages of research synthesis as enumerated by Cooper are[241]:

- formulating the problem;
- searching the literature;
- gathering information from studies;
- evaluating the quality of the studies;
- analysing and integrating the outcomes of the studies;
- interpreting the evidence; and
- presenting the results.

The problem identified was to assess the impact on the effectiveness of a protocol when it is displaced from one line of therapy to the next. This was investigated by identifying trials where

trial participants were randomised to receive the same protocol, but in different lines of therapy.

This type of study design can be thought of as a variation of a crossover trial (pseudo-crossover) where participants receive more than one intervention. An example is shown in Figure 34.[242] The comparison made in this instance is between protocol A used in first line treatment (arm 1 of the trial) versus protocol A used in second line treatment (arm 2 of the trial).

As these trials were randomised trials participants in both arms should have the same characteristics in aggregate at the point of recruitment. However, when protocol A is compared across the arms, the effectiveness may differ because participants in arm 2 received chemotherapy prior to being given protocol A while those in arm 1 did not. This is termed a carryover effect; that is the treatment given in the first period has an effect that impacts on second period.[242]

This is analogous to what may happen if a new protocol is introduced and the existing protocol is displaced to the next line of therapy. If displacement does not affect the effectiveness of a protocol, it should be equally effective regardless of its use as first or second line therapy. However, if protocol A is affected by displacement, the introduction of a new protocol and displacement of protocol A will affect its effectiveness (and potentially its cost-effectiveness). It is necessary to measure the impact of changing a line of therapy on the effectiveness of a protocol to reject the hypothesis that the clinical outcomes of a protocol are unaltered by its displacement into a later line of therapy.

This type of trial design can produce two or more comparisons per trial. In the example below, two comparisons are possible within the same trial, one for protocol A and one for protocol B. For this reason, the number of comparisons available may be larger than the number of trials.

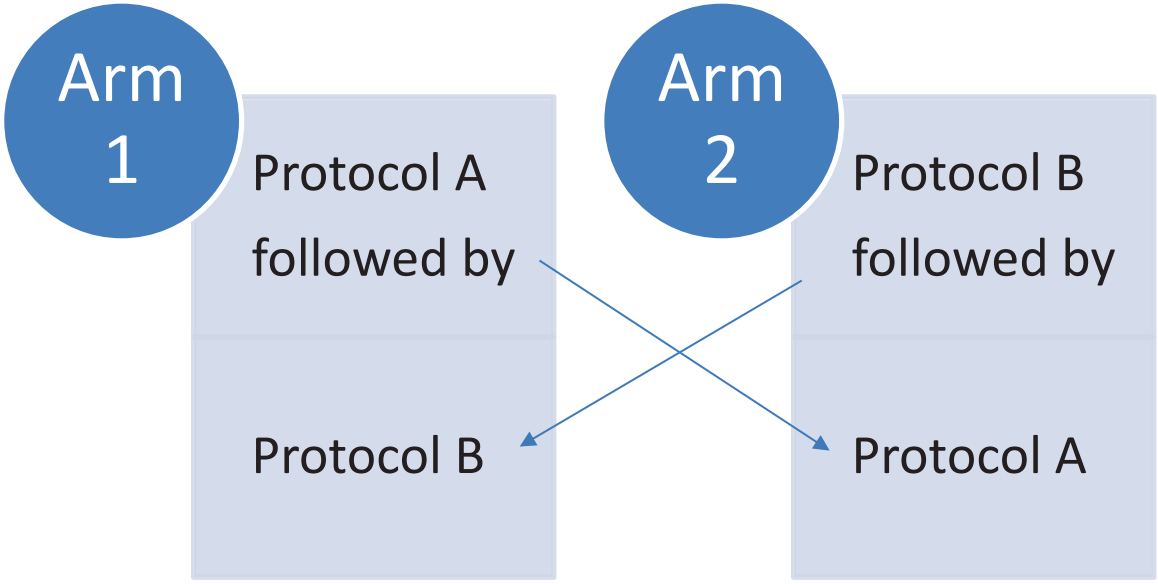


Figure 34: Schemata of trials and protocols

The three measurements of effectiveness that were included in the analysis were tumour response to treatment, progression free survival and toxicity. These were chosen on the basis that are regularly reported clinical trial endpoints of potential significance.[243]

One method of assessing the effectiveness of a protocol is by measuring tumour response to treatment. This is to evaluate whether the protocol reduces the tumour burden (overall response) or that the tumour burden does not increase it (disease control). In the guideline on the "evaluation of anticancer agents in man" the European Medicines Agency suggests that, despite its shortcomings, response rate is a convincing measure of tumour activity.[115] Overall response rate and disease control have been shown to be correlated with overall survival in some cancers but to a lesser extent than progression free survival (PFS).[244]

One of the features of chemotherapy is that it is toxic, that is, it produces significant adverse events which affect patients' health and wellbeing. It is conventional for trials of oncology treatments to collect and publish information on common toxicities associated with the administration of chemotherapy. Toxicity can be very important in terms of its impact on the effectiveness and cost-effectiveness of a cancer protocol.[50] It can result in treatment breaks, dosage reductions or cessation of the treatment, reduce the quality of life of patients and may result in costly medical intervention.[50]

There is a theoretical reason to suggest that displacing a protocol from one line of therapy to the next may impact on the toxicity experienced by patients. Essentially, chemotherapy affects a patient's reserve or capacity to cope with further chemotherapy without experiencing adverse consequences.[245]

Toxicity of chemotherapy treatment is often reported based on the type and grade of adverse events associated with treatment. Type or category of toxicity is based on the kind of adverse event, for example, low white cell count, low haemoglobin, haemorrhage, biochemical abnormality, fatigue, nausea, pain etc. The grade is a measure of the intensity or severity of the toxic event with higher grades usually representing a more toxic episode.[246] In one system of categorising adverse events, the common terminology criteria for adverse events (CTCAE) are grades based on a scale from one to five. One represents a minor or mild adverse event and five represents death. Not all toxicities have all five grades associated with them; for example, the toxicity of allergic rhinitis (sneezing and nasal stuffiness) is only allowed to be graded 1 or 2. At the upper end of the scale, elevated cardiac troponin (associated with cardiac disorders) only has grades 3, 4 and 5 associated with it.

A higher incidence of toxicity may not result in increased healthcare costs. Some lower grade adverse events may not result in increased healthcare costs or have a significant impact on quality of life or wellbeing. However, most adverse events with grade 3 severities are symptomatic and will require treatment which will be associated with an increased use of healthcare resources. Therefore, it is reasonable to suggest that an increased incidence of significant toxicities associated with a treatment would increase costs and decrease quality of life. Ceteris parabis, a treatment which results in an increase in the incidence of the higher grades of toxicity, will be less cost-effective.

6.3.1 Methods

A systematic literature search was undertaken with an emphasis on RCTs. The search was designed to identify literature reporting the results of trials or other research which compared the sequential administration of two or more lines of systematic therapy for carcinomas with the same protocol being administered in at least two arms of the trial in different lines of therapy. Therefore, a trial had to involve a choice of treatment in lines of therapy associated with displacement of a protocol.

Medline, Pubmed and EconLit were searched using a variety of key words (outlined in the Appendix E). Abstracts were reviewed and if the article was thought to be potentially informative a full-text review was undertaken.

Articles were included if they contained either data or a discussion relating to two or more lines of therapy given sequentially for the treatment of cancer separated by failure, which could be represented by progression or intolerable toxicity. One protocol was required to be given in different lines of therapies.

Only carcinomas were considered.[xv] Citation pearl searching of included papers was undertaken with the reference list hand searched and articles that cited the original paper (identified through the citing function in PubMed and Medline) were also hand searched. The recovered literature was required to be in English (or an English translation available).

The details of the literature search and the data extraction are presented in Appendix E and Appendix F. Briefly, details of the protocols, study design, population, rationale for undertaking the study, the number of enrolled patients, chemotherapy regime and tumour location were extracted.

Specific information about effectiveness parameters of displaced therapy including overall survival, progression free survival, the toxicity associated with the lines of therapy, the response of the tumour to the protocol in terms of both overall response and disease control and the number of adverse events reported were also extracted from the relevant papers. The length of time on treatment in each line of therapy and the intensity of the treatment was also extracted.

The quality of the included RCT studies was evaluated using the CONSORT checklist[247] STROBE was used to evaluate the quality of the observational studies.[248]

A second quality assessment was used to judge the information provided regarding the pseudo-crossover studies. The assessment used a scoring system produced after an initial review to ensure statistical combination of the trials was possible. The components and development of the checklist are detailed in the Appendix F. The statistical quality assessment produced a score from zero to six based on the completeness and ease of the extraction of the appropriate information for a meta-analysis.

[xv] Sarcoma, leukaemia, lymphoma and myeloma and brain and spinal cord cancer were excluded.

Meta-analysis refers to the combining of results, through statistical methods, of the results of two or more separate studies.[102] It usually involves a two-step process The first step is the extraction of a summary statistic from each of the studies involved.[249] The second step is the calculation of a weighted average of the statistics across studies. Problems can arise when an article does not report all the information required for an input to the meta-analysis.[250]

The summary statistics can be combined using either fixed effects methods (which assume one true effect size which is shared between studies and that any differences are due to sampling) or random effects methods (which allow for a degree of heterogeneity of the effect size between studies because of differences in numbers of participants or treatments[102]). As the studies included a variety of different pharmacological treatments and cancers, it would be unreasonable to assume that there was a common treatment effect, and a random effects model was considered the most appropriate. The predictive interval, the range over which the results of a subsequent trial would be expected, was calculated.

A traditional method of displaying the results of a meta-analysis is via a forest plot where each study has an associated square and horizontal line.[249] The size of the square represents the weight of the study and the line represents the confidence interval. The summary effect is usually represented with a diamond and the predictive interval with lines radiating from the diamond.

The meta-analysis was conducted comparing the same protocols within different arms of a trial: Protocol A in one line of therapy versus Protocol A in another line of therapy (as shown in Figure 34 above [displacement]).

The random effects meta-analyses of the comparison of protocols in one line of therapy to a later line of therapy included overall response of the tumour to treatment (a dichotomous outcome) and disease control of the tumour to treatment (a dichotomous outcome).

The number of studies included in each of the meta-analyses was determined by the presence of the summary statistics from each of the identified trials and the inclusion of only RCT studies or both RCT and observational studies. The non-RCTs were not included in the other statistical analysis.

The median PFS in each of the lines of therapy was also compared using a ratio. If the number of events or the number of at risk persons were reported, the hazard rate was calculated from the available information making the assumption of an exponential function using the

methods outlined in Hacksaw (2009).[251] The results were calculated for each protocol, tumour type and an overall combined hazard ratio.

The median and mean time of therapy was also extracted from the papers and compared naively using ratios of the different lines of therapy.

For the adverse events, a dichotomous variable, the presence or absence of a grade 3 or grade 4 adverse event was combined using a meta-analysis; the relative risk ratio was the outcome measure. A random effects model was used for the reasons discussed above.

As a secondary analysis, the percentage of participants who had specific adverse events (for example neurological events or low haemoglobin) was estimated. The ratio of adverse events in each line of therapy was calculated. The probability of adverse events per cycle was calculated using an assumed exponential survival function from the median or mean number of cycles and the ratio comparing the second line to the initial lines was calculated. The median or mean number of cycles were weighted by the intensity of treatment when available. The results were reported separately for the means and medians. This calculation was repeated for the probability based on the progression free survival when available.

Stata version 15 was used to conduct the statistical analysis.[173] The metan command was used for the analysis and the graphical representation of the meta-analysis.[249]

6.3.2 Results

The details of the Medline search (the search with the most prolific return) are shown in Table 61 below. The full details of the literature search are provided in Appendix E.

Table 61: Details of literature search in Medline

Action	Criteria	Return
Search Medline	"sequenc*".m_titl	128 940
Search Medline	"algorith*".m_titl	19 863
Search Medline	chemotherapy.mp. or Drug Therapy/	321 289
Search Medline	Combined the results with "and"	617
Removal of duplicates	Using endnote duplicate function	608
Abstract review	Reviewed abstract to consider for full review	76
Full review	Kept from full review	19

A CONSORT diagram is outlined in Figure 35. Three electronic databases were queried, Medline (617 records screened), EconLit (1 330 records screened) and PubMed (217 records screened). The last data extraction was on 27/06/2017. Additionally, pearl searching recovered 25 records from the Medline search, three records from the EconLit search and two records from the PubMed search.

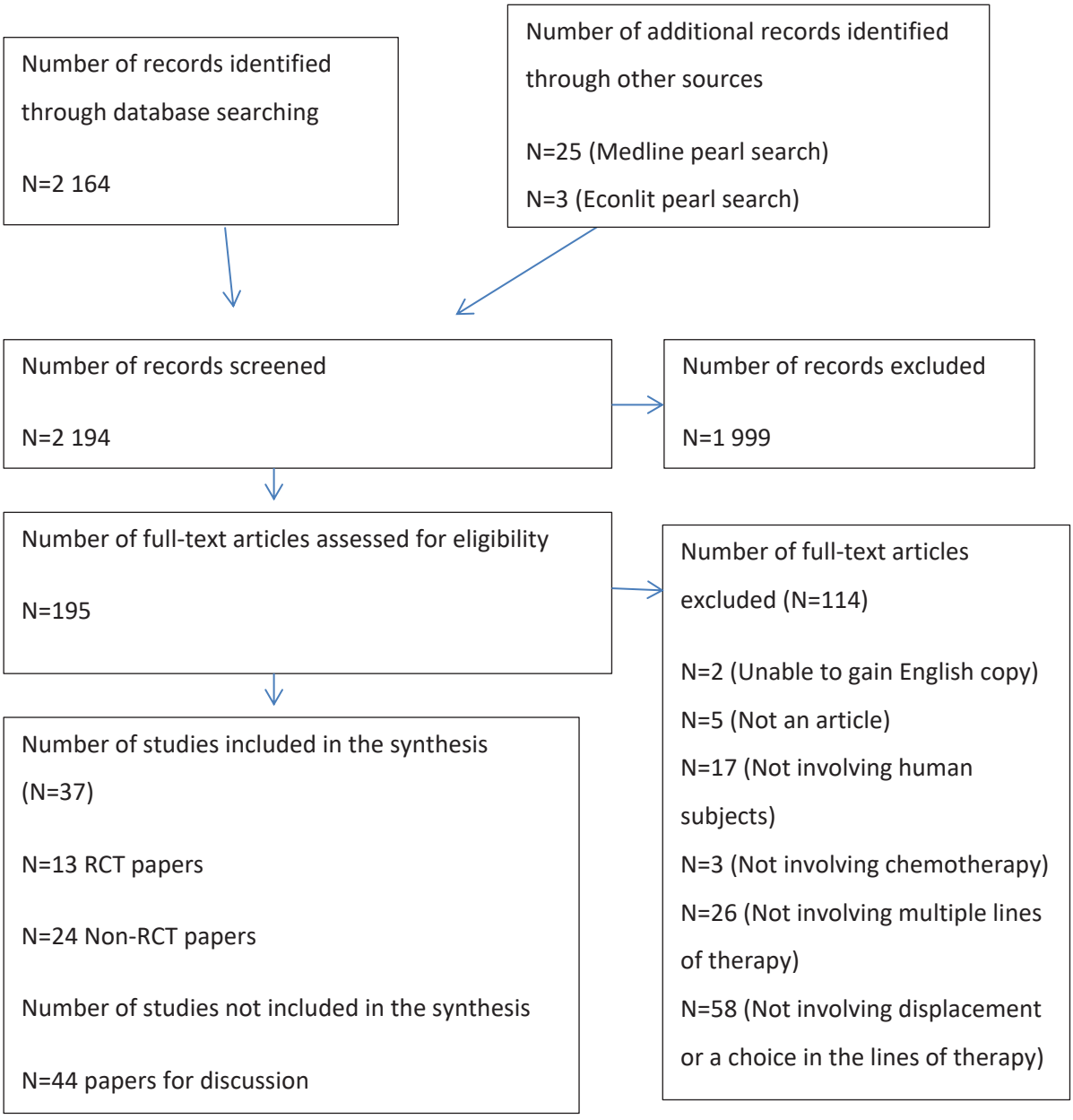


Figure 35: Systematic literature review of clinical studies involving multiple lines of therapy

The literature recovered was divided into three types of articles.

1. RCTs involving the preplanned use of multiple lines of therapy separated by failure are included in this Chapter. Thirteen papers were identified, two examined the same trial[252,253] and the latter was included. These papers were included in the meta-analysis synthesis.
2. Non-RCT collections of evidence regarding effectiveness and toxicity of the use of multiple lines of therapy separated by failure are discussed in this Chapter. Twenty-four papers were identified, of which 20 had unique extractable information. These papers were included in the sensitivity analysis and discussion.
3. Discussion pieces that did not involve the generation of new information were included in this Chapter and as background information in Chapter 2. Forty-four papers were identified are were included in the discussion.

A broad set of information about the 12 RCTs is shown in Table 62. The most common cancer investigated was CRC and the next most studied was NSCLC. CRC was investigated in the first decade of the 21st century and lung cancer in the second decade. This broadly corresponded to the introduction of new pharmaceutical agents into general treatment use; oxaliplatin and irinotecan for CRC and erlotinib for NSCLC. In each of the trials, two or more protocols were compared and some of the arms of the trial reversed the sequence of protocols. For example, in Manegold et al. (2005)[254] the two protocols evaluated were gemcitabine and docetaxel. In one arm of the trial participants received gemcitabine initially; if the disease progressed or there was unacceptable toxicity, they received docetaxel. In the other arm of the trial participants received docetaxel first and gemcitabine after progression.

Table 62: Recovered randomised control trials

Study	Title	Year published	Cancer	Number of participants	All participants could receive the same pharmaceuticals
Tournigand et al. (2004)[68]	FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study	2004	CRC	226	Yes
Manegold et al. (2005)[254]	Randomized Multicenter Phase II Study of Gemcitabine Versus Docetaxel as First-Line Therapy with Second-Line Crossover in Advanced-Stage Non–Small-Cell Lung Cancer	2005	NSCLC	147	Yes
Koopman et a. (2007)[71]	Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial	2007	CRC	820	Yes
Seymour et al. (2007)[72]	Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial	2007	CRC	2 135	Yes
Dahan et al. (2010)[255]	Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301)	2010	Pancreatic	202	Yes
Ducreux et al. (2011)[256]	Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial	2011	CRC	410	Yes
Kim et al. (2011)[257]	Docetaxel/cisplatin followed by FOLFIRI versus the reverse sequence in metastatic gastric cancer	2011	Gastric	58	Yes
Le Caer et al. (2011)[100]	A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study)	2011	NSCLC	99	Yes
Gridelli et al. (2012)[258]	First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial	2012	NSCLC	760	Yes

Study	Title	Year published	Cancer	Number of participants	All participants could receive the same pharmaceuticals
Le Caer et al. (2012)[99]	A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study)	2012	NSCLC	100	Yes
Eichelberg et al. (2015)[118]	SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer	2015	Renal cell carcinoma	365	Yes
Motzer et al. (2014)/Knox et al. (2017)[252,253]	Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC	2014/2017	Renal cell carcinoma	471	Yes

Abbreviation: CRC: colorectal cancer; NSCLC: non-small cell lung cancer; RCC: renal cell carcinoma

The CRC studies were primarily concerned with the sequencing of the small number of available pharmaceuticals that had shown activity in trials of first and second line treatment. The CRC trials had as their underlying question "What is the best sequence of treatment?" Tournigand et al. (2004)[68] was designed to determine the "best sequence to treat patients with metastatic colorectal cancer." Seymour et al. (2007)[72] was concerned with answering the question "in the context of non-curative cancer treatment, how should active drugs be sequenced to provide patients with the maximum duration of disease control and minimum of adverse events?" There was a concern that the results of previously conducted trials in CRC could not be interpreted in terms of the overall survival benefit because of the lack of detail about additional lines of therapy (called salvage therapies) that had been given after the completion of the trials.[71,72] This was especially problematic because the availability of these treatments was variable during the time the trials were undertaken.[256] This was part of the rationale for CRC trials. It was believed that the use of additional lines of therapy may have resulted in upwardly biased estimates of overall survival benefits, essentially attributing increased survival to the initial use of a pharmaceutical. In Seymour et al. (2007)[72] the multiple ways in which the pharmaceuticals were sequenced produced five arms. The results of these trials have been synthesised previously and it was concluded that the order of treatment does not matter to the outcome.[31]

The NSCLC RCTs were conducted mainly in elderly patients who were unable to be treated with the aggressive therapy that would be given to younger patients with lung cancer. The rationale for the trials was that current clinical knowledge provided potential alternatives for treatment, but the evidence did not exist regarding their sequencing or order. The NSCLC trials involving erlotinib, an agent associated with a specific type of NSCLC, produced evidence that there were large differences in effectiveness between sequences.[100,258] When erlotinib was used in the first line of therapy it resulted in poorer performance compared to its use in the second line. Erlotinib performed better in patients whose tumour had a specific gene mutation. Although this information was not known at the time the pharmaceutical was approved,[259] it is possible that patients with the gene mutation are more likely to survive to receive second line treatment. Thus, erlotinib may be more relatively more successful in the second line of therapy when the proportion of the treatment group with the necessary mutation increases.[259] This suggests that prognostic gene mutations that are also a target for therapy may be important in the consideration of treatment sequences.

The articles reporting the results of RCTs for gastric cancer, renal cell carcinoma and pancreatic cancer also noted the lack of clinical trials directly involving treatment sequences as part of the rationale for the trials.[252,253,255,257]

Twenty-four non-randomised publications were included in the review. Twenty had extractable information. Renal cell carcinoma (9), prostate cancer (4) and NSCLC cancer (3) were the most common cancers. Other cancers covered by this type of study included ovarian cancer (1), CRC (2) and gastric cancer (1). Seventeen of the 20 extractable studies were retrospective in nature while three were prospective.

As was noted for the RCTs, a major underlying theme identified in the majority of the non-randomised studies was the lack of definitive knowledge about the optimal sequencing of therapies to improve survival. This was noted in articles covering prostate cancer,[260] renal cell carcinoma[261] and ovarian cancer.[245] Most studies also commented on the lack of knowledge of the outcomes following the use of in subsequent lines of therapy of treatments shown to be effective in the first line of therapy. That is, the impact on the clinical outcomes of displacing a treatment from the first line of therapy to the second line of therapy was recognised to be unknown.

Within the non-randomised control studies, nine examined the sequencing of pharmaceuticals with a similar action for the same cancer. These studies focused on the tyrosine kinase inhibitors (sorafenib and sunitinib) used to treat metastatic renal cell carcinoma. Both agents target the same set of molecules and researchers were concerned about cross-resistance between the agents.[262]

The discussion sections of the non-RCT papers focused on the optimal sequencing of protocols for lung cancer,[14] breast cancer[263] and prostate cancer.[23] All papers identified a paucity of high level evidence to guide rational choices about sequencing treatments. A summary of the information extracted from each RCT paper is shown in Table 63.

Table 63: Type of information extracted from RCTs

Study	OR by line	DC by line	PFS_{01}	PFS_{12}	Toxicity by line	Cycles by line	Intensity by line
Tournigand[68]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Koopman[71]	Yes	Yes	Yes	No	No	Yes	No
Manegold[254]	Yes	Yes	Yes	No	No	Yes	No
Seymour[72]	Yes	Yes	Yes	Yes	Yes	Yes	No
Dahan[255]	Yes	Yes	Yes	No	Yes	Yes	No

Study	OR by line	DC by line	PFS_{01}	PFS_{12}	Toxicity by line	Cycles by line	Intensity by line
Kim[257]	Yes	Yes	Yes	No	Yes	Yes	Yes
Ducreux[256]	Yes	Yes	Yes	No	Yes	Yes	Yes
Le Caer et al. (2011)[100]	Yes	Yes	Yes	No	Yes	Yes	Yes
Gridelli[258]	Yes	No	Yes	No	No	No	No
Le Caer et al. (2012)[99]	Yes	Yes	Yes	No	Yes	Yes	Yes
Eichelberg[118]	Yes	Yes	Yes	Yes	Yes	No	No
Knox[253]	No	No	Yes	No	Yes	Yes	Yes
Totals	**92%**	**83%**	**100%**	**25%**	**75%**	**92%**	**50%**

Abbreviations: DC: disease control; OR: overall response; PFS: progression free survival

All the studies reported the progression free survival from the start of the trial to the first progression (PFS_{01}). Most studies did not report the progression free survival from the first progression to the second progression (PFS_{12}) separately. Two of the three studies that reported this information specified the number of events (progressions and deaths).

All the RCT papers reported information about adverse events but in a variety of formats including aggregating the lines of therapy. Adverse events of grade 3 or grade 4 severity were consistently reported. The category of adverse event reported differed between the trials. The breakdown of adverse events reporting was usually "by patient."

"By patient" means that the incidence of the adverse events was reported as the number of participants experiencing at least that grade of adverse event. For example, in Ducreux et al. (2011),[256] 2% of participants were reported to have experienced a grade 3-4 cardiac event. What was not reported was the number of times that patients experienced that adverse event or adverse events of a lower grade. In this example, 2% of participants had a cardiac event but they could have had multiple cardiac events. Accordingly, it would not be accurate to suggest that the cardiac event rate was 2% in the trial. One trial, Kim et al. (2011),[257] reported the haematological adverse events by the total number of cycles received.

The majority of studies (11) were considered to be of satisfactory quality. One study was considered to have significant flaws and was regarded as poor quality. Manegold et al. (2005)[254] did not report confidence intervals around the primary endpoint or overall survival and did not report how randomisation occurred.

In the majority of studies, information was missing about how randomisation occurred and the methods of blinding, for example, if the assessment of tumour response was blinded to the intervention or clinical assessment of progression. Only one study (Ducreux et al. [2011][256])

provided complete details on randomisation, blinding and assessment. The details of the literature are presented in Appendix F.

Four studies reported significant changes after the commencement of the trial: Ducreux et al. (2011)[256] ceased recruitment because the addition of targeted agents changed the standard of care. Manegold et al. (2005)[254] was ceased because of poor recruitment and poor feasibility of the docetaxel arm, which was confirmed by contemporaneous trials. Kim et al. (2011)[257] had poor recruitment because the standard of care for first line treatment was altered after the commencement of the trial. Gridelli et al. (2012)[258] was terminated early because the inferiority threshold was crossed at the interim analysis.

One study, Gridelli et al. (2012)[258] was missing information about several areas of the interest. Three studies - Seymour et al. (2007),[72] Eichelberg et al. (2015)[118] and Tournigand et al. (2004)[68] - included more information than the remainder of the studies, notably, extractable information about PFS_{01} and PFS_{12} (see Table 64).

Table 64: Quality of information extracted from the RCTs

Study	Tournigand[68]	Manegold[254]	Koopman[71]	Seymour[72]	Dahan[255]	Ducreux[256]	Kim[257]	Le Caer (2011)[99]	Gridelli[258]	Le Caer (2012)[100]	Eichelberg[118]	Knox[253]	Average
PFS_{01} and PFS_{12}	1	0	0	1	0	0	0	0	0	0	1	0	25%
Number at risk or number of events	0	0	0	1	0	0	0	0	0	0	1	0	17%
OS and 1-year survival	0.5	0	1	1	1	1	0.5	1	0.5	1	0.5	0.5	71%
Overall response (OR) and disease control (DC)	1	1	1	1	1	1	1	1	1	1	1	0	92%
Adverse effects	1	0	0	1	1	1	1	1	0	1	1	1	75%
Usage	1	1	1	1	1	1	1	1	0	1	1	1	92%
Sum	4.5	2	3	6	4	4	3.5	4	1.5	4	5.5	2.5	3.7

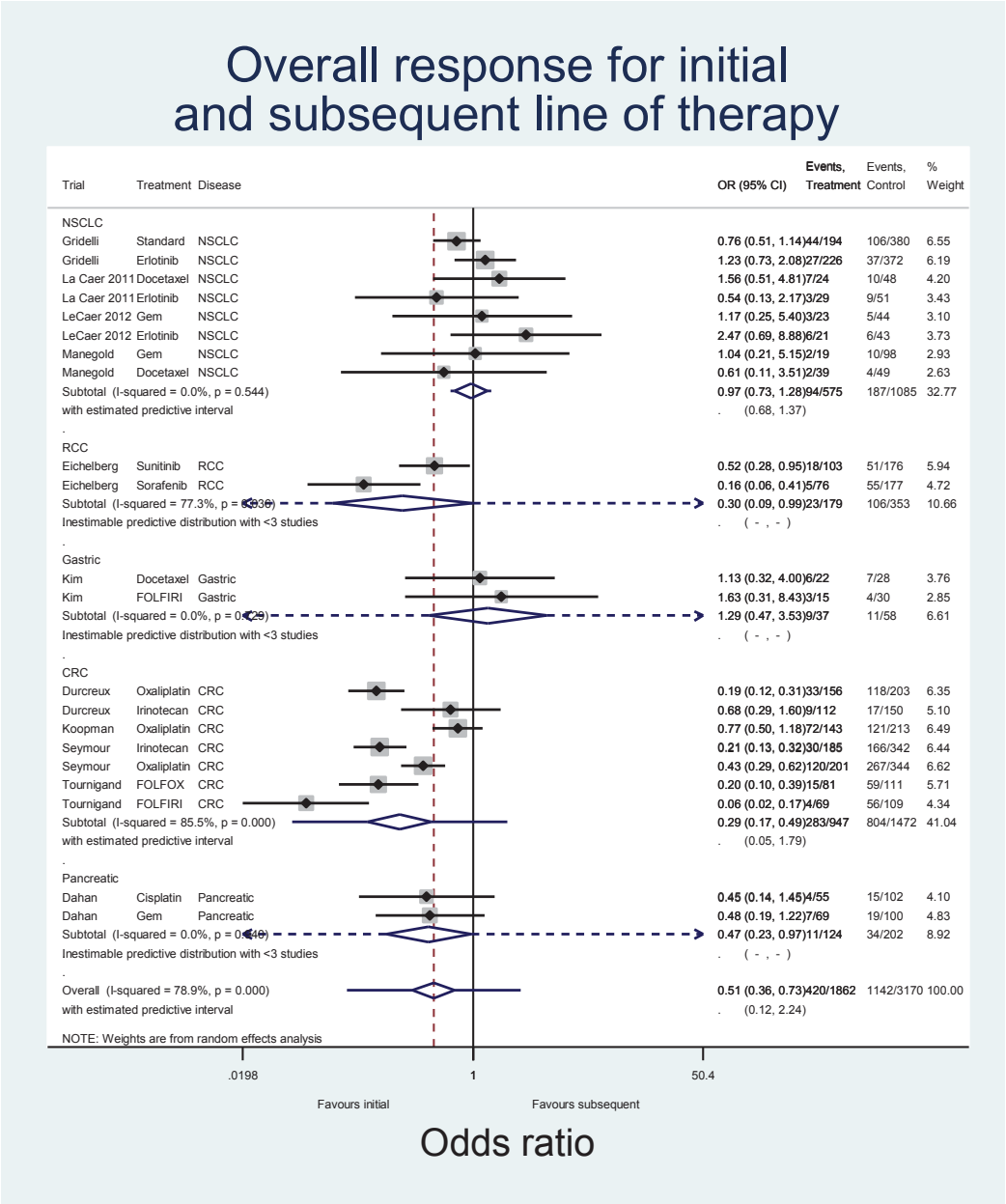
Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

The results of the meta-analysis for overall response is shown in Figure 36 below. The results illustrate the odds ratio of achieving an overall response (at least some shrinking of the tumour) to a protocol. Here the control (usual treatment) is the initial line of therapy and the intervention is giving the protocol in a subsequent line of therapy.

The figure breaks down the odds ratio for each of the cancer types seen. The number of participants who received an initial line of therapy exceeded the number of patients who received second line therapy. Approximately 60% of participants received a subsequent line of therapy in these analyses.

An odds ratio of less than one suggests that the initial line of therapy is more effective at producing a response. An odds ratio of more than one suggests that the subsequent line of therapy is more effective at producing a response. The trials are grouped into cancer types and the protocol used.

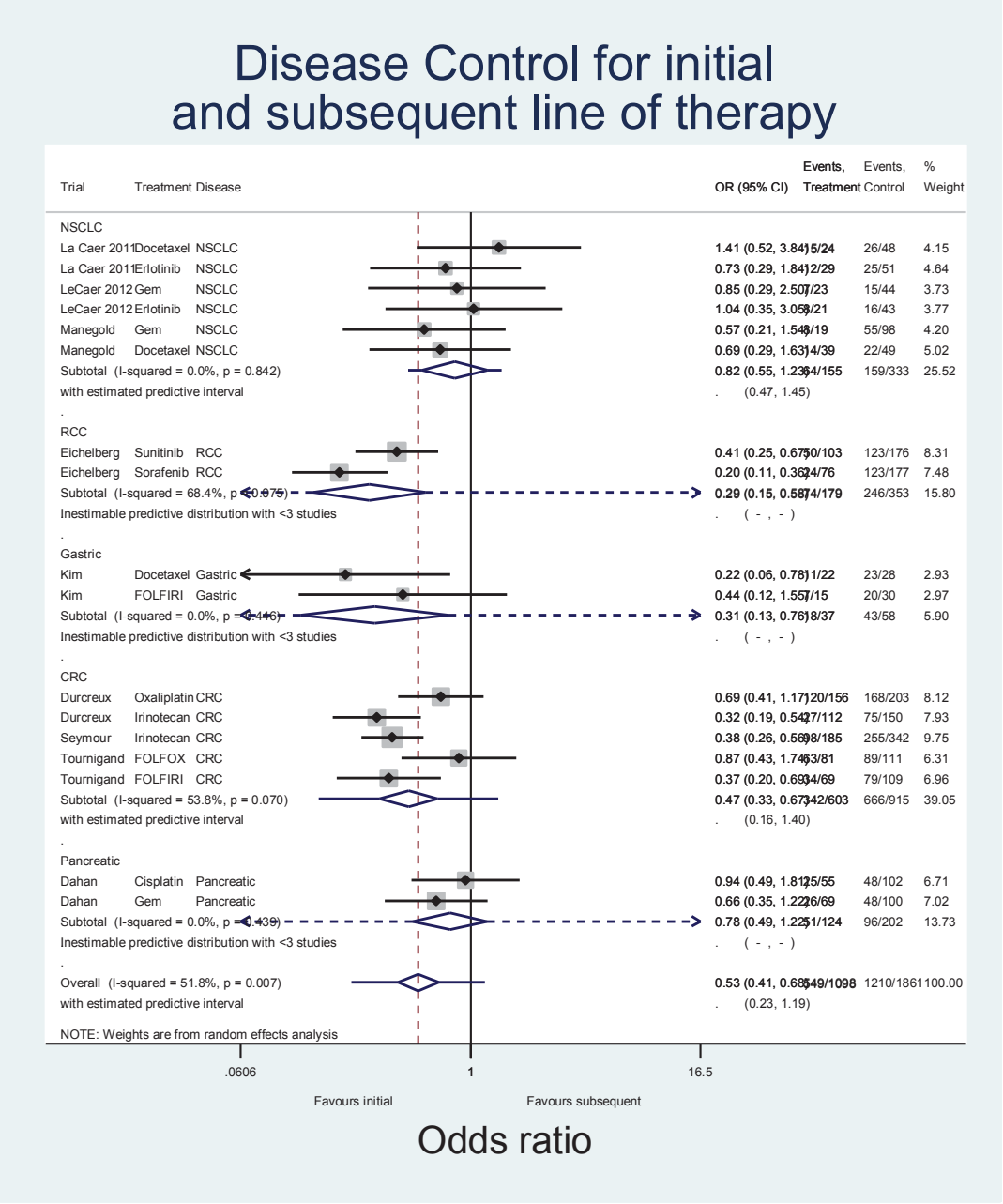
In aggregate, there was a statistically significant reduction in the proportion of participants who responded to treatment. There was a high degree of heterogeneity (I^2 = 78.9%) consistent with a priori expectations that the results should not be combined with an expectation of a single mean treatment effect. The mean treatment effect was an odds ratio of 0.51. However, the estimated predictive interval, that is, the estimated range of the treatment effect for 95% of protocols given in the subsequent line of therapy varied between odds ratios of 0.1 and 2.2.



Abbreviations: CI: confidence interval; CRC: colorectal cancer; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; Gem: gemcitabine; NSCLC: non-small cell lung cancer; OR: odds ratio; RCC: renal cell carcinoma

Figure 36: Forest plot of meta-analysis results comparing overall response between initial and subsequent lines of therapy

A similar forest plot is shown for disease control in Figure 37. This excludes one trial that was included in Figure 36, namely Gridelli et al. (2012)[258] because it only reported overall response. Therefore, the numbers are slightly different. The degree of heterogeneity and the predictive interval are lower for disease control than for overall response.



Abbreviations: CI: confidence interval; CRC: colorectal cancer; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; Gem: gemcitabine; NSCLC: non-small cell lung cancer; OR: odds ratio; RCC: renal cell carcinoma

Figure 37: Forest plot of meta-analysis results comparing disease control between initial and subsequent lines of therapy

Several of the non-RCT papers included sufficient information to allow the extraction of overall response and disease control data. These were added to those extracted from the RCTs and the aggregate results are shown in Table 65 below. The results were similar to those produced by the RCT only meta-analysis. There continues to be a high degree of heterogeneity and the predictive interval exceeds one (indicating some chemotherapy may be more effective in the second line of therapy).

Table 65: Odds ratio of response to treatment in a subsequent line of therapy (RCT and non-RCT) meta-analysis

Outcome	OR (95% CI)	I^2	Number of comparisons	Predictive interval
Overall response	0.49 (0.37-0.64)	71.5%	40	0.12-1.92
Disease control	0.59 (0.47 to 0.74)	62.6%	32	0.21-1.63

Abbreviations: CI: confidence interval; OR: odds ratio; RCT: randomised controlled trial

Several sensitivity analyses were conducted on the meta-analysis.

1. Excluding the RCT studies ranked as poor.
2. Excluding the RCT studies that were subject to significant changes after the start of recruitment.
3. Excluding the RCT studies with fewer than 50 participants in the first line of therapy.
4. Treating each RCT study (and the arms within it) as a single piece of information.

Table 66: Sensitivity analysis for meta-analysis

Analysis of RCTs	Overall response (95% CI) as odds ratio	Overall response predictive interval as odds ratio	I^2	Disease Control (95% CI) as odds ratio	Disease control predictive interval as odds ratio	I^2
Base	0.51 (0.36 to 0.73)	0.12 to 2.24	78.9%	0.53 (0.41 to 0.68)	0.23 to 1.19	51.8%
Exclude studies ranked with quality of poor	0.5 (0.34 to 0.72)	0.11 to 2.27	80.8%	0.52 (0.4 to 0.69)	0.21 to 1.27	56.9%
Exclude studies that were subject to significant change	0.42 (0.27 to 0.66)	0.09 to 2.03	78.1%	0.57 (0.41 to 0.79)	0.2 to 1.61	62.6%
Exclude studies with less than 50 participants in initial arm	0.4 (0.27 to 0.69)	0.09 to 1.75	81.9%	0.49 (0.37 to 0.64)	0.21 to 1.14	57.4%
Each study entered once	0.54 (0.36 to 0.8)	0.13 to 2.18	84.6%	0.53 (0.41 to 0.69)	0.25 to 1.16	60%

Abbreviations: CI: confidence interval; RCT: randomised controlled trial

The exclusion of the study ranked as having poor quality had minimal impact on the estimates. The sensitivity analysis shows a similar pattern to the base case. That is, the estimates of the odds ratios for both mean overall response and mean disease control of a protocol that was displaced is less than one, while the predictive interval exceeds one.

Only three trials (6 arms) provided information about progression free survival for both an initial and subsequent line of therapy.[68,72,118] Two of these involved the same cancer type (CRC) and the same protocols. The third was for renal cell carcinoma.

Table 67: Association between PFS and displacement for RCTs

Study	Protocol	PFS_n	PFS_{n+1}	PFS_{n+1}/ PFS_n
Tournigand et al. (2004)[68]	FOLFIRI	8.5 months	2.5 months	29%
	FOLFOX	8 months	4.2 months	53%
Seymour et al. (2007)[72]	FOLFIRI	8.5 months	4.4 months	55%
	FOLFOX	8.7 months	4.8 months	52%
Eichelberg et al. (2015)[118]	Sorafenib	5.9 months	2.8 months	47%
	Sunitinib	8.5 months	5.4 months	64%

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; PFS: progression free survival

The number of events (progression and death) in each line of therapy was available for Seymour et al. (2007)[72] and the hazard ratio was calculated using the approximation suggested by Hacksaw (2009)[251] assuming an exponential distribution. The hazard ratio for FOLFOX was 1.8 (95% CI 1.5 to 2.2) and for FOLFIRI it was 1.9 (95% CI 1.6 to 2.3). Combined the hazard ratio was 1.869 (95% CI 1.646 to 2.123).

The hazard ratio associated with sunitinib in the second line was 1.57 (95% CI 1.16 to 2.15) and the hazard ratio for sorafenib was 2.1 (95% CI 1.53 to 2.9). The combined hazard ratio was 1.81 (95% CI 1.45 to 2.26). If both cancer (four arms) were combined, the hazard ratio in being displaced from first to second line was 1.855 (95% CI from 1.66 to 2.07)

Most results from the non-randomised studies were consistent with those from the RCTs. Studies of prostate cancer,[260,264] CRC[265] and NSCLC.[266] showed a reduction in the PFS with treatment in a subsequent line of treatment. The non-RCT publications had 28 comparisons for PFS between an initial line of therapy and a subsequent line of therapy, 23 showed a decrease in PFS for a subsequent line of therapy, one the same and four an increase in the PFS for a subsequent line of therapy. The average PFS_{12}/PFS_{01} ratio across the treatments was 74%.

The median length of treatment in the second line of therapy is, on average, 80% of the median length of treatment in the first line of therapy. In one case, erlotinib, the length of treatment in the second line exceeded that of the first line treatment.

The difference in the intensity of treatment was not statistically significantly in the subsequent line of therapy compared to the initial line of therapy. The average intensity of treatment in

the subsequent line of therapy was 100% of the average intensity of treatment in the initial line of therapy (Table 68).

Table 68: Intensity of treatment in different lines of therapy

Study	Protocol	Pharmaceutical	Intensity in initial line	Intensity in subsequent line	Ratio (subsequent /initial)
Tournigand et al. (2004)[68]	FOLFIRI	Irinotecan	85.9%	87.3%	101.6%
		5-FU	22%*	11%*	
	FOLFOX	Oxaliplatin	84.7%	90.1%	106.4%
		5-FU	33%*	10%*	
Kim et al. (2011)[257]	Docetaxel	Docetaxel	95.1%	92%	96.7%
		Cisplatin	95.1%	92%	96.7%
	FOLFIRI	Irinotecan	86.2%	87.5%	101.5%
		5-FU	86.2%	87.5%	101.5%
Ducreux et al. (2011)[256]	FOLFOX6	Oxaliplatin	69%	77%	111.6%
		5-FU	81%	81%	100.0%
	FOLFIRI	Irinotecan	81%	82%	101.2%
		5-FU	79%	78%	98.7%
Le Caer et al. (2011)[100]	Gemcitabine/ Docetaxel	Gemcitabine	79%	74%	93.7%
		Docetaxel	85%	90%	105.9%
Le Caer et al. (2012)[99]	Gemcitabine	Gemcitabine	65%	51%	78.5%
Knox et al. (2017)[253]/Motzer et al. (2014)[252**]	Everolimus	Everolimus	94%	98%	104.3%
	Sunitinib	Sunitinib	85%	87%	102.4%
Mean (SD)			**83.4% (8.5)**	**83.6% (11.1)**	**100% (7.4)**

Note: * The reported percentage were the proportion of individuals who received the maximal amount of 5-FU in a cycle, these are not included in the calculations of mean and standard deviation
** The intensity results for Knox et al. (2017)[253] came from Motzer et al. (2014)[252]
Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; SD: standard deviation

There was no information about the intensity of treatment in the non-RCT studies. Information was presented about median length of treatment in three studies (six comparisons); the average ratio across the comparisons was 64%. One study (two comparisons) presented mean length of treatment and the average ratio was 85%.

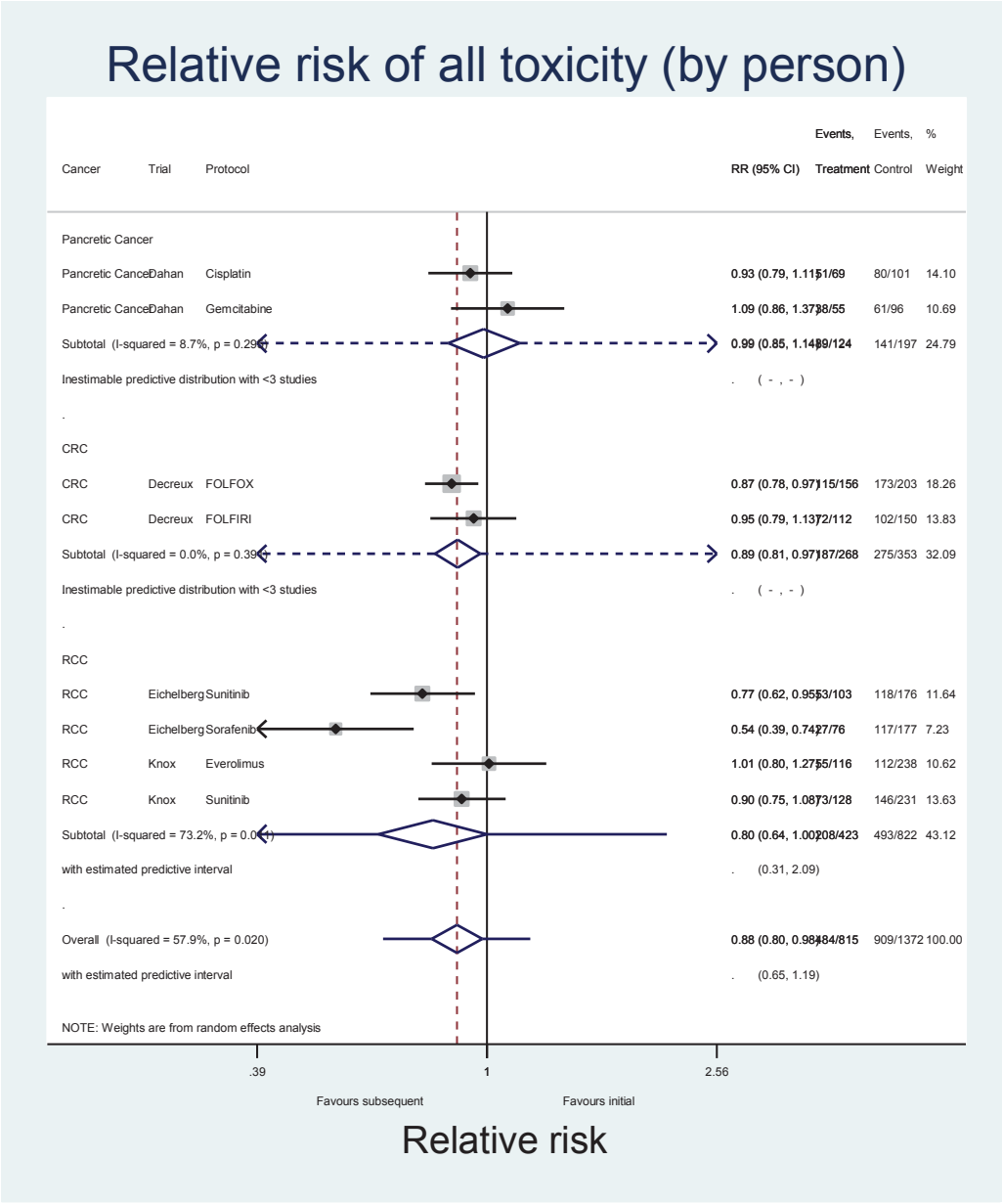
Nine trials reported the toxicity outcomes using different measures (Table 69). Most reported "by person," whereas one trial[257] reported the haematological adverse events by actual number of events. The non-haematological adverse events were reported "by person." Four studies reported the number of people who experienced grade 3 and grade 4 adverse events in the first and second lines of therapy.

Table 69: Adverse event outcomes in RCTs

Study	Some adverse events	All adverse events	Treatment available	Intensity of treatment available	Both PFS available
Tournigand et al. (2004)[68]	Yes	No	Median	Yes	Yes
Seymour et al. (2007)[72]	Yes	No	Median	No	Yes
Dahan et al. (2010)[255]	Yes	Yes	Median	No	No
Kim et al. (2011)[257]	Yes	No	Mean	Yes	No
Ducreux et al. (2011)[256]	Yes	Yes	Median	Yes	No
Le Caer et al. (2011)[100]	Yes	No	Mean	Yes	No
Le Caer et al. (2012)[99]	Yes	No	Mean	Yes	No
Eichelberg et al. (2015)[118]	Yes	Yes	Mean	No	Yes
Knox et al. (2017)[253]	Yes	Yes	Median	Yes	No

Abbreviations: PFS: progression free survival; RCT: randomised controlled trial

The results of the meta-analysis of the presence or absence of grade 3 or grade 4 adverse events in shown in Figure 38. There was a small decrease in the risk of adverse events with the displacement of a protocol from one line of therapy to a subsequent line of therapy.



Abbreviations: CI: confidence interval; CRC: colorectal cancer; RCC: renal cell carcinoma; RR: relative risk

Figure 38: Meta-analysis of relative risk of toxicity in subsequent line (compared to initial line)

Table 70 shows the ratio between the subsequent and initial lines of therapy for the CRC RCTs where the progression free survival was available for both lines of therapy.[68,72] A number greater than one indicates a higher PFS in the subsequent line of therapy. As with the meta-analysis of risk (Figure 38) the ratio of adverse events in the subsequent line of therapy to the initial line of therapy was less than one. The average ratio, adjusted by the mean PFS, was 1.92. That is, the rate of adverse events was, on average, 92% higher in a subsequent line of therapy, compared to the initial line of therapy per unit time.

Table 70: Ratio of adverse events of CRC studies with PFS01 and PFS12

Grade 3 and above category of adverse event	Naïve ratio of probabilities (range)*	Ratio of rate per PFS month (range)**	Ratio of probability per PFS month (range)***
	Haematological		
Anaemia	1 (1 to 1)	2.65 (1.9 to 3.4)	2.64 (1.9 to 3.38)
Thrombocytopenia	5 (5 to 5)	9.52 (9.52 to 9.52)	9.52 (9.52 to 9.52)
Neutropenia	0.8 (0.48 to 0.94)	1.83 (0.93 to 2.97)	1.76 (0.8 to 2.85)
Febrile neutropenia	0.14 (0.14 to 0.14)	0.48 (0.48 to 0.48)	0.47 (0.47 to 0.47)
	Non-haematological		
Alopecia	0.75 (0 to 1.5)	1.44 (0 to 2.89)	1.45 (0 to 2.9)
Cutaneous	0.25 (0 to 0.5)	0.47 (0 to 0.95)	0.47 (0 to 0.94)
Diarrhoea	0.62 (0.45 to 0.8)	1.38 (0.86 to 1.94)	1.34 (0.83 to 1.86)
Fatigue	0.95 (0.25 to 1.66)	2.01 (0.85 to 3.17)	2.01 (0.83 to 3.19)
Hand/Foot Syndrome	1 (1 to 1)	1.87 (1.81 to 1.93)	1.87 (1.81 to 1.93)
Lethargy	1 (0.95 to 1.04)	1.87 (1.72 to 2.02)	1.86 (1.7 to 2.02)
Mucositis	2.15 (0.3 to 4)	4.31 (1.01 to 7.61)	4.34 (0.98 to 7.71)
Nausea	1 (0 to 2)	1.9 (0 to 3.8)	1.92 (0 to 3.85)
Nausea and vomiting	0.63 (0.5 to 0.77)	1.18 (0.96 to 1.4)	1.16 (0.94 to 1.39)
Neurological	0.58 (0.58 to 0.58)	1.12 (1.12 to 1.12)	1.02 (1.02 to 1.02)
Pain	0.87 (0.63 to 1.11)	1.62 (1.22 to 2.01)	1.59 (1.17 to 2.02)
Sensory Neuropathy	0.4 (0.3 to 0.5)	0.75 (0.54 to 0.96)	0.74 (0.52 to 0.96)
Stomatitis	1 (0.5 to 1.5)	1.84 (0.96 to 2.71)	1.84 (0.96 to 2.72)
Vomiting	0.65 (0.3 to 1)	1.46 (1.01 to 1.9)	1.44 (0.98 to 1.9)
Average across adverse events	0.94	1.92	1.90

Note * ratio of risk (relative risk)
** the rate for each line of therapy was calculated by dividing the number of events by the mean PFS
*** the probability for each line of therapy was calculated by using an exponential distribution over the assumed mean PFS, analogous to a hazard rate ratio
Abbreviation: PFS: progression free survival

Most of the non-randomised studies did not report toxicity by line of therapy. In those that did, it was noted that toxicity was higher for a protocol used in a later line of therapy compared to an earlier line, namely for ovarian cancer,[245] prostate cancer[264] and CRC.[265] Others reported similar rates of adverse events in the initial line of therapy to the subsequent line of therapy.

6.4 Discussion

A priori, a random effects model was determined to be the appropriate method of meta-analysis. The mean of the odds ratio for overall response to a protocol was estimated as 0.51 (95% CI 0.36 to 0.73) in a subsequent line of therapy compared to an initial line of therapy. The estimated predictive interval was calculated as being between 0.12 and 2.24. The corresponding estimate of the mean for disease control was 0.53 (95% CI 0.41 to 0.70) and the predictive interval was 0.23 and 1.19.

These results suggest that on average the effectiveness of a protocol decreases as it is displaced. However, it suggests that this is not the case for all protocols.

Results from published research have shown that response to treatment has a lower correlation with overall survival than PFS has with overall survival.[244] The most robust evidence of changes in clinical outcomes associated with displacement demonstrated that disease control and overall response are correlated with patient relevant outcomes (increased survival and quality of life). However, PFS has a higher correlation with overall survival but was reported less comprehensively in the trials used in the meta-analysis. The three trials that reported PFS for the second line of therapy separately all demonstrated a reduced PFS for the subsequent line of therapy relative to the initial line of therapy.

The relative risk of adverse events in the second line of therapy decreased (RR=0.88). However, this did not consider the relationship between toxicity and benefit. The benefit of chemotherapy (as measured by PFS) fell by a greater amount so the impact of adverse events per unit time is likely to have increased. The probability of experiencing at least one adverse event of grade 3 or greater severity was estimated at 66% (Figure 38). A meta-analysis of trials reported a similar result of 70%.[267]

It is reasonable to conclude that, on average, the use of a protocol in a subsequent line of therapy results in a decreased response to treatment (OR and DC); probably a shorter PFS and possibly an increased level of toxicity per period of time. This is consistent with clinical expectations that prior treatment with chemotherapy is likely to have an impact on the outcomes of subsequent chemotherapy treatment.[268] A multivariate analysis by Lyman et al. (2011)[268] suggested that the odds ratio of severe febrile neutropenia was 1.9 (95% CI 1.345 to 2.755) for those who had received prior chemotherapy relative to those who had not.[268] This result is consistent with the results of the toxicity analysis in this Section for CRC. This analysis found that the rate of adverse events per unit time was on average 1.9 times greater in the second line of therapy relative to the initial line of therapy.

Haematological adverse events are more common in the first cycle of treatment,[269] in patients with comorbidities,[270] in older patients[268] and in those who had prior chemotherapy treatment.[268] All these factors are likely to increase in participants who receive a protocol in a later line of therapy.

Approximately 57% of participants who initially received a line of therapy had a subsequent line of therapy. This ranged from 39% for NSCLC to 76% for CRC. This is consistent with

observational studies where 70% of CRC patients in a trial received a second line of therapy.[271] It is lower than the portion of the EoCC cohort that received a second line of therapy (88%) (see Section 4.3). However, the EoCC cohort was biased upwards for the number of lines of therapy because recruitment occurred after the initiation of treatment. The proportion of the EoCC cohort who received an additional prospective line of therapy was 53% (see Section Chapter 5), albeit with some censoring.

The trials used in the meta-analysis were of a specific form, described as pseudo-crossover. Crossover is defined when each individual receives multiple treatments and acts as their own control.[242] One of the areas of concern about crossover trials is the existence of a carryover effect.[102] In this analysis, the carryover effect was the subject of analysis. As such, individual participants would be included in multiple comparisons; for example, in the Manegold et al. (2005)[254] trial an individual participant could be in the gemcitabine comparison (for the initial line of therapy) and the docetaxel comparison (for the later line of therapy if they received it). This may violate the usual assumption, in a meta-analysis, that the individual comparisons are independent.[241]

Accordingly, a sensitivity analysis was conducted in which the arms within trials were combined in one comparison (Table 66) so that individual comparisons were independent. This made minimal difference to the results. The meta-analysis was based on the aggregated results of the RCTs. Patient level data may have allowed stronger conclusions to be drawn. The high level of heterogeneity confirms that there is variation between studies and the point estimate is not a reliable guide to the effect size of an individual protocol.

A more precise association between displacement and the impact on PFS and toxicity was demonstrated with a less statistically robust method than was used to evaluate the response to treatment. Naïve comparisons, means and weighted medians were used, primarily because the data available from the published trials were inconsistent in terms of comprehensiveness and the use of medians in the time to event statistics. The number of events and the number of patients at risk were not consistently reported. The lack of this information results in unstable estimates of standard errors with reconstructed statistics.[272] As other authors have noted, the reporting of life tables and sufficient statistics to enable data from published RCTs to be used in meta-analyses would be useful.[273] Three studies (six comparisons) had sufficient information to allow the calculation of the difference between an initial and subsequent line of therapy (assuming an exponential distribution). These results suggested that the hazard ratio was higher in the subsequent line of therapy.

The difficulties of combining information about toxicity in other systematic reviews has been noted.[274] The increase in toxicity with increasing lines of therapy is consistent with evidence from cohort studies that demonstrate an association between increased numbers of adverse events, prior treatment and worsening clinical function.[268] Additionally, more lines of therapy will result in higher cumulative doses of chemotherapy which, in turn, is associated with increased rates of some adverse events.[275]

The literature review and meta-analysis confirm that the results of trials of treatments used in different lines of therapies do not represent current clinical practice. In the Australian context, cancers such as breast cancer were not represented in either the RCTs or nonrandomised studies. Even those cancers that were well represented, such as CRC and lung cancer, were not represented in studies covering all available protocols, notably the protocols that include antibody therapies. Except for erlotinib, the treatments for lung cancer and CRC are cytotoxic compared to the more recently developed targeted therapies. Therefore, the external validity of the results presented in this Section is limited when applied to current practice.

While the problem identified by the non-RCT studies is an important one, their contribution was of limited value. This was primarily due to the retrospective nature of most of the data reported in the studies. This type of study design results in a significant issue of selection bias which in turn affects the interpretability of the results. Three main problems were identified.

First, inclusion in a retrospective study requires a participant to have received two lines of therapy. In the RCT literature between 46% and 73% of participants who received an initial line of therapy received two or more lines of therapy. Therefore, in the case of the non-RCT literature, there is an inherent sample selection bias whereby selection of participants who received two lines of therapy was only a proportion of those who might have been considered for two lines of therapy at the beginning of their treatment. It is likely that this group was biased towards participants who are clinically more robust than those who did not receive two lines of therapy. Therefore, the results are not applicable to a population commencing initial treatment.

The second problem flowed from the non-randomised nature of selection to treatment sequences. It is possible that patients might have been selected to receive one or other treatment initially based on unobserved information. As such, it is likely that the relative benefits of the selected treatment sequences were not directly comparable. For example, if there are significant differences in the adverse event profile of the alternatives, a choice might

be made to give an individual one protocol rather than another if a clinician judges that the patient has a higher probability of experiencing that adverse event. For example, patients with a pre-existing risk for a haematological adverse event may be prescribed a treatment with a more neurological toxic profile. One advantage of non-randomised studies is that they may provide a more realistic picture of the relative impact of toxicity and PFS in practice. Unfortunately, the toxicity data reported in the retrospective studies was not as detailed as that available for RCTs. Hence, it was not possible to undertake the same type of statistical review of the relative toxicity of first line versus second line therapy as was possible using the RCT data.

The third problem was that it was unclear in several papers how many additional lines of therapy had been given either prior to or after the therapies of interest. If the number of treatments was different between the alternatives, then a biased comparison will be made. It was also difficult to be confident regarding the comparison of overall progression free survival times.

Together, these issues made it very difficult to use the information from the non-randomised studies. Therefore, there are significant caveats on the conclusions drawn from them. The lack of information available in the RCTs about PFS_{12} (as opposed to PFS_{02}) and the number of participants at risk made it impossible to conduct a formal meta-analysis on more patient relevant issues, such as PFS.

Four of the trials included in the RCTs reported significant changes to the trial design after recruitment had started. The main reason given was the changing nature of expected or usual care during the trial period. The potential for changes to usual care during a trial is likely to increase as the number of new anticancer pharmaceuticals entering the market increases. Therefore, RCTs comparing multiple lines of therapy may not be a realistic trial design in the future and estimation of multiple lines of therapy will require the use of non-RCT information. Information will be required from the period after the completion of an RCT and the modelling of cost-effectiveness from multiple sources will continue to be necessary.

6.5 Conclusions

There is the potential for displacement in Australia. There is limited evidence for the length of treatment sequence and increasing availability of treatments. As shown in Chapter 4, the limited evidence does not restrict the use of treatments with 13% to 18% of participants in the Elements of Cancer Care cohort receiving four or more lines of therapy.

There is also evidence from RCTs that displacement alters the clinical effectiveness of a treatment protocol. Displacement is associated with decreased effectiveness as measured by overall response and disease control. It is also associated with a reduced progression free survival time. It is possible that the increased rates of toxicity (measured per unit time). That is, treatments are more toxic and less effective when displaced.

The results also show that only a proportion of those initially treated receive subsequent lines of therapy. This is consistent with the results of Chapter 4 but is not consistent with some of the economic evaluations of treatments sequences discussed in Chapter3.

These conclusions are limited by the external validity of the trials, which mainly involved traditional chemotherapy agents and not the newer targeted treatments.

Chapter 7 Modelling the cost-effectiveness of displacement

The previous Chapters have demonstrated limited economic evidence regarding treatment sequences is, at least partially, the result of a lack of clinical evidence (Sections 3.1,3.2 and Chapter 6). There is limited clinical evidence available for later lines of therapy to treat breast, colorectal and non-small cell lung cancer (Section 6.1). The Elements of Cancer Care (EoCC) cohort received a greater number of lines of therapy than the evidence supported (Chapter 4).

Previous modelling work has demonstrated a lack of consideration of heterogeneity and an assumption of constant costs over time within and between lines of therapy (Section 3.1 and 3.2).

There is potential for a loss of social welfare if protocols of treatments are displaced in therapy from one line to another without consideration of the changes in their costs and effectiveness (Chapter 2). The empirical evidence from the EoCC data supported these results. It suggested that the time to next treatment is shorter in later lines of therapy and that the cost per month increased in later lines of therapy, even after adjusting for bias (Chapter 5).

If displacement occurs, it can alter the clinical outcomes of a protocol (Chapter 6). On average the clinical effectiveness of a protocol worsened with displacement in meta-analysis of randomised controlled trials.

The motivation of this Chapter is to estimate the economic impact of displacement. The relationship between costs and benefits must be estimated to show this economic impact.

This Chapter has two aims.

1. The first aim is to model the change in cost-effectiveness and net monetary benefit of displaced simple protocols. The protocols varied in their marginal cost and administration schedules.
2. The second aim is to model the changes in cost-effectiveness and net monetary benefit of displaced simulated protocols. These protocols are based on real-world applications to the Pharmaceutical Benefits Scheme (PBS). The results reported in Chapters 5 and 6 are used to populate the models.

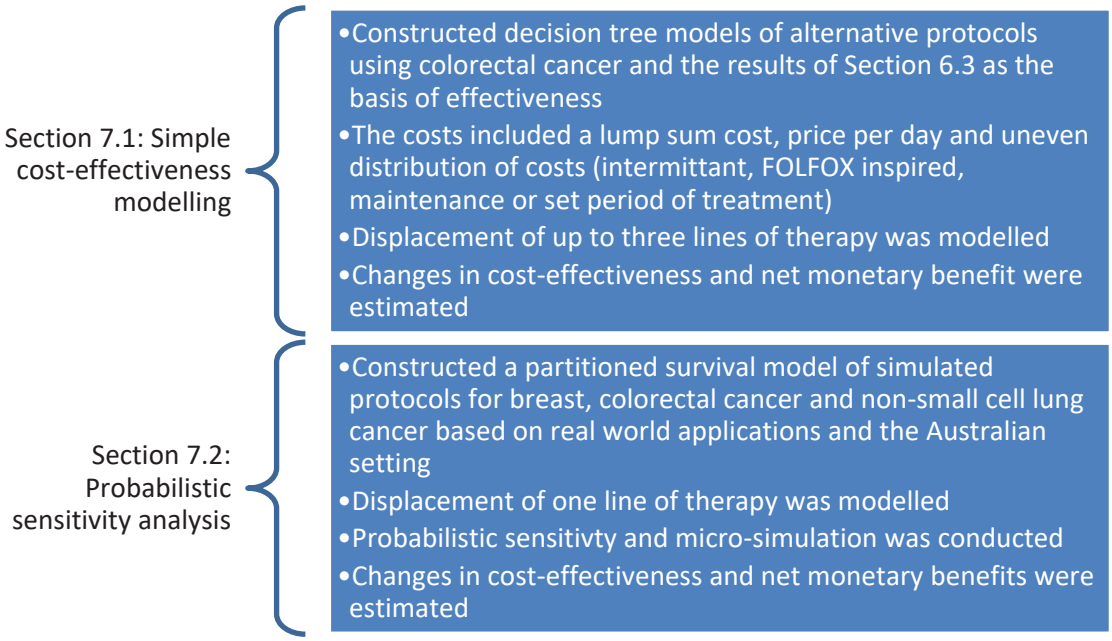


Figure 39: Components of Chapter 7

The Sections in the Chapter are shown in Figure 39. Section 7.1 constructed a decision tree analysis of displacement using different cost structures. Section 7.2 constructed a probabilistic sensitivity analysis based on the results of Chapter 5, Chapter 6 and recent submissions to the Pharmaceutical Benefits Advisory Committee (PBAC). The detailed parameters and further sensitivity analysis (including tornado diagrams) are included in Appendix G. No ethics approval was sought for this Chapter. Ethics approval has been given for the use of the EoCC project (see Chapter 4).

7.1 Simple cost-effectiveness analysis

A cost-effectiveness analysis that modelled the consequences of displacement was developed. Several different relationships between costs and benefits were assumed (lump sum cost, constant cost, intermittent infusion etc.).

The context for decision-making is shown in Figure 40 (which is a breakdown of the steps described in Table 1 in Chapter 2). Two protocols were accepted for subsidisation. Initially protocol A was accepted as a result of a decision based on the relative cost-effectiveness of two alternatives, no treatment and protocol A.

A subsequent decision was made based on a cost-effectiveness comparison between two alternatives, protocol B and protocol A. The current cost-effectiveness problem was to

estimate the incremental benefit and cost of the alternatives protocol B followed by protocol A (protocol B→ protocol A) versus protocol B followed by no further treatment.

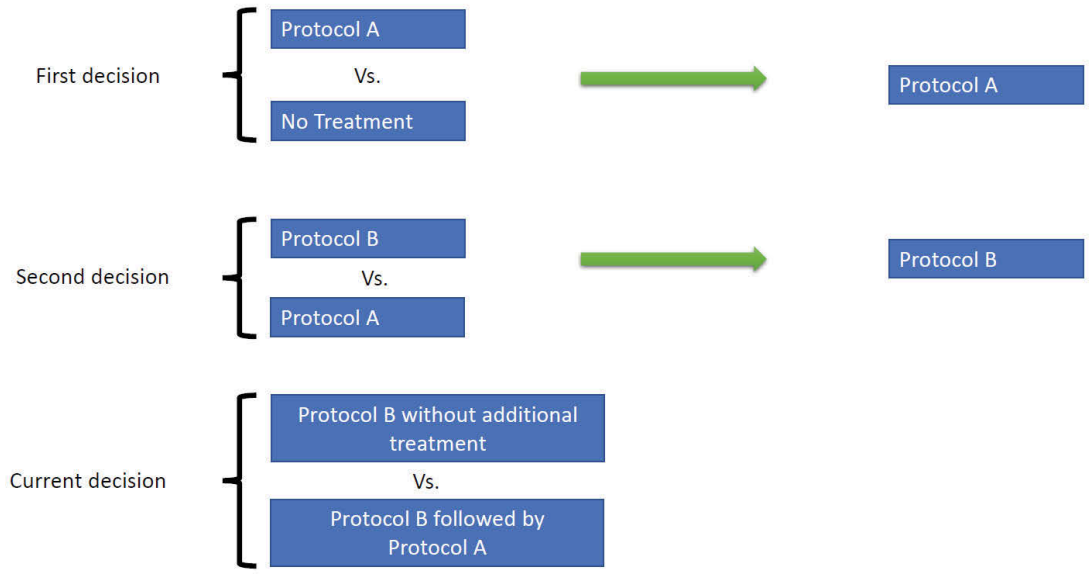


Figure 40: Context of decision-making for displacement

7.1.1 Model and structure

The perspective adopted was the Australian health system perspective. This healthcare system was detailed in Section 4.2 and was the setting for the cost-effectiveness analysis. A lifetime time horizon was applied using quality adjusted life years (QALYs) as the measure of outcome. Costs were estimated in 2015 Australian dollars. A discount rate of zero was assumed in the base case as the mean lifetime survival was less than two years.

The most common approach in the published literature used to model multiple lines of therapy was the additive approach to progression free survival (PFS) as an estimate of health outcome (Section 3.1). This approach was used in Rautenberg et al. (2014)[2] and Wong et al. (2009)[1] and is used in this Section.

The modelled scenario was that a manufacturer offers a pharmaceutical at a price, with that price either accepted or rejected by the decision-maker. If accepted, the pharmaceutical is available for use without restriction. There is a threshold willingness to pay (WTP) for QALYs at which the decision-maker will list the pharmaceutical for reimbursement and this is known by the manufacturer.

The offering price will always be such that the incremental cost-effectiveness (ICER) is equal to the threshold because the manufacturers of the pharmaceutical were aware of the decision-makers threshold. A lower price would result in less profit for the manufacturer and a higher price would result in rejection of the listing and the manufacturer making no profit.

The following specific assumptions were made.

1. The total benefit of all treatments is the addition of the benefit for each treatment (an additive model).
2. The listing of new pharmaceuticals for treatment is undertaken so that all treatments can be considered in all lines of therapy.
3. The initial price at which a pharmaceutical is listed is set to ensure a constant cost per QALY (the threshold willingness to pay).
4. There is no discounting of either costs or consequences. That is, the timing of the costs and consequences did not impact on their calculated value.
5. There were no other disease conditions and costs associated with patients with cancer.
6. There could be survival and utility associated with a post-treatment phase. This was assumed to be equal for all treatment sequences and therefore did not impact on the incremental cost-effectiveness.

The focus was on the change in the treatment/protocol (*j*) as the line of therapy changes (*i*). This displacement was a result of additional treatments/protocols earlier in the treatment pathway and therefore an increasing treatment sequence. The functional form of the model is that the total benefit is the sum of the benefit in each line of therapy. The benefit is the quality adjusted PFS. PFS is the mean survival gain in the line of therapy and u is the utility weight as shown in Equation 15.

$$Total\ Benefit\ of\ treatment \sum_{n=1}^{i} = u_{jn} PFS_{jn} \qquad (15)$$

$$where\ i\ is\ the\ number\ of\ lines\ of\ therapy$$

$$and\ j\ is\ the\ protocol\ used\ in\ the\ \text{nth} line\ of\ therapy, each\ j\ can\ only\ be\ used\ once$$

Assuming this model represents an appropriate method of calculating the total benefit achieved, the problem was reduced to assessing the benefit in each line of therapy. This requires survival and utility to be combined in each line of therapy and then summed across the lines of therapy.

To calculate cost-effectiveness, the cost of each line of therapy must be calculated. It was also assumed that the cost is additive, that is, the costs of each line of therapy can be summed over the lines of therapy. It was assumed that the cost of treatment is related to the PFS by a function, as reflected in Equation 16.

$$Total\ Cost\ of\ treatment = \sum_{n=1}^{i} f(PFS_{jn}) \quad (16)$$
$$where\ i\ is\ the\ number\ of\ lines\ of\ therapy$$
$$and\ j\ is\ the\ protocol\ used\ in\ each\ line\ of\ therapy, each\ j\ can\ only\ be\ used\ once$$

To estimate the cost-effectiveness of *j* in line of therapy *i*, two calculations were required: the benefit of *j* in the line of therapy *I*; and the cost of *j* in line of therapy *i*.

The incremental benefit of Protocol B followed by Protocol A versus Protocol B followed by no treatment (assuming the additive separate model and no discounting) is shown in Equation 17.

$$Incremental\ Benefit = \sum_{n=1}^{2} u_i PFS_{jn} - \sum_{n=1}^{1} u_{ji} PFS_{jn} \quad (17)$$
$$= u_{B1} PFS_{B1} + u_{A2} PFS_{A2} - u_{B1} PFS_{B1} = u_{A2} PFS_{A2}$$
$$and\ j\ is\ the\ protocol\ used\ in\ each\ line\ of\ therapy\ (A, B), each\ j\ can\ only\ be\ used\ once$$

A similar calculation for the costs demonstrated that the incremental cost is $f(PFS_{A2})$. This result occurred because the cost and benefit of protocol B is common to both alternatives and was removed in an incremental analysis.

The benefit is determined by two factors: the length of survival and the average utility of that survival. The total benefit is modelled as two factors, the utility without adverse events and a utility loss associated with adverse events.

There is:

- a mean survival gain (PFS_{j1}) greater than zero associated with the use of the protocol in the first line of therapy;
- a utility value associated with the (non-adverse event modified) survival gain of (u_{j1}) between one and zero in the first line of therapy; and
- an adverse event profile occurring at probability (q_{j1}) in each time frame at greater than zero and resulting in a QALY decrement (-d), where d is greater than zero.

$$Total\ benefit\ of\ protocol\ j\ in\ first\ line\ of\ therapy = PFS_{j1}(u_{j1} - q_{j1}d) \quad (18)$$

Transforming the benefit associated with protocol j from the first line of therapy to subsequent lines of therapy must be considered for each of the components included in Equation 18. Specifically, these were PFS, the rate at which adverse events occur and utility in each line of therapy.

It is assumed that there is a relationship between PFS in the second line of therapy and that of PFS in the first line of therapy. The relationship between the two is also assumed to be linear (shown in Equation 19).

$$PFS_{j2} = f(PFS_{j1}) = \beta PFS_{j1} \quad (19)$$
$$\beta\ from\ zero\ to\ infinity$$

Similarly, there is also a relationship between the adverse events for protocol *j* in the first line of therapy and the second line of therapy. The rate of adverse events per time in the second line of therapy is estimated from the first line of therapy. The number of adverse events occurring in the second line of therapy is influenced by the total time spent in the second line of therapy, the rate at which adverse events occurred in the first line of therapy and a modified impact of the protocol being used in the second line (γ). The rate at which adverse events occur in the first line is estimated at *q*. Therefore, the number of adverse events that occur in the first line of therapy is shown in Equation 20.

$$Total\ number\ of\ adverse\ events\ in\ first\ line = q_{j1}PFS_{j1} \quad (20)$$

The total number of adverse events that occur in the second line of therapy is shown in Equation 21.

$$Total\ number\ of\ adverse\ events\ in\ second\ line = q_{j2}PFS_{j2} \quad (21)$$
$$= \gamma q_{j1}\beta PFS_{j1}$$

Summing the benefits together (Equations 19 and 21) and adjusting by the utility of being in the second line of therapy (u_{j1}) results in Equation 22.

$$Total\ benefit\ of\ protocol\ j\ in\ second\ line\ of\ therapy = \beta PFS_{j1}(u_{j2} - \gamma q_{j1}d) \quad (22)$$

A generalisation to subsequent lines of therapy of Equation 22 is shown in Equation 23, assuming that the same relationship exists between the first and second line, as the second and third and so on.

$$Total\ benefit\ of\ protocol\ j\ in\ ith\ line\ of\ therapy = \beta^{(i-1)}PFS_{j1}(u_{ji} - \gamma^{(i-1)}q_{j1}d) \quad (23)$$

Two categories of costs were considered based on activities. First, the costs associated with administration of the protocol including the costs of the chemotherapy agents, time costs, monitoring costs and consumables. The second category of costs were associated with the treatment of adverse events.

Other categories of costs that might be considered were costs associated with the disease independent of treatment (for example, palliative care) and other healthcare costs associated with conditions other than cancer (see Table 16 for a breakdown of costs). These costs were not included in the model.

The cost of adverse events was assumed to be a cost (a) multiplied by the number of adverse events that occur in the line of therapy (Equation 24).

$$Total\ adverse\ event\ cost\ of\ protocol\ j\ in\ ith\ line\ of\ therapy = \beta^{(i-1)}PFS_{j1}\gamma^{(i-1)}q_{j1}a \quad (24)$$

7.1.2 Methods

The relationship between the length of time in a protocol and the costs of a protocol was modelled using a range of assumptions about the relationship between PFS and costs. Three general approaches were used: a lump sum cost (not seen in the clinical literature, marginal cost is zero), a constant cost per unit time (such as for regorafenib, a pharmaceutical taken daily, marginal cost is constant) and a marginal cost that alters over time.

The same approach was used in each of the different costing methods per protocol. Seven steps were undertaken.

1. The relationship between the cost and the length of time in the PFS state was established.

2. The price was determined in the first line of therapy to ensure cost-effectiveness was equated to the threshold willingness to pay.
3. The costs and benefits were transformed into the subsequent line of therapy.
4. The change in cost-effectiveness was calculated.
5. The reduction in the price of the protocol required to return the cost-effectiveness to the threshold was calculated.
6. The net monetary benefit or cost was calculated.
7. A one-way sensitivity analysis was conducted.

The alternative to displacing the protocol into a later line of therapy was not to fund the protocol in that line of therapy, with an assumed cost and benefit of zero. The net monetary benefit (NMB) was calculated as Equation 1 in Chapter 2.

$$NMB = (threshold * incremental\ QALY) - incremental\ cost \quad (25)$$

The calculation of NMB required estimating the number of participants receiving the protocol in the initial and subsequent lines of therapy. Not all patients who receive a protocol in an initial line of therapy would receive the same protocol in a subsequent line of therapy once displaced. In the second line of therapy the net monetary benefit will be the population receiving treatment, multiplied by the net monetary benefit per person.

Several different cost structures were modelled.

1. Lump sum costs.
2. Constant cost per day.
3. Uneven distribution of costs - intermittent infusion.
4. Uneven distribution of costs - FOLFOX inspired.
5. Uneven distribution of costs - maintenance.
6. Uneven distribution of costs - strictly limited treatment.

Lump sum costs

For the lump sum costs it was assumed that there was a single cost for the protocol, irrespective of the length of time in the progression free survival state (i.e. zero marginal cost of the treatment with respect to time). In practice, there are no 'lump sum' anticancer agents; this type of cost typically applies to diseases such as infections and heart failure. However, lump sum costs were included because this enables the modelling of a very short treatment period relative to the progression free survival time. Moreover, lump sum costs could

represent a payment system whereby a single payment was made for the provision of treatment within a line of therapy.

Constant cost per day

An alternative distribution of costs is when the total cost paid is proportional to the time spent in the progression free state. This applies the assumption that marginal cost with respect to time is constant.

Intermittent infusions

Between the two extremes of the zero marginal cost and constant marginal cost models are models where the costs of the protocol are distributed unevenly over time, that is, over the progression free survival period. In these models the marginal cost relative to time is variable. Specific real-world examples that represent this assumption include regular infusions such as FOLFOX for colorectal cancer, platinum based treatment for NSCLC (with and without maintenance therapy) and ipilimumab for metastatic melanoma.

For example, consider a monthly infusion, initially two pharmaceuticals for four months, then one pharmaceutical afterwards, a mean PFS of 1.025 years and an exponential distribution of survival. The number of infusions received using the mean survival would be 13 (one on the first day of every month), consisting of four infusions of two pharmaceuticals and nine with one pharmaceutical. While a similar number of infusions are received by using the exponential distribution, the number of cycles with two pharmaceuticals is lower, approximately 3.6 versus 4. A similar issue occurred in the displaced line of therapy (with a mean PFS of 6.6 months). In this example, the mean pharmaceutical consumption is not equal to the pharmaceutical consumption of the mean survival (see Table 71). Unless otherwise mentioned the summing of weighted survival probabilities was used to determine consumption of pharmaceuticals whose costs alter with time (changing marginal cost).

Table 71: Comparison of mean pharmaceutical use with use associated with mean survival

First day of month	Pharm 1	Pharm 2	Using mean survival	Using exponential survival	Using mean survival after displacement	Using exponential survival after displacement
1	1	1	100%	100%	100%	100%
2	1	1	100%	92%	100%	86%
3	1	1	100%	85%	100%	74%
4	1	1	100%	78%	100%	64%
5	1	0	100%	72%	100%	55%
6	1	0	100%	67%	100%	47%

First day of month	Pharm 1	Pharm 2	Using mean survival	Using exponential survival	Using mean survival after displacement	Using exponential survival after displacement
7	1	0	100%	61%	100%	41%
8	1	0	100%	57%	0%	35%
9	1	0	100%	52%	0%	30%
10	1	0	100%	48%	0%	26%
11	1	0	100%	44%	0%	22%
12	1	0	100%	41%	0%	19%
13	1	0	100%	38%	0%	16%
14	1	0	0%	35%	0%	14%
Modelled consumption	**Pharmaceutical 1**		**13**	**12.8**	**7**	**6.15**
	Pharmaceutical 2		**4**	**3.56**	**4**	**3.24**

Abbreviation: Pharm: pharmaceutical

Intermittent treatment involves treatment on an intermittent basis, typically three weekly or monthly. An example is three weekly infusions of docetaxel in prostate cancer or breast cancer. It was assumed that the treatment occurred at the start of each period and that a proportion of participants progressed prior to the next treatment.

The costs associated with intermittent treatment and a changing marginal cost required an additional assumption regarding the distribution of survival (which was assumed to be exponential). The costs were modelled by summing a series of sums of geometric series involving the hazard rates and weighted costs (Table 72).

FOLFOX inspired

The FOLFOX protocol for colorectal cancer is a combination of two anticancer agents, 5-FU and oxaliplatin. Oxaliplatin is a platinum based anticancer agent and is associated with neurotoxicity, a common dose limiting toxicity. When this happens only the 5-FU component of treatment will continue. It follows that probability of having both agents, and therefore the cost for the initial cycle, is likely to be higher than subsequent cycles. Other treatment protocols have a similar profile, including ECF (a protocol consisting of epirubicin, cisplatin and fluorouracil) for gastric cancer, and docetaxel and trastuzumab for breast cancer. In these examples, the marginal cost with respect to time of treatment is lower than the average cost, particularly after the fourth cycle has been completed.

Strictly limited

Another possible cost structure is when the length of treatment with a protocol is strictly limited in time, as occurs in dual agent platinum therapy for NSCLC, for which a maximum of four cycles are given. This is similar to the lump sum model and was not explicitly modelled.

Maintenance

Maintenance therapy can also be given for NSCLC. In this scenario the treatment involves three anticancer agents in the protocol, two for a set length of time (as in the dual agent platinum therapy described above), followed by a third agent which is given until progression occurs. These anticancer agents all have different prices. Therefore, a reduction in the length of time in a PFS state will alter the average cost per time by altering the balance between the three agents. The maintenance agent can be more expensive, per unit time, than the initial treatments, as is the case with erlotinib compared to platinum therapy. In this case, the marginal cost with respect to time is higher than the average cost after the fourth cycle.

The fourth example is ipilimumab, an immunological therapy for metastatic melanoma. When ipilimumab is first administered, it may temporarily increase the size of the tumour and clinical guidelines suggest that the response be measured after two months. If there is a reduction in the length of PFS time when the pharmaceutical is displaced to a later line of therapy, an increased proportion of patients may receive treatment for longer than their PFS.

Each of these different methods of administering a protocol has a different implication for the modelled cost for the PFS. The different costs are shown in Table 72. The costs are related to survival, modelled using the hazard rate. The change in cost with displacement was determined by the change in hazard rate (for the exponential distribution).

Table 72: Framework of models with altering marginal cost with time

Type of protocol	Assumptions used	Example	Relative price	Modelled cost (price multiplied by pharmaceutical usage)
Intermittent	Treatment A given	Monthly docetaxel	A=1	A/(1-exp(-hazard rate))
FOLFOX inspired	Treatment B given for X cycles, Treatment A given all cycles	FOLFOX given monthly	A=1 B=2	A/(1-exp(-hazard rate)) + B/(1-exp(-hazard rate)) B*(exp(X*-hazard rate))/ (1-exp(-hazard rate))
Maintenance	Treatment A given for X cycles Treatment B given after X cycles	Maintenance after dual platinum therapy	A=1 B=2	A/(1-exp(-hazard rate)) -A/(1-exp(X*-hazard rate))/ (1-exp(-hazard rate)) +B*(exp(X*-hazard rate))/ (1-exp(-hazard rate))
Treatment no matter outcome for set period	Treatment A given for X cycles irrespective of outcome then every cycle	Ipilimumab	A=1	X*A +A*(exp(X*-hazard rate))/ (1-exp(-hazard rate))

Abbreviation: FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

The parameters of interest in the modelling are described below in Table 73, using CRC as an example. The majority have been sourced from Section 6.2, notably from the two colorectal RCTs with the highest quality score in the systematic review and meta-analysis. The utility values have been sourced from a recent systematic review of CRC utilities.[276] Costs have been sourced from a costing of adverse events in Australia.[277] A one-way sensitivity analysis was conducted using the ranges shown.

Table 73: Model parameters

Description	Parameter in equation	Value	Source/Justification	Range used in one-way sensitivity analysis
Survival Gain	PFS_{j1}	1.025 years	Median of median PFS_{01} in Table 67 for CRC converted to mean assuming exponential function	0.745 to 1.142 (limits of 95% confidence interval for first line treatment from trial in Table 67 assuming exponential function)
Survival gain distribution	-	-	Assumed to be exponential distribution, used in the modelling of non-constant costs	-
Utility	u_{j1}	0.81	Systematic review of CRC utility weights – Table 5, HUI3.[276]	0.6 to 0.9
Adverse event rate (per month)	q_{j1}	5.14% per month	Total number of grade 3 and grade 4 adverse events divided by assumed mean time for haematological events, diarrhoea, nausea and vomiting for CRC	0.3596% to 0.654898 per month, the range of number of adverse events per month
Adverse event decrement	d	0.15 on utility decrement for one month (0.0125)	Mean of decrement associated with adverse events.[276] Range was from 0.08 to 0.21	0 to 0.1 in total
Adverse event cost	a	$4 794	Average of the four adverse event costs for anaemia, vomiting, diarrhoea and neutropenia adjusted by health inflation into AUD $ (2015)[277]	$165.83 to $17 100 (range of costs)
Decision-maker threshold	π	$60 866 per QALY	Assumption (in the PBAC range of $45 000 to $75 000). Adjusted the estimate for life saving treatment estimated	$35 000 to $85 000

Description	Parameter in equation	Value	Source/Justification	Range used in one-way sensitivity analysis
			by Harris et al. (2008)[278] by health inflation that gave an estimate of AUD (2015) $60 866.	
Size of population	r	5 000	Assumption based on the majority of anticancer treatment being based on a population treatment size of less than 10 000 per year.[279]	1 000 to 20 000
Portion who would move lines of therapy	α	60%	From pseudo-crossover RCT (Section 6.2).	19.38% to 79.59% (the range in the pseudo-crossover RCTs)
Reduction in effectiveness with displacement	β	54%	Median of ratio of PFS_{01} and PFS_{12} for CRC in Table 67.	30% to 113% (13% improvement) based on the predictive interval for disease control (Figure 37)
Increase in adverse events per period with displacement	γ	1.7	The ratio of adverse events in the initial line of therapy to the subsequent line of therapy.	0.49 to 4.31 (the range in Table 70)
Utility decrease with the displacement of a line of therapy	-	-	Assumption	95%

Abbreviations: AUD: Australian dollar; CRC: colorectal cancer; HUI3: Health Utilities Index Mark 3; PBAC: Pharmaceutical Benefits Advisory Committee; PFS: progression free survival; QALY: quality adjusted life years; RCT: randomised controlled trial

7.1.3 Results

Lump sum cost

The cost of providing the protocol is a lump sum *p* is shown in Equation 26.

$$Total\ administration\ cost\ of\ protocol\ j\ in\ the\ ith\ line\ of\ therapy = p \qquad (26)$$

The price satisfying the constraint of meeting the threshold willingness to pay was derived by subtracting the additional costs associated with adverse events (Equation 24) from the monetary value of the benefit (Equation 18). This is shown in Equation 27.

$$p = PFS_{j1}(\pi(u_{j1} - q_{j1}d) - q_{j1}a) = \pi PFS_{j1}(u_{j1} - q_{j1}d) - PFS_{j1}q_{j1}a \qquad (27)$$

Therefore, the threshold cost-effectiveness ratio (solving for π in Equation 27) is shown in Equation 28.

$$ICER=\pi = \frac{c}{e} = \frac{p+PFS_{j1}q_{j1}a}{PFS_{j1}(u_{j1}-q_{j1}d)} = \frac{\pi PFS_{j1}(u_{j1}-q_{j1}d)-q_{j1}a)+PFS_{j1}q_{j1}a}{PFS_{j1}(u_{j1}-q_{j1}d)} \quad (28)$$

As the protocol was displaced from first to second line therapy (an increase in *i* from 1 to 2) several changes were made:

- a proportion of people were treated in the subsequent line of therapy who would have been treated in the first line- α (α being between 0 and 1, inclusive);
- the mean PFS in the subsequent line of therapy is a function of PFS in the first line of the therapy ($PFS_{j2}= \beta PFS_{j1}$-Equation 19) (β is greater than zero); and
- the adverse event rate changes by γ (Equation 21) (γ is greater than zero).

Therefore, the cost-effectiveness ratio for protocol j in the second line of therapy is reflected in Equation 29.

$$ICER=\frac{Cost}{Effectiveness} = \frac{p+\beta\gamma PFS_{j1}q_{j1}a}{\beta PFS_{j1}(u_{j2}-\gamma q_{j1}d)} \quad (29)$$

The cost-effectiveness ratio may increase or decrease depending on the values of the parameters. If it was assumed that β is between zero and one, and γ was greater than one and $u_{j2} = u_{j1}$, then the cost-effectiveness ratio from Equation 29 can be split into two portions (shown in Equation 30).

$$\frac{p+\beta\gamma PFS_{j1}q_{j1}a}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} = \frac{p}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} + \frac{\beta\gamma PFS_{j1}q_{j1}a}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} \quad (30)$$

The denominator is reduced if β<1 and $(u_{j1}-\gamma q_{j1}d) < (u_{j1}-q_{j1}d)$. Then, the first fraction in Equation 30 is greater than the equivalent term in the first line of therapy, shown in Equation 28. The relationship for the first fraction is shown in Equation 31.

$$\frac{p}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} > \frac{p}{PFS_{j1}(u_{j1}-q_{j1}d)} \quad (31)$$

The second fraction is larger in the second line of therapy (Equation 30) relative to the first (Equation 29), because γ was assumed to be greater than one (shown in Equation 32).

$$\frac{\beta\gamma PFS_{j1}qa}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} > \frac{PFS_{j1}qa}{PFS_{j1}(u_{j1}-q_{j1}d)} \quad (32)$$

Since both components increased, their sum also increased. Therefore, given the assumptions over β, γ and u_{j2} the cost-effectiveness of *j* in the second line of therapy was unambiguously worse than in the first line of therapy.

Assuming the transitions between subsequent lines of therapy were the same as between the first and second lines the resulting cost-effectiveness ratio for protocol *j* in line of therapy *i* is shown in Equation 33.

$$ICER = \frac{p+\beta^{(i-1)}\gamma^{(i-1)}PFS_{j1}q_{j1}a}{\beta^{(i-1)}PFS_{j1}(u_{j1}-\gamma^{(i-1)}q_{j1}d)} \quad (33)$$

The cost-effectiveness ratio was returned to the required rate of π (the threshold willingness to pay) by altering p. The change in *p* is denoted by *cp* where *c* was the factor required to return the cost-effectiveness ratio to the threshold (Equation 34). Solving for c (Equation 35), ensured that the cost-effectiveness in the second line of therapy was equal to the cost-effectiveness in the first line of therapy (and equivalent to the threshold willingness to pay).

$$\boldsymbol{\pi = \frac{cp+\beta\gamma PFS_{j1}q_{j1}a}{\beta PFS_{j1}(u_{j1}-\gamma q_{j1}d)} = \frac{p+PFS_{j1}q_{j1}a}{PFS_{j1}(u_{j1}-q_{j1}d)}} \quad (34)$$

$$c = \frac{\beta(u_{j1}-\gamma qd)(p+PFS_{j1}q_{j1}a)}{(u_{j1}-q_{j1}d)p} - \frac{PFS_{j1}q_{j1}a}{p} \quad (35)$$

Using the parameters outlined in Table 73, solving for the price gave a cost of $47 020 for the treatment in the first line of therapy. Table 74 below shows the implications for the cost-effectiveness of protocol *j* moving between lines of therapy. That is *i* being varied from 1 to 4. It was assumed that the parameters stay the same in moving from the first to second line of therapy as they do from second to third line of therapy etc.

There was little change in cost per patient but there was a rapid escalation in the cost-effectiveness ratio of the protocol (Table 74). The column entitled “price reduction required” is the decrease in the price that is required to return the cost-effectiveness ratio to the original threshold ($60 866). If displacement occurred into the fourth line of therapy, the price had to be reduced by almost 90% to restore the threshold level of cost-effectiveness.

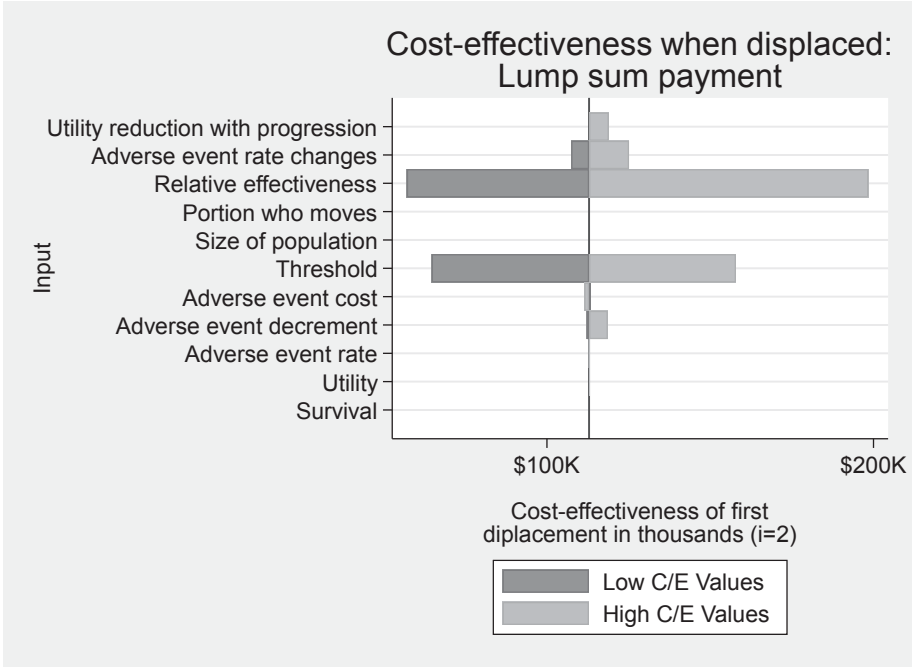
The net monetary benefit was negative for all lines of therapy greater than one. The displacement of the protocol was allocatively inefficient. The net monetary benefit was worst for the first displacement into the second line of therapy. While it remained negative, the NMB improved with displacement into subsequent lines of therapy. This occurred because fewer participants received the protocol in later lines of therapy.

Table 74: Cost-effectiveness in different lines of therapy for fixed price protocol

Line of therapy (*i*)	Total Cost per patient in line *i*	Total QALY gain per patient in line *i*	Cost per QALY	Price reduction required	Total cost (in millions)	NMB (in millions)
1 (original use)	$50 053	0.82	$60 866	0%	$250.3	$0.0
2 (one displacement)	$49 804	0.44	$112 915	49%	$148.8	-$68.6
3 (two displacements)	$49 576	0.24	$210 569	75%	$88.5	-$62.9
4 (three displacements)	$49 366	0.12	$396 142	89%	$52.6	-$44.5

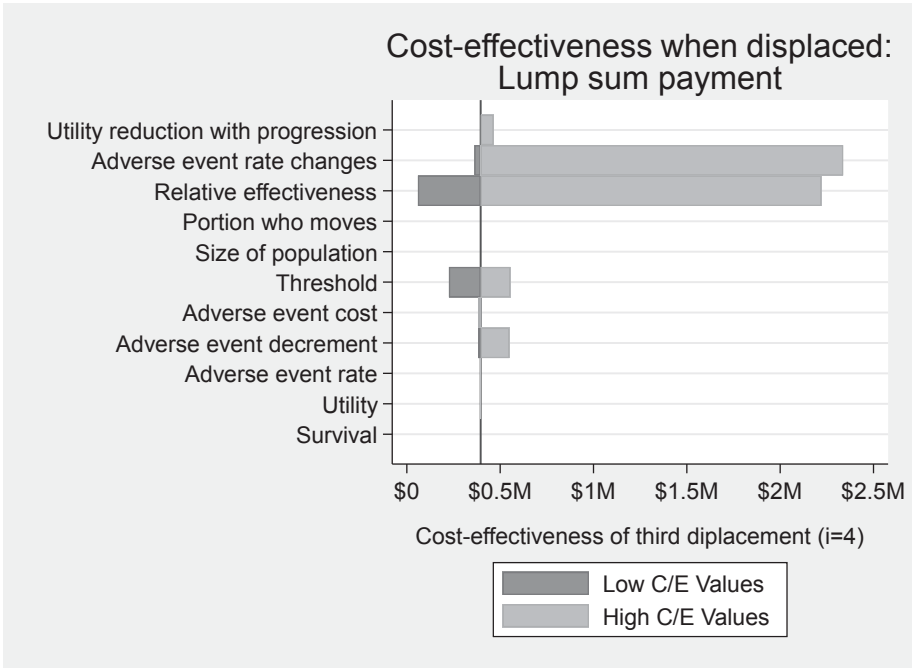
Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years

The one-way sensitivity analysis for the cost-effectiveness of the lump sum cost is shown in Figure 41 for one displacement (into the second line of therapy [i=2]) and in Figure 42 for three displacements (into the fourth line of therapy [i=4]). The tornado diagram shows the relative changes in cost-effectiveness compared to the calculated cost-effectiveness ratio for one displacement ($112 915) or three displacements ($396 142). For one displacement into the second line of therapy the relative effectiveness of treatment had the largest impact on the cost-effectiveness. After being displaced three times in the fourth line of therapy, the increase in rate of adverse events occurring with displacement had the largest impact on the predicted cost-effectiveness. The relative effectiveness of treatment in the subsequent lines of therapy had the next largest impact. Both resulted in cost-effectiveness ratios of over $2 million.



Abbreviation: C/E: cost-effectiveness

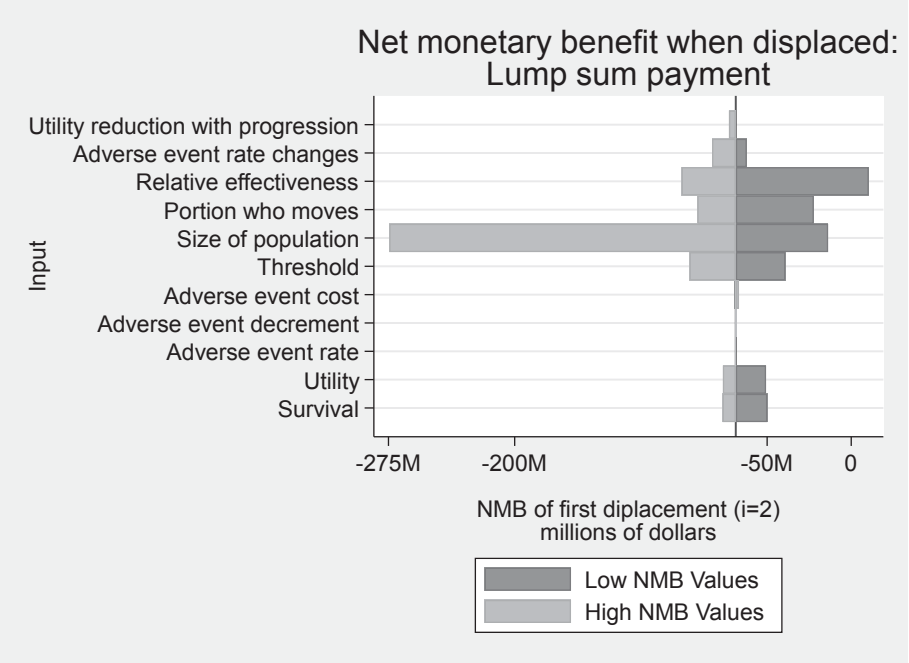
Figure 41: One-way sensitivity analysis of cost-effectiveness (lump sum model) (i=2)



Abbreviation: C/E: cost-effectiveness

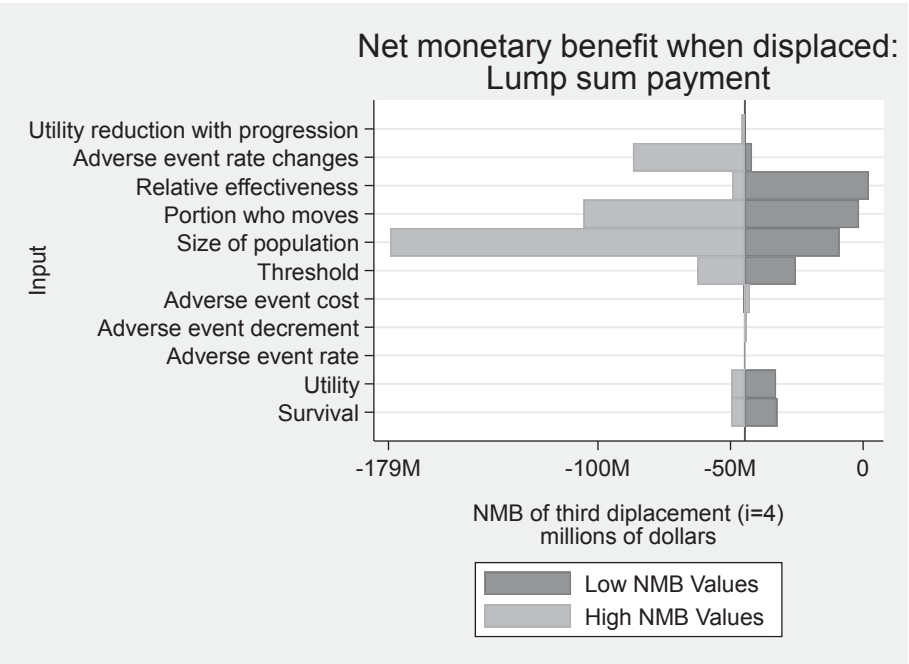
Figure 42: One-way sensitivity analysis of cost-effectiveness (lump sum model) (i=4)

The size of the population had the largest impact on the estimation of net monetary benefit with one displacement into the second line of therapy (Figure 43 [i=2]). With the third displacement into the fourth line of therapy (Figure 44 [i=4]), the size of the population continued to have the largest impact on the net monetary benefit, followed by portion of the population who received a subsequent line of therapy and the adverse event rate.



Abbreviation: NMB: net monetary benefit

Figure 43: One-way sensitivity analysis of net monetary benefit (lump sum model) (i=2)



Abbreviation: NMB: net monetary benefit

Figure 44: One-way sensitivity analysis of net monetary benefit (lump sum model) (i=4)

Constant cost

The constant cost assumed the cost is $p_1 = PFS_{j1}p^1$ in first line and $p_2 = \beta PFS_{j1}p^1$ in second line and $p_n = \beta^{(n-1)}PFS_{j1}p^1$ in line n of treatment, where p^1 represents the cost of the protocol per unit time. This eliminated the impact of reduced effectiveness and the resultant

length of treatment from the cost-effectiveness modelling. The changes in cost-effectiveness were driven by the changing rate of adverse events in subsequent lines of therapy.

Cost-effectiveness in the second line is shown in Equation 36.

$$\frac{Cost}{Effectiveness} = \frac{p^1 + \gamma q_{j1} a}{\left(u_{j2} - \gamma q_{j1} d\right)} \tag{36}$$

Generalising Equation 36 for the cost-effectiveness in line *i* is shown in Equation 37.

$$\frac{Cost}{Effectiveness} = \frac{p^1 + \gamma^{(i-1)} q_{j1} a}{\left(u_{ji} - \gamma^{(i-1)} q_{j1} d\right)} \tag{37}$$

Using the same parameters (Table 73), assuming $u_{j2} = u_{ji} = u_{j1}$ and solving for the price, p^1 is $29 109.

Table 75 below uses the same information as Table 74 above but the price paid has been recalculated as a function of line of therapy with *i* being varied from 1 to 4. As expected, the total QALYs in each line of therapy were the same as in the previous lump sum cost model. However, the total cost and the cost-effectiveness ratio were much lower than in the lump sum cost model. In this case, the increased cost-effectiveness ratio was only due to the increased rate of adverse events. As the number of adverse events increased per unit time, the required price reduction increased. The net monetary benefit loss associated with displacement was found to be substantially lower the lump sum cost.

Table 75: Cost-effectiveness of treatment assuming constant cost

Line of therapy (*i*)	Total cost per patient in line *i*	Total QALY gain per patient in line *i*	Cost per QALY	Price Reduction required	Total Cost (in millions)	NMB (in millions)
1 (original use)	$50 053	0.82	$60 866	0%	$250.3	$0.0
2 (one displacement)	$28 175	0.44	$63 877	5%	$84.2	-$4.0
3 (two displacements)	$16 267	0.24	$69 092	14%	$29.0	-$3.5
4 (three displacements)	$9 750	0.12	$78 240	29%	$10.4	-$2.3

Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years

The sensitivity analysis for the remainder of the models is shown in the Appendix G.

Uneven distribution of costs models

Intermittent treatment (modelled monthly [Table 76]) demonstrated changes in cost-effectiveness and net monetary benefit similar to, but slightly worse than, the cost per day model (Table 75).

Table 76: Cost-effectiveness of treatment assuming intermittent treatment model

Line of therapy (*i*)	Total cost per patient in line *i*	Total QALY gain per patient in line *i*	Cost per QALY	Price Reduction required	Total Cost (in millions)	NMB (in millions)
1 (original use)	$50 053	0.82	$60 866	0%	$250.3	$0.0
2 (one displacement)	$29 052	0.44	$65 866	8%	$86.8	-$6.6
3 (two displacements)	$17 645	0.24	$74 946	22%	$31.5	-$5.9
4 (three displacements)	$11 450	0.12	$91 882	42%	$12.2	-$4.1

Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years

The cost-effectiveness ratios for one displacement (i=2) and three displacements (i=4) show that changes in relative effectiveness alter the cost-effectiveness (unlike the cost per day model).

The implications of a FOLFOX model is shown in Table 77. With displacements, the average cost-effectiveness of treatment with a protocol increased because the time on treatment decreased with the use of lower cost agents.

Table 77: Cost-effectiveness of treatment (FOLFOX model)

Line of therapy (*i*)	Total cost per patient in line *i*	Total QALY gain per patient in line *i*	Cost per QALY	Price Reduction required	Total Cost (in millions)	NMB (in millions)
1 (original use)	$50 053	0.82	$60 866	0%	$250.3	$0.0
2 (one displacement)	$34 956	0.44	$79 252	25%	$104.4	-$24.2
3 (two displacements)	$25 301	0.24	$107 464	48%	$45.2	-$19.6
4 (three displacements)	$18 423	0.12	$147 837	67%	$19.6	-$11.6

Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years

The implications of a maintenance model for cost-effectiveness and net monetary benefit are shown in Table 78. The average cost-effectiveness of treatment decreased with displacements

because the time on treatment decreased with the use of higher cost agents. The maintenance model has minimal impact on net monetary benefit.

Table 78: Cost-effectiveness of treatment (maintenance model)

Line of therapy (*i*)	Total cost per patient in line *i*	Total QALY gain per patient in line *i*	Cost per QALY	Price Reduction required	Total Cost (in millions)	NMB (in millions)
1 (original use)	$50 053	0.82	$60 866	0%	$250.3	$0.0
2 (one displacement)	$26 386	0.44	$59 822	-2%	$78.8	$1.4
3 (two displacements)	$14 189	0.24	$60 265	-1%	$25.3	$0.3
4 (three displacements)	$8 302	0.12	$66 620	12%	$8.9	-$0.8

Abbreviations: NMB: net monetary benefit; QALY: quality adjusted life years

7.1.4 Discussion

The method by which a protocol is administered or reimbursed is important in determining the impact of displacement because of the distribution of the costs over time differs. Displacement has the least impact on cost-effectiveness when there is a constant marginal cost with respect to time.

When the marginal cost of a protocol is not constant, displacement has a larger impact. The cost-effectiveness increases (deteriorates) if the marginal cost decreases over time and (improves) if the marginal cost increases over time.

Further, the frequency of adverse events is an important factor in assessing the impact of displacement. When the marginal cost is constant, the modelling of adverse events drives changes in the cost-effectiveness produced by displacement. The use of the expectation of mean PFS to determine mean cost may not result in the correct outcome and modelling results may be biased.

Displacing a protocol can result in large changes in cost-effectiveness, especially when the marginal cost is not constant. The modelling conducted in Chapter 5 suggested that the costs were not constant over time and a varying marginal cost was empirically plausible. A constant marginal cost was a common assumption in the literature (see Chapter 3). This simplifying assumption potentially results in a biased estimate of displacement's impact.

7.2 Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) of a single displacement was conducted. This analysis used the information from the meta-analysis, systematic reviews of treatments and the characteristics of the pharmaceuticals presented in the public summary documents for the anticancer treatments for NSCLC, breast cancer and CRC (as discussed in Section 6.2). Explicit modelling of the marginal cost with respect to time was included.

Simulation of the process of subsidisation and displacement in Australia was conducted. One million simulated protocols were generated, had their price calculated to be cost-effective in the first line of therapy and then were subsequently displaced in the second line of therapy. The million simulated protocols were divided between NSCLC, breast cancer and CRC.

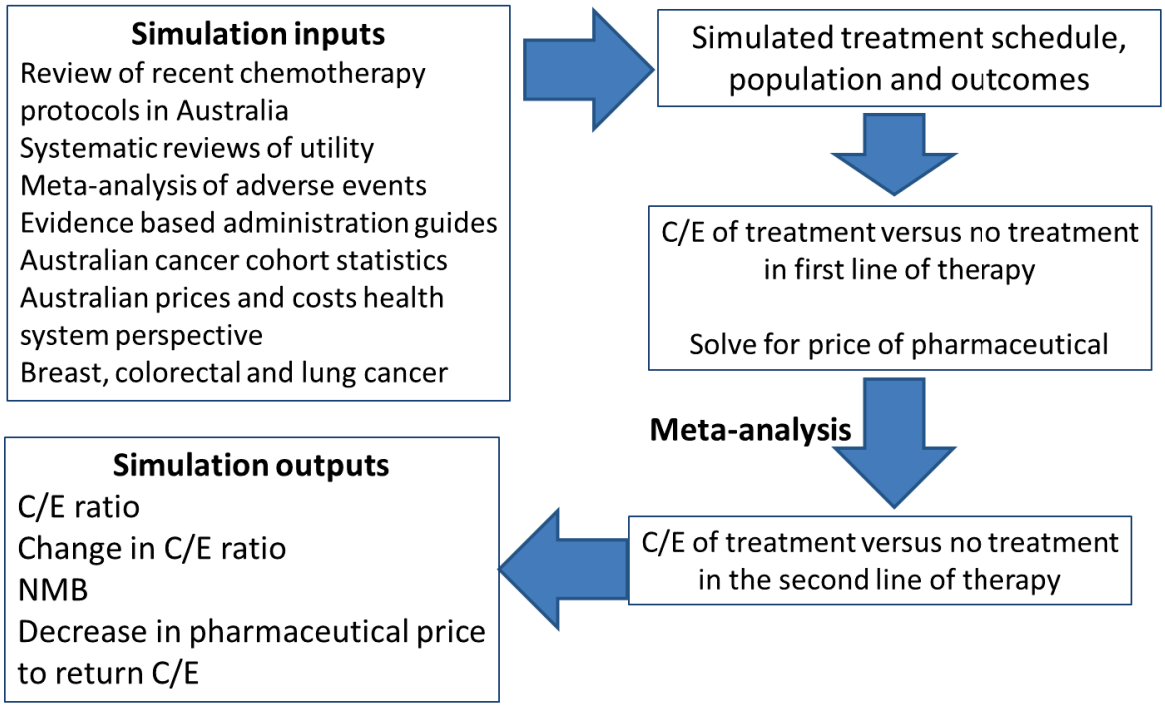
As well as heterogeneity in cancer type, variation in administration, number of pharmaceuticals in a treatment protocol, number of cycles of treatment, adverse events, size of the treated population, biomarkers, utility, survival, the acceptable cost-effectiveness threshold and the tests required when progression occurred was modelled.

The objective of the modelling was to estimate the impact of displacement in an Australian PBS system by including real-world variation in the treatments, the outcomes of the treatments and the populations treated.

7.2.1 Model and structure

Figure 45 outlines the steps undertaken for the PSA. The steps were as follows.

1. A simulated protocol in the first line of therapy with a treatment schedule, populations and outcomes was constructed using information gathered earlier in this Chapter, Chapter 6 and from external sources.
2. The price of the treatment was calculated by binding the threshold.
3. The protocol was displaced into the second line of therapy, using the results of the meta-analysis (Section 6.3) and several outputs calculated. These outputs included the cost-effectiveness ratio in the second line of therapy (compared to no treatment) and the required change in the price of the treatment to restore the cost-effectiveness to its original value.



Abbreviation: C/E: cost-effectiveness; NMB: net monetary benefit

Figure 45: Scheme of the probabilistic sensitivity analysis

7.2.2 Methods

The alternatives modelled were either displacement of a protocol by one line of therapy followed by a period of post-progression palliative care, or no treatment and starting palliative care without chemotherapy. The perspective adopted was that of the health system and there was no discounting in the base case. The clinical outcome measured was survival. Survival was weighted to quality adjusted life years (QALYs).

The incremental cost-effectiveness ratio of the displaced protocol in the second line of therapy and the net monetary benefit of the displaced protocol in the second line of therapy were the outputs of interest. Additionally, the incremental cost-effectiveness acceptability curve and the differences in the estimated cost-effectiveness between the initial and second lines of therapy were estimated.

The incremental cost-effectiveness ratio (ICER) was calculated as shown in Equation 38.

$$ICER = \frac{Cost\ of\ protocol - cost\ of\ no\ treatment}{QALY\ with\ protocol - QALY\ of\ no\ treatment} = \frac{incremental\ cost}{incremental\ QALY} \quad (38)$$

The net monetary benefit was calculated as shown in Equation 39 (the same as Equation 1).

$$NMB = (threshold * incremental\ QALY) - incremental\ cost \quad (39)$$

The difference in the cost-effectiveness ratio (diffCE) was calculated as shown in Equation 40.

$$diffCE = \frac{incremental\ cost\ in\ second\ line}{incremental\ QALY\ in\ second\ line} - \frac{incremental\ cost\ in\ first\ line}{incremental\ QALY\ in\ first\ line} \quad (40)$$

The PSA included CRC, breast cancer and NSCLC. The survival benefit was calculated using a partitioned survival analysis, where each partition used an area under the curve approach, to which a utility weight was attributed. The pre-progression survival was subsequently modified by post-progression survival and adverse events. Costs were attributed according to characteristics of the protocol and the proportion of the population that would be impacted by the activity.

This model was chosen because of the use of a solitary parameter (hazard rate) to alter survival between the first and second lines of therapy and the use of different cycles lengths and costs within cycles.

A Markov model was considered but rejected as a modelling approach because the timing of the treatment cycles and costs was not consistent within or between protocols. Similarly, a simple decision tree approach was considered and discarded because of the complexity of the events considered.

The size of the population was calculated as two separate pieces of information: an estimate of the potential population with metastatic disease; and the proportion of the population treated using the protocol. This is because different protocols may be associated with specific bio (or genetic) markers and therefore the size of the group treated for the same cancer differed. Additionally, a more complicated version of costs was considered because discounting has an impact on the costs and benefits associated with post-progression palliative care.

The model for the PSA was run once using variation in parameters and then run a second time, with variation in parameters and a microsimulation of individuals in the population. Survival in each line of therapy was estimated using the user written STATA command *survsim*. The changes for the microsimulation are described below. Both the PSA and the microsimulation was run on Stata 15.[173]

Each parameter was calculated, and the price of the treatment was calculated for the first line of therapy to bind the threshold. If a price of less than zero was calculated for the first line of therapy it was discarded, without replacement; the number of discarded protocols were reported. The costs and benefits were then transformed to the second line of the therapy and the cost-effectiveness and net monetary benefit calculated based on the incremental analysis of the displaced protocol compared to no treatment.

Credible intervals were calculated using a non-parametric approach. For protocols dominated by no treatment the total number of dominated protocols was reported, and the dominated protocols removed prior to calculation of the credible interval. The 95% credible interval for the net monetary benefit was calculated using the 2.5 and 97.5 percentiles. The 95% credible interval for the incremental cost-effectiveness ratio was calculated in the same manner.

An additional measure - the change in the cost-effectiveness ratio - was also calculated as the cost-effectiveness ratio in the second line of therapy minus the cost-effectiveness ratio in the first line of therapy. This was only calculated for non-discarded (viable) protocols.

The incremental cost-effectiveness acceptability curve was calculated as the proportion of the outputs that were below the acceptable threshold drawn through the origin. This included dominant and dominated alternatives.

Analysis of covariance (ANCOVA) was used to estimate the influence of the inputs on the total QALYs and total costs.

Several scenario analyses were conducted using the PSA to test the importance of some of the assumptions and specific scenarios. These included:

- introduction of discounting;
- reduction of the post-treatment period according to the number of treatments;
- introduction of a disease cost;
- introduction of a lower utility weight for the displaced treatment;
- alteration of the adverse events to log normal distribution with the standard deviation of the information presented in Table 70; and
- correlation of the length of post-progression survival with the probability of receiving a second line of therapy in a microsimulation.

Discounting was conducted using a monthly cycle. The discount rate was applied monthly at the midpoint of each month. A half cycle correction was applied using a triangular approach

(beginning and end of each month summed and divided by two). A discount rate of zero was also estimated for comparative purposes. The triangular approach may not produce the same results as the mathematical approach because of a combination of rounding errors and differences in the calculations. The timing of adverse events was assumed to occur in earlier cycles of treatment.

As the unit of analysis was protocols (not individuals), estimates of the distribution of means (rather than estimates of distributions of individuals) were used. Conversion into other distributions was undertaken to ensure realistic values (for example probabilities, utility weights and decrements). Table 225 with all the parameters and distributions is included in Appendix G.

Parameters and distributions

Protocols for breast, colorectal and non-small cell lung cancer were generated with a one-third probability for each type of cancer.

Estimates of the median PFS for first line therapy for breast cancer, CRC and NSCLC were identified from systematic reviews. The 95% confidence interval covered the upper and lower estimates and the mean between these estimates.

The systematic review of first line treatment for NSCLC indicates that the disease has a median PFS between 3 and 8.4 months.[274] CRC has a median PFS between 9.7 and 12.1 months.[280] Breast cancer has a range of PFS from 6.4 to 14.2 months for HER2 cancer[281] and 5.7 to 10 months for triple negative breast cancer.[282] These estimates were converted to means assuming an exponential distribution.

A palliative care (or best supportive care) period of three months (12 weeks) was used. This was applied after the final progression occurred. Three months was used because this is the time frame in which costs increased in previous research.[200] Three months was also the figure given by expert opinion for the post-progression survival after the second line of therapy.[4]

The threshold was assumed to vary between assessed protocols based on a mean of $60 866. A standard deviation of $10 000 was assumed. This is derived from inflating the mean cost per QALY estimate of life saving treatment being funded at a 50% probability in Harris et al. (2008).[278] This was consistent with the PBAC range of cost-effectiveness of $45 000 to $75 000 on average.

Systematic reviews for breast cancer,[283,284] CRC,[276] and NSCLC[285] were used for the baseline utility values. A standard deviation of 0.04 was used.

The palliative care utility was a mean of 0.55 and a standard deviation of 0.15 was used based on the results of Paracha et al. (2016).[284]

In the microsimulation, a standard deviation of 0.15 around the population mean was assumed, unless the mean utility was 0.9 or greater in which case a variation of 0.05 was used to ensure realistic values were derived.

The results of the systematic review for breast cancer[283,284] were used for estimates of decreasing utility with increasing lines of therapy. The utility values reported ranged from 0.648 to 0.8 in the first line of therapy and from 0.41 to 0.66 for second line treatment.[284] The range for "at least" second line therapy was between 0.64 and 0.66.[284] The regression analysis of utility values in Peasgood et al. (2010) [283] suggest that progressed states have a lower utility than non-progressed states (-0.135 to -0.203). The meta-regression with the highest R^2 had a mean reduction in utility of 0.135 with a standard error of 0.138. The model does not include any incremental reduction in utility values for subsequent lines of therapy in the base case, given the lack of evidence of a difference in utility. This was tested in the sensitivity analysis.

The results of a systematic review of adverse events by Shabaruddin et al. (2013)[286] were used to determine the mean value of a utility decrement. The standard error was used for the distribution. The results were converted into a beta distribution.

The results from the meta-analysis reported in Section 6.3.2 were used as the proportion of the population who experienced an adverse event, which was approximately 66%.

For the discounting, a distribution over the cycles was assumed with 50% occurring in the first cycle, 20% in the next cycle and the rest at a constant rate.[287]

The costs of adverse events were estimated using the results of Pearce (2013).[288] Pearce (2013)[288] used Australian administrative data to determine that the cost of adverse events ranged between $7 500 and $10 600 in an elderly cohort, but cautioned that this was likely to be an underestimate. Vouk et al. (2016)[289] using a Delphi technique estimated the cost of grade 3-4 diarrhoea as AUD (2013) $1 332.88 and grade 3-4 neutropenia as AUD (2013) $1 005.45.

Overseas estimates using real-world data indicate higher costs for adverse events than those reported above. Rashid et al. (2016)[290] estimated the average cost for adverse events for breast cancer at USD (2013) $30 000 to $35 000 (AUD [2015] $47 000 to $54 000). Hurvitz et al. (2014)[49] estimated lower costs of between USD (2010) $854 and $3 547 (AUD [2015] $1 400 to $5 900).

As the context for this research is Australian, a log normal distribution was assumed using the range reported by Pearce (2013) covering 66% (one standard deviation) of the distribution after adjustment for inflation (median, AUD [2015] $11 311).

The cost of the pharmaceutical was priced to ensure the cost-effectiveness ratio was equal to the threshold in the first line of therapy. The other costs and QALYs were calculated and then the price of the pharmaceutical determined from the threshold and the expected usage of pharmaceutical. For protocols with multiple pharmaceuticals a ratio of the prices was determined a priori.

Administration costs, including monitoring, differed according to the type of payment schedule. Daily treatment was assumed not to involve intravenous administration while intermittent and FOLFOX inspired protocols would involve infusions.

The cost of monitoring included blood tests, supportive treatment, imaging, and specialist and GP consultations. The type of imaging, testing and frequency of attendances varied by protocol. The costs were based on the 2015 Medicare Benefits Schedule (MBS) book. A minimum of biochemistry (MBS item 66512), haematology (MBS item 65070), specialist attendance (MBS item 133), and general practitioner attendance (MBS item 23) was considered ($178.85). The monitoring costs were applied at the start of each month, including the first. An exponential distribution over time was assumed.

The addition of an infusion was required for the intermittent and FOLFOX inspired protocols (MBS item 13918; $83.3). The infusions were applied per cycle with an exponential distribution over time assumed.

The addition of another line of therapy may require investigation of the current genetic makeup of the tumour and documentation of the degree of progression. The potential for a scan and genetic tests were included. A random Poisson distribution was used, with an expected value of two. A selection of costs from HER-2 testing (plus biopsy [MBS item 30075 and MBS item 73332]), EGFR testing (plus biopsy [MBS item 30075 and MBS item 7338]), CT

scan (MBS item 56801) and nuclear medicine bone scan (MBS item 56801) were included. Two additional specialist attendances were also included (MBS item 13918).

The post-treatment palliative care costs do not alter the incremental cost in the non-discounted analysis because they are common to all alternatives. However, these costs do alter the results in the discounted analysis because the differences in timing of the post-progression palliative care costs and benefits were included. Seventy per cent of the weighted average of the cost of the last six months of health service use (being the proportion associated with the last three months) from Langton et al. (2016)[200] was inflated to AUD (2015) $21 642. A gamma distribution with a mean of AUD (2015) $21 642 and standard deviation of AUD (2015) $346 was used.

The size of the population treated was determined by three factors;

- the size of the population potentially eligible for treatment without a targeted agent;
- whether the protocol required a biomarker; and
- the proportion of the population that was covered by a protocol associated with a biomarker.

The biomarker was not required to be genetic. It could, for example, be histological.

The size of the population was estimated using the prevalence, incidence and rates of death associated with each cancer. The prevalence used was that reported in the Australian Institute of Health and Welfare (AIHW) survival and prevalence publications.[43] Five-year prevalence was estimated as 55 537 for breast cancer, 45 763 for bowel (colorectal) cancer and 12 606 for lung cancer.[43]

The incidence used was that reported in the AIHW ACIM (Australian Cancer Incidence and Mortality Books[xvi] on the 31/05/2017). The incidence data was from 2013 and the mortality data was from 2014. The number of new breast cancer cases was 16 045 and the number of deaths was 2 844. For CRC, the number of new cases was 14 962 and the number of deaths was 4 071. The number of new lung cancer cases was 11 174 and the number of deaths was 8 251.

It was assumed that the number of deaths approximated the lowest number of potential patients for a therapy (as it represents an estimate of a protocol in the last line of therapy).

[xvi] http://www.aihw.gov.au/acim-books/

Fifteen per cent of the prevalence rate was used as an upper estimate of the population available for breast cancer treatment, this being the proportion of the early breast cancer population who develop further disease.[291] For CRC, the figure was 12.8%.[292] The midpoint of these two numbers was used as the mean and it was assumed that 99% of all protocols would fall between the two bounds. The results were a mean of 8 330 and a standard deviation of 914 for breast cancer (mean: 4 964, sd: 298 for CRC and mean: 6 303, sd: 649 for NSCLC).

The pharmaceuticals assessed by PBAC for metastatic CRC, metastatic breast cancer and NSCLC (Table 59 in Section 6.2) were used to determine the proportion of protocols used only in the presence of a specific biomarker. Forty-three per cent of protocols did not use a biomarker (57.1% did use a biomarker) and these percentages were used in the modelling.

The mean (30.1%) and standard deviation (0.203) of the percentage of cancers with the biomarker for treatment were used to model the percentage of the population who were eligible for treatment. These were used to develop a beta distribution. Populations of less than 50 were replaced with 50. That is, 50 patients represented the lower bound of the population.

The last 21 PBAC submissions for anticancer agents for NSCLC, breast and colorectal metastatic cancer were reviewed (Table 59 in Section 6.2) and a payment schedule assigned to each. These schedules were either daily use – assumed to be on a monthly prescription (38.1%), periodic (either two, three or four weekly) (23.8%) and multiple pharmaceuticals with some or all of the pharmaceuticals being removed over time (38.1%). This last schedule is equivalent to the FOLFOX inspired model discussed above (Section 7.1). As Chapter 6 demonstrated that there was no difference in dose intensity between the initial and subsequent line of therapy the dosage was not reduced after displacement.

The relative frequency of the weekly cycle was 10% one week, 40% two weeks, 40% three weeks and 10% four weeks, based on the relative frequencies of the EViQ protocols (see Section 6.2).

The length of time of use of the higher cost pharmaceuticals was estimated as a random proportion of the truncated length of treatment in the initial line of therapy. The minimum number of cycles was four, being the minimum number of cycles seen in the EViQ protocols (see Section 6.2). The portion of FOLFOX type protocols which did not continue any treatments was 50% in the EViQ database.

For the remaining 50%, there was a wide variation in the relative cost of the pharmaceuticals that were ceased versus continued in a FOLFOX type protocol. For breast cancer, if anti-HER2 therapy was continued while chemotherapy was ceased, the ratio was 0.01 to 0.08. In CRC, some protocols are similar to breast cancer where a high cost therapy is continued (such as cetuximab). The mean cost ratio of the pharmaceutical being ceased to the pharmaceutical continuing was 0.025 with a standard deviation of 0.00064.

The mean (57%) and variance of the pseudo-crossover trials discussed in Section 6.3.2 were used to estimate the proportion of the protocols population that moved from one to a subsequent line of therapy. The population was rounded to the nearest integer.

For the microsimulation, a binomial distribution was used with the chance of success being equal to the proportion of the population who move a line of therapy in the non-stochastic PSA. The number of trials in the binomial distribution was the size of the first line population.

The portion of adverse events after displacement was sourced from the meta-analysis in Section 6.3.2. A relative risk of 0.88 and a predictive interval corresponding to 1.96 standard deviations was used. A random normal distribution was used and then exponentiated into a relative risk.

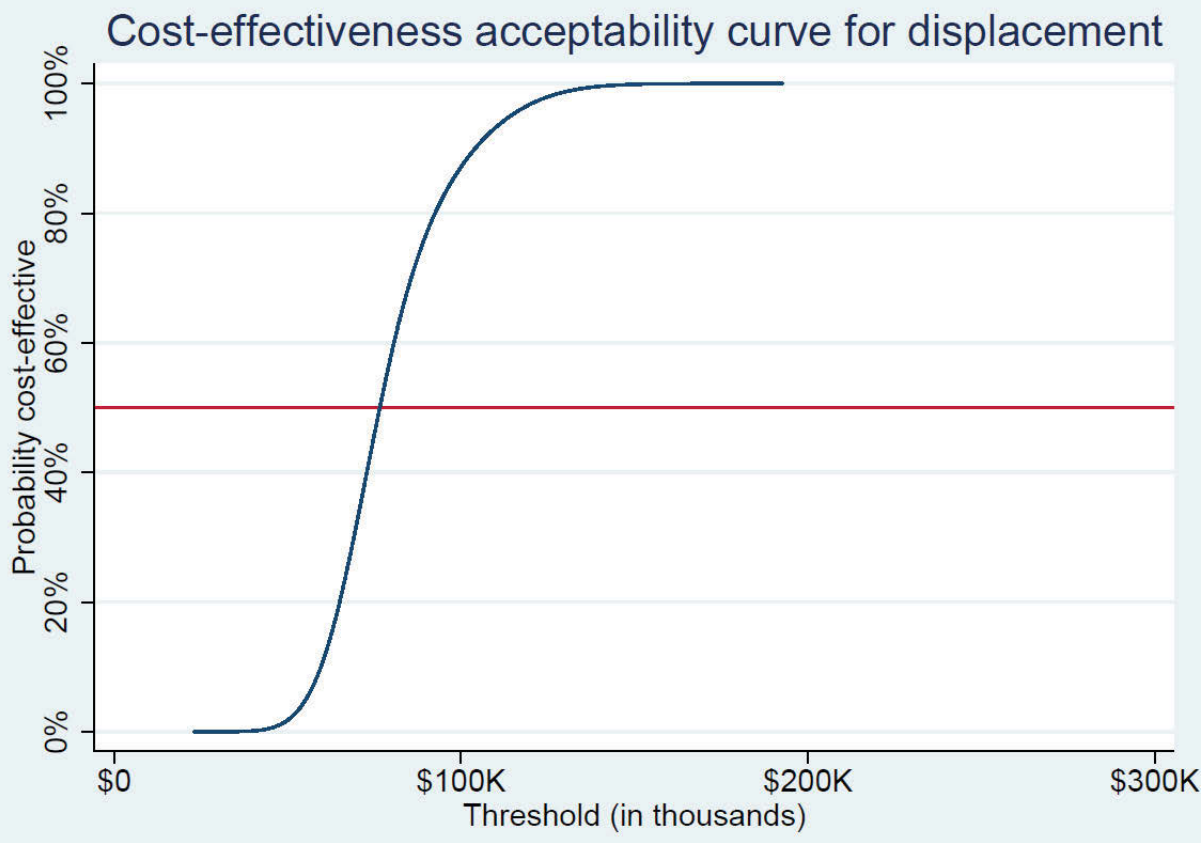
The result of the changes in the hazard ratio of the CRC trials for which there was information were combined using a meta-analysis.[72] These trials reported an increased hazard ratio of 1.869 (95% CI 1.646 to 2.1233) in the subsequent line of therapy (see Section 6.3.2). This increase was applied to the hazard rate in the first line of therapy and the mean survival in the second line of therapy was calculated assuming an exponential distribution.

7.2.3 Results

Approximately 10 360 (1.0% of all protocols) were not viable for subsidisation, either requiring a price of less than zero to bind the threshold in the first line of therapy or being dominated by no treatment (or both).

The mean (median) cost-effectiveness of the displaced protocols in the second line was $77 977 ($75 042) compared to $60 964 ($60 937) for the protocols in the first line. The 95% credible interval for the cost-effectiveness of the second line was between $50 275 and $121 801. The 95% credible interval for first line therapy was $41 528 to $80 506; the difference in cost-effectiveness between first and second line therapy was statistically significant ($p<0.01$). The cost-effectiveness acceptability curve (Figure 46) shows that at a

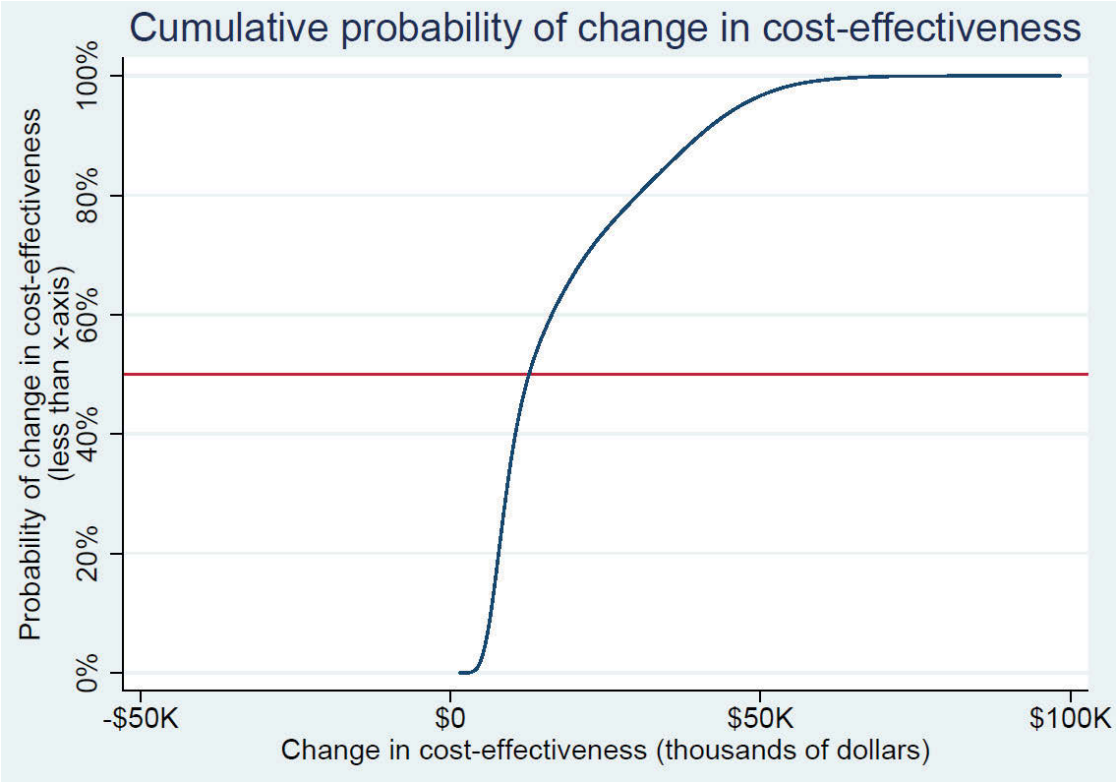
threshold of $50 000, the chance of the displaced protocol being cost-effective is 2.4%. At a threshold of $60 866, the chance of the displaced protocol being cost-effective rose to 14%. At a threshold of $100 000 the chance of the displaced protocol being cost-effective was 88%.



Symbol: K: thousand

Figure 46: Cost-effectiveness acceptability curve for displacements

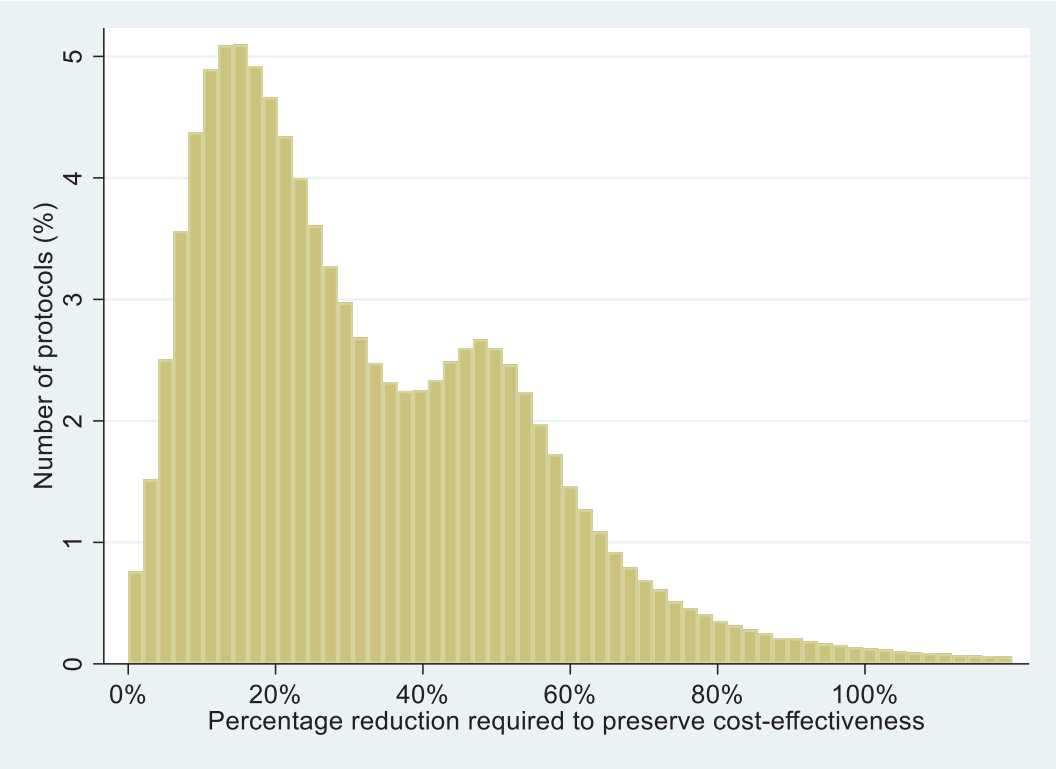
Regarding the net monetary benefit, the credible interval was between a loss of $63 million and a loss of $350 000. The mean (median) NMB was a loss of $12 million ($7.4 million). The standard deviation of the NMB was large ($16 million). The mean (median; standard deviation) change in the cost-effectiveness ratio for a displaced protocol was $17 013 ($11 292; $13 637) (Figure 47).



Symbol: K: thousand

Figure 47: Cumulative probability of size of change in cost-effectiveness with displacement

A small proportion of protocols (7%), when displaced, would not achieve a cost-effectiveness ratio equivalent to the threshold, even if the price was zero. The remainder of the protocols could achieve a cost-effective ratio equivalent to the threshold. For those protocols the required reduction was a mean (median) of 32% (24%). Figure 48 is a histogram of the required price reduction. There is a bimodal distribution corresponding to the different types of protocol administration (FOLFOX versus intermittent or daily).



Symbol: K: thousand; %: per cent

Figure 48: Histogram of price reduction required to restore cost-effectiveness

The results differed both by the type of cancer and the payment mechanism. Daily use required a similar price reduction (26%) to intermittent use (26%) but a lower price reduction than that for FOLFOX inspired protocols (41%). The required price reductions were higher for NSCLC (50%), compared to breast cancer (27%), and CRC (22%).

ANCOVA regression analysis showed the variance in the total QALYs gained in the displaced line of therapy is mostly explained by the mean PFS in the first line of therapy (50%), the utility weight (34%), the type of cancer (13%) and the increase in adverse events associated with displacement (3%). The cost in the displaced line of therapy was mostly explained by the mean PFS in the first line of therapy, the utility weight and the threshold.

The use of microsimulation resulted in an increased number of protocols that were unviable in the first line of therapy (i.e. with a negative price or dominated). These unviable protocols numbered approximately 35 000. A small number of protocols resulted in no participants receiving treatment in the second line of therapy (39). When displaced a line of therapy, fewer than 0.6% of protocols were dominated by no treatment.

The mean (median) cost-effectiveness of the displaced protocols in second line was $116 927 ($81 770). The 95% credible interval for the cost-effectiveness of the second line was between $50 112 and $208 121. The microsimulation demonstrated a consistently higher cost-

effectiveness ratio for displaced protocols than that estimated using the parameter only cost-effectiveness analysis. For a cost-effectiveness ratio of $50 000 the probability of acceptability was 2.4%. For a cost-effectiveness ratio of $100 000 the probability of acceptability was 76%.

The microsimulation resulted in a lower net monetary benefit. The credible interval varied between a loss of $58 million and a gain of $20 000. The mean (median) NMB was a loss of $14 million ($9 million). The standard deviation of the NMB was large ($13 million). There was a 2.6% chance that the NMB for the displaced line of therapy was positive. The mean (median) change in the cost-effectiveness ratio was larger at $56 000 ($20 025), excluding the dominated protocols.

A larger proportion of protocols (10%) when displaced could not be restored to a cost-effectiveness ration equivalent to the threshold, even when the price was zero. The remainder of the protocols could, and for those protocols the required price reduction was a mean (median) of 39% (34%).

Inclusion of discounting had a minor impact on the results. The cost-effectiveness ratios for the displaced therapy increased (less cost-effective) when the discount rate increased. This occurred because the discounted value of the cost of death increased with displacement (as it occurred closer to the commencement of therapy in the second line of therapy compared to the first). There was no impact of discounting on the cost-effectiveness in the first line because the price was set to bind the threshold willingness to pay for a discounted QALY.

Table 79: Impact of discounting on the cost-effectiveness of displaced treatments

Discount rate	Cost-effectiveness in first line (mean) per discounted QALY	Cost-effectiveness with displacement (mean)
0%	$60 964	$77 975
3%	$60 964	$79 723
5%	$60 964	$80 012
7%	$60 964	$82 327
10%	$60 964	$86 634

Abbreviation: QALY: quality adjusted life years

The use of a rate per time of the adverse events that increases with displacement was an alternative method of modelling adverse events (as opposed to presence or absence), based on the results of Table 70. This did not result in substantial changes in the calculated parameters; the mean (median) cost-effectiveness in the second line of therapy was $77 925 ($75 035). The net monetary benefit loss was a mean of $13 million and the mean change in

the cost-effectiveness ratio was $17 000. Decreasing either the post-progression survival or the utility in the second line of therapy had a substantial impact on the results.

Table 80: Results of scenario analysis of PSA

Scenario	Mean cost-effectiveness in second line	Mean NMB	Mean change in cost-effectiveness	Mean price change required
Base case	$77 977	-$12M	$17 013	32%
Modelling adverse events as a rate per time	$77 925	-$13M	$17 056	31%
Cost per month of care	$75 774	-$10M	$14 508	28%
Decreased utility in the second line of therapy	$82 871	-$15M	$21 906	38%
Decreased post-progression survival after the second line of therapy	$92 946	-$17M	$31 981	43%
Correlating probability of second line treatment with post-progression survival	$80 989	-$14M	$20 025	39%

Symbol: M; million

7.3 Conclusions

When a new protocol or treatment is introduced into a current treatment sequence, existing protocols may move from their current line to a subsequent line of therapy. This is likely to affect the effectiveness, cost and the adverse events associated with the protocol. These changes will flow through to the assessment of the cost-effectiveness of the existing protocol in its new place in therapy unless the price is adjusted.

From the perspectives of pricing and allocative efficiency, it would be preferable that such a move have no impact. However, this was not supported by the clinical evidence (Section 6.3) which suggested that the effectiveness of a treatment decreased, and its toxicity increased when it was displaced into a later line of therapy.

These changes had a predictable impact on the cost-effectiveness of a protocol if the marginal cost of that protocol was constant with respect to time; that is, the cost-effectiveness ratio increases as a protocol was displaced from one line of therapy to the next. In the case of one

displacement, the net monetary benefit was sensitive to the size of the population and the proportion of the population receiving the protocol after it had been displaced. If a protocol or treatment was displaced more than once, the importance of the adverse events (both rate and cost) increases.

When the marginal cost with respect to time was not constant the results were more ambiguous. Depending on the distribution of costs through time, one displacement resulted in either an increase or decrease in the cost-effectiveness ratio.

The deterioration in cost-effectiveness was likely to be larger if the initial cost-effectiveness threshold was higher, the adverse event cost was larger and/or there was an increase in the number of adverse events associated with a displaced protocol. The deterioration was also likely to be larger if the marginal cost with respect to time was lower than the average cost.

The probabilistic sensitivity analysis was undertaken using a construction of simulated protocols that drew upon the combination of characteristics of anticancer agents recently submitted to the PBAC. A small number of the simulated protocols were not viable in the first line of therapy (requiring a price of less than zero). On average, displacement resulted in a worsening of the cost-effectiveness ratio and loss of net monetary benefit.

Two PSAs were conducted, one involving a microsimulation and one based on parameter variation only. The microsimulation included heterogeneity of outcome, with participants more likely to receive the displaced treatment if they had a longer post-progression survival time after the failure of the first treatment.

These results suggested that the relationship between how the treatment is administered and funded relative to its benefit in improving survival is important in considering the impact of displacement. The results also demonstrated that altering the price was a potentially viable mechanism for returning the cost-effectiveness of a protocol to the threshold in the majority, but not all cases. A minority of protocols (7% to 10%) are not cost-effective at a price of zero.

There were substantial assumptions and corresponding weaknesses in the construction of the estimated values. These weaknesses result from the usual sources of uncertainty in an economic evaluation as well as some of the specific requirements of the economic problem investigated. The limitations of the clinical information (as discussed in Section 6.3) were the lack of representativeness of the trials and the lack of information reported in the trials.

Parameter uncertainty was dealt with using both with one-way and probabilistic sensitivity analysis, with the ranges used drawn from the clinical evidence and prior economic investigations. The extent to which the clinical evidence provides an accurate estimation of the potential uncertainty is limited by its representativeness and completeness. Important issues like the cost and number of adverse events were limited by the manner of reporting in the oncology trials.[50] Likewise, the relationship between utility values in an initial and a subsequent line of therapy was not known with certainty.[284] While the results of the one-way sensitivity analysis confirm the broad impact of displacement (that it results in a worsening cost-effectiveness and a negative net monetary impact), the magnitude of the impact of displacement varied widely depending on plausible changes to the assumptions. Moreover, the range of price reductions required to restore cost-effectiveness varied widely (from small increases to 90% reductions).

Heterogeneity between cancer types and between different anticancer protocols was an important source of uncertainty in these models. Reductions in the effectiveness of a protocol because of displacement may differ between cancer types, as demonstrated in Section 6.3. There may also be differences between types of anticancer agents. While the majority of anticancer agents used in the meta-analysis were traditional chemotherapy agents, at least 55% of more recent submissions to the PBAC were targeted agents.

Only pharmaceutical, monitoring, infusion, death, progression and adverse event costs were included in the modelling. This is consistent with the economic evaluations that were critiqued in Section 3.1 (Table 16). The inclusion of other costs that do not alter with displacement (such as a constant disease related cost) alters the prices but does not alter the changes that occur with displacement.

The structural uncertainty of this model was high. It is worth considering the potential issues with the structural form which are associated with the summation of different lines of therapy and the estimation of protocol (*j*) in different lines of therapy (*i*). The assumption of an additive model of benefit and cost across lines of therapy allows a single line of therapy to be considered in comparison to no treatment and calculations and estimates to be taken on that line of therapy. It is the dominant model structure used in the multiple lines of treatment for economic evaluations (see Section 3.1). However, the relationship between PFS and overall survival is not consistent in all cancers.[293] Additionally, the assumption of an exponential distribution of time to event is not always an accurate representation of the real-world

outcomes,[294] although where there is a lack of individual level data it can be used to approximate the outcomes.[251,295]

The importance of the potential correlation between the outcomes associated with no treatment and those associated with the displaced therapy are important in determining the cost-effectiveness of the displaced therapy. It is reasonable to assume that the use of an additional treatment is more likely in those who remain clinically robust and therefore are more likely to have a higher survival without treatment. If this was modelled, as in the stochastic PSA, it increases the cost-effectiveness ratio. Alternative methods of modelling the impact of adverse events did not have as large an impact and the results were robust to alternative choices for modelling.

The model assumes that displacement occurs following the introduction of a new protocol. In Australia, this does not always happen as restrictions on prescribing can be used to ensure that effectiveness and cost-effectiveness are maintained in practice. However, there is a substantial potential for pharmaceuticals to be used outside the rules suggested by the PBS.[296] It has been demonstrated that a minority of participants receive treatment beyond that for which evidence exists (Section 4.3).

Similarly, the use of a threshold price does not represent reality in Australia, where no published threshold exists and where other considerations are taken into account in making recommendations about listing or not listing a pharmaceutical on the PBS. This also assumed that the decision-maker's demand is perfectly elastic at the threshold price. The probabilistic sensitivity analysis used a range of thresholds to model the fact that there is not a single threshold price for QALYs in Australia. However, the assumption was made that the threshold stayed stable with displacement.

No discounting was used in this majority of this analysis. This may not be an important issue for metastatic cancer, but it is not consistent with the usual decision-making process. However, the lack of discounting makes the calculation of the incremental cost and benefit less computationally difficult as costs common to both alternatives can be removed without regard for their timing. Discounting was undertaken as part of the scenario analysis and increased the cost-effectiveness ratio associated with the displaced therapy.

The results of the modelling demonstrate that displacement is a significant economic issue with an opportunity cost both in terms of resources required for treatment of adverse events and administration. Additionally, it may result in a lower return than would be gained by

alternative uses of the monetary resources within the health system. Reducing the price of the pharmaceuticals was an option for restoring the cost-effectiveness ratio to the threshold value in 90% of protocols simulated.

Displacement, as modelled, results in an economic loss in the majority of cases. This is because the alternative uses of the required resources resulted in a greater benefit than that received by a displacement of a protocol. The median economic cost associated with displacement was approximately $8.8 million for breast cancer, CRC and NSCLC. This suggests that displacement results in allocative inefficiency with the alternative use of resources potentially resulting in a larger benefit. However, allowing displacement may be productively efficient because it is the least expensive method of ensuring benefit for metastatic carcinoma patients.

There was, however, a wide variation around this figure of $8.8 million. This was partly because of variation in the characteristics of the displaced protocols. There is also a lack of certainty about several of the parameters underlying these results, mainly from a lack of clinical evidence. The available modelling does not result in precise estimates. The size of the treated population and the proportion who receive a second line of therapy are important factors in determining the uncertainty associated with the net monetary benefit.

A small proportion of the displaced protocols required a price reduction greater than one hundred per cent. This presents two issues for a decision-maker. First, the displaced protocol will not be cost-effective at any price. Therefore, the decision-maker must choose to either accept the resultant higher cost-effectiveness ratio (and the associated allocative inefficiency) or disinvest the reimbursement of a treatment which is known to be effective. Second, if disinvestment does occur and the treatment is funded by another mechanism (e.g. out of pocket funding by the patient, private health insurance or compassionate funding), the cost of adverse events and administration will represent a net loss to society. This occurs because the monetary value of the benefit to society is less than the societal expenditure on treating adverse events and the MBS contribution to monitoring and administration. Therefore, for those who can fund these treatments, it results in further cost-ineffective use of resources. This represents a potential equity issue.

Chapter 8 Generalisation and implications

8.1 Contribution to the literature

Cancer is an important public health problem. There is increasing availability of treatments for cancer, but these treatments are expensive. It is important that methods of reimbursement ensure the sustainability of the public system of access to these treatments in Australia over time. This requires ensuring the continuing cost-effectiveness of an increasing number of cancer treatments. It also requires the appropriate evaluation of the potentially increasing costs of longer and more complex treatment sequences.

This thesis has made theoretical and applied contributions to the literature of economic evaluation in treatment sequences resulting from displacement. Displacement is where existing older treatments are used later in a treatment sequence because of the introduction of new treatments (rather than being replaced).

This thesis addressed three main questions.

1. Does the displacement of a treatment, from one line of therapy to a later line, alter its cost-effectiveness compared with alternative treatments, or no treatment?
2. If the cost-effectiveness becomes less favourable can any resulting societal welfare loss be corrected by changing the price?
3. Can the required price change be calculated in Australia using administrative data?

The development of a treatment sequence through displacement was formalised and the theoretical implications for allocative and dynamic efficiency were demonstrated. The proposed solution of altering prices of existing pharmaceuticals was shown to eliminate allocative and dynamic inefficiencies. Therefore, theoretically, this addressed the question posed by the thesis as to whether societal welfare loss resulting from displacement may be corrected by changing the price of displaced treatments (Question 2).

The framework developed in Chapter 2 assumed a specific manner in which treatment sequences develop. Three features were highlighted: the dynamic nature of the set of treatments that are available (increasing over time); the adoption of new treatments altering the use of existing treatments, and the new use of existing treatments which may not have been evaluated for cost-effectiveness and clinical effectiveness in their new line of therapy. These features are present in other ways that treatment sequences develop.

Chapter 3 examined the current economic evaluation literature, including common assumptions and modelling techniques associated with oncology and the modelling of multiple lines of therapy or a specific treatment in different lines of therapy. Two different sets of literature were reviewed. The first set was published economic evaluations of treatment sequences involving multiple lines of therapy in carcinomas. The second set was published economic evaluations of a pharmaceutical (cetuximab) used in different lines of therapy for treatment of colorectal cancer (CRC).

Chapter 3 concluded that the reviewed literature had significant gaps. Common modelling assumptions included using a constant cost per period, not including adverse event costs and restricting the evaluations to published clinical literature. These assumptions necessarily restrict the analysis to a set of treatments and lines of therapy that do not represent how treatments may be used in practice. These economic evaluations suffer from limited external validity.

Chapter 4 examined the completeness of administrative data by comparing the Pharmaceutical Benefits Scheme (PBS) to the Elements of Cancer Care (EoCC) cohort. The specificity and the sensitivity of the PBS for detecting anticancer pharmaceuticals was assessed. The sensitivity of the administrative PBS data was found to be poorly performing for high cost pharmaceuticals in the EoCC cohort. It was concluded that the data infrastructure related to the funding mechanisms are incomplete. Therefore, this thesis found that Australian administrative data could not be used to correctly calculate the required price changes to return the cost-effectiveness of displaced treatments to their original value (Question 3).

Chapter 4 also demonstrated that the number of lines of therapy used in the real-world EoCC cohort exceeded the number of lines of therapy used in economic evaluations. Real-world practice (in the EoCC cohort) demonstrated a greater use of treatments than that for which randomised controlled trial (RCT) evidence existed. A minority of participants in the EoCC cohort received four or more line of therapy. This conclusion was robust to alternative methods of estimation and demonstrated the potential for displacement in Australia.

This result was achieved by developing a method for calculating the number of days for which all new treatments should be considered as one protocol. This replaced earlier methods that relied on assumptions.[161] This method was also used to allocate costs to lines of therapy for the EoCC cohort.

Prior work on the cost of cancer care in Australia[63] was supplemented in this thesis by an analysis which included the costs of additional lines of therapy controlling for multiple sources of bias, including censoring. Chapter 5 found the estimated cost in each line of therapy was consistent with increasing cost per month for increasing lines of therapy. The use of econometric modelling to control for various bias did not alter these conclusions. The results were also consistent with a decreasing marginal cost with respect to increasing time within a line of therapy. These results are inconsistent with the common modelling assumptions used in the economic evaluations reviewed. The observation that the marginal cost of an additional month fell within a line of therapy is an important finding. This has implications for economic evaluations that estimate the impact of treatment sequences.

There are limitations to these results because of the external validity of the dataset used, as regards the types of cancer, the funding of pharmaceuticals in New South Wales compared to other jurisdictions within Australia and the use of fixed effect panel data modelling techniques. However, the key conclusions are consistent across subgroups and robust to sensitivity analysis.

Chapter 6 presented the potential for displacement within the Australian health system. Information from treatment guidelines and the introduction of new pharmaceutical treatments was used to show that displacement is probable within the current oncology environment.

A systematic review and meta-analysis was undertaken of clinical trials that involved displacement. The results demonstrated that the clinical literature, as with the economic literature evaluated in Chapter 3, had significant limitations in terms of both scale and scope. The results were consistent with displacement altering the effectiveness of a protocol once it is displaced. However, the results were heterogeneous, differing between cancer types, limiting the applicability to an individual protocol.

The change in cost-effectiveness with displacing a protocol was estimated in Chapter 7. The cost structure of protocols was found to influence the results of displacement. A decreasing marginal cost was associated with a greater fall in net monetary benefit after displacement.

Simulation of the process of subsidisation and displacement in Australia was conducted. One million simulated protocols were generated and displaced using a partitioned survival model. It was found that displacement of a treatment from one line of therapy to a subsequent line of therapy alters its cost-effectiveness. This addressed the question posed by the thesis as to

whether displacement of a treatment from one to another altered its cost-effectiveness (Question 1).

The displacement model has limitations which influence its external validity and hence its policy utility. These limitations included the relatively small coverage of the meta-analysis of the type of chemotherapy, the type of cancer and the number of displacements. Nonetheless, the results showed that the implications of displacement include a significant potential opportunity cost with associated allocative inefficiency.

The results suggested it was possible for price adjustments to restore the incremental cost-effectiveness of a displaced treatment in most cases. However, for a small proportion of cases, even with a price of zero, the cost-effectiveness of a displaced treatment increased. This is more likely to occur with treatments for which there is a decreasing marginal cost over time. Therefore, it was concluded that most, but not all, of the societal welfare loss could be corrected by an adjustment in the price of treatments. Therefore, practically, this addressed the question posed by the thesis as to whether societal welfare loss resulting from displacement may be corrected by changing the price of displaced treatments (Question 2).

The results of the investigation of displacement as contained in this thesis need to be extended as they represent an abstraction. Two extensions are discussed in this final Chapter. The first is to consider a wider spectrum of treatment sequences than displacement. The second is to consider the implications for future research and the PBS arrangements in Australia.

8.2 Moving beyond the displacement framework

While the displacement framework may represent some clinical situations accurately, there are some alternative issues to consider with the introduction of new pharmaceuticals. One key issue is heterogeneity between individuals either in the benefit they receive or ideal treatment sequences.

Heterogeneity could cause stratification in the average benefit that patients may experience based on the genetic makeup of the tumours or other patient characteristics. Therefore, it is predictable that the addition of new treatments will not only cause displacement but will also cause heterogeneity in the order in which pharmaceuticals are administered to individual patients. That is, the optimal sequence may differ between individuals based on identifiable characteristics prior to treatment commencing.

Genetic heterogeneity is not the only reason there may be heterogeneity in the treatment sequence that individuals receive. Different chemotherapy treatments or protocols can produce different adverse events. Accordingly, there may be patient preferences between those adverse events, which may be traded off against survival or other adverse events.

The economic evaluations discussed in section 3.1 demonstrated that multiple sequences may produce the same expected clinical outcome. An example is the use of FOLFOX (an oxaliplatin based protocol) and FOLFIRI (an irinotecan-based protocol) in sequence for the treatment of CRC and the subsequent use of cost-minimisation analysis because of the assumed similarity of clinical outcomes.[93]

FOLFOX is more likely to result in neurological toxicities and FOLFIRI is more likely to result in gastrointestinal toxicities. Some genomic studies have suggested there is a link between the presence of particular genes and neurological toxicities such that it may be better for those with these genes to be treated with FOLFIRI first.[297] This is because the chance of receiving FOLFOX and the expected total dosage decreases if it is used in the second line of therapy as opposed to the first line of therapy (see Chapter 6).

The presence of pre-existing disease may magnify the disutility associated with toxicities. For example, pre-existing diabetes may exacerbate neurological toxicities and FOLFIRI may be preferred as the first line of therapy. Alternatively, for a patient already suffering from ulcerative colitis (or other gastrointestinal conditions), FOLFOX may be preferred as the first treatment. Personal preferences may also alter the proposed sequence. For example, a professional violist might prefer to minimise the chances of long term neurological adverse events relative to gastrointestinal adverse events because of the importance of sensory feedback and dexterity in performing.

A more concrete example occurs with genetic heterogeneity. The potential for sequence heterogeneity is illustrated by cetuximab. As discussed in Section 3.2, the initial trials occurred prior to knowledge about the genetic information and therefore could not (and did not) take into account that heterogeneity in response is dependent on the genetic makeup of the cancer. Thereafter, the treatment sequence differed between KRAS wild type and KRAS mutant populations.

Another cause of observed sequence treatment heterogeneity is the regulatory or reimbursement environment. For example, cetuximab was reimbursed initially in Australia in the context of use either alone or with irinotecan, as second or later line therapy.[152] In this

context, it might be appropriate for those patients whose tumour has the genetic makeup to respond to cetuximab to have oxaliplatin as their first line therapy (to preserve the option of use of irinotecan in the second line of therapy with cetuximab). Those without the requisite tumour genetic makeup would not gain from preserving the option value of using irinotecan in the second line of therapy. Therefore, their optimal treatment sequence would be more likely to include irinotecan in the first line of therapy.

The potential for new treatments to generate new treatment sequences differs between groups. There may not be simply displacement of treatments for the entire population. However, this does not alter the results of this thesis. The presence of multiple groups each with a different ideal treatment sequence suggests the need for multiple prices for each pharmaceutical, stratified by use. This is because each group may have a different position for each treatment, therefore, requiring a price for the treatment in the first, second and third line of therapy. This occurs because the treatment has a different benefit in each of these lines of therapy. This is consistent with the results shown in Chapter 2. In practice this could be achieved by the use of a weighted average price based on average cost-effectiveness.

An alternative method would be to price the treatment on its incremental benefit for the population of cancer patients without reference to the lines of therapy. This use would require substantially more information than displacement and may not be possible in all circumstances.

8.3 Recommendations

The finding in this thesis have implications for:

- future research;
- economic evaluation of multiple lines of therapy in oncology;
- undertaking research using the PBS and Medicare Benefits Schedule (MBS) for oncology;
- the PBS and the Australian health system; and
- the consideration of treatments that may not be cost-effective at any price when displaced.

Recommendations for each of these areas are suggested.

8.3.1 Recommendations for future research

Changes to the PBS system such as the inclusion of under co-payment pharmaceuticals and the inclusion of the trastuzumab data are important additions to the PBS administrative data. Replication of the approach taken using a different dataset and in other jurisdictions within Australia would be useful to confirm or refute the observations made about additional treatments. The conclusion that costs increase with increasing lines of therapy needs to be tested and either confirmed or rejected using other datasets.[163]

The distribution of costs within lines of therapy should be investigated further using other sources of real-world data. The finding that pharmaceutical costs decrease within a line of therapy over time should be confirmed in different datasets and especially for newer targeted treatments. Confirming or refuting this would be a useful addition to empirical work on the cost structure of chemotherapy.

Further research into the cost of adverse events in different lines of therapy should be undertaken using real-world data. This should test the assumption that adverse events have a constant cost and impact on health status.

Finally, it would be useful if the distribution of costs within a line of therapy and the distribution of costs in subsequent lines of therapy be included in future RCTs that include economic evaluation. This would allow greater inclusion of post-progression treatments in economic modelling and consequently a reduction in uncertainty.

8.3.2 Recommendations for economic evaluations of multiple lines of therapy in oncology

The question for each economic evaluation of multiple lines of therapy should be clearly defined, especially with regard to considering a real-world scenario or RCT literature. The potential lack of available RCT literature should be explicitly considered and the question altered accordingly. The cost-effectiveness in the Australian setting of multiple lines of therapy using the available RCT literature is not the same question as the cost-effectiveness of multiple lines of therapy as currently used within the Australian health system.

The appropriateness of the modelling method chosen should be made explicit relative to other potential choices and justified. The potential biases should be acknowledged, especially in relation to the setting.

Assumptions around the appropriateness of a simple Markov model should be explicitly discussed. These include the assumption of a constant cost per cycle and how utility values in different lines of therapies were determined. The sensitivity of the results to these assumptions must be explored. Using cycle specific costs should be considered.

The assumptions about moving from one line of therapy to the next should be made explicit. Assuming living participants receive additional treatments is not consistent with the evidence from the RCTs or the real-world information provided in Chapter 5. Assumptions around the proportion of the modelled cohort that receive multiple lines of therapy should be the subject of a sensitivity analysis over a plausible range.

The potential correlation between additional lines of therapy and higher performance status should be considered. The potential bias that this patient level heterogeneity could introduce should be discussed. As shown in Chapter 7, assuming a constant post-progression best supportive care period for all patients produces a different outcome compared to assuming that patients who received additional treatments would have had a longer post-progression survival without treatment.

The costs of adverse events were an important driver of the results. Adverse events must either be included in economic evaluations of multiple lines of therapy or the bias resulting from their exclusion should be discussed.

Displacement and the potential for additional post-progression treatments to be given should be considered. The sensitivity of the results to these assumptions should be explored.

Finally, efforts should be made to include observational or real-world data from the setting of the economic evaluation to determine the number of lines of therapy either for modelling or for discussion about the external validity of the economic evaluation to its setting. However, as discussed in Chapter 5, the assessment of medical costs is complicated and subject to numerous biases and endogeneity that must be carefully considered.

8.3.3 Recommendations when undertaking research using the PBS and MBS for oncology

Future research should investigate if additional therapies are present or absent using MBS infusion data and evaluate whether this is important in terms of the conclusions drawn, especially about cost and effectiveness.

The assumptions used to avoid double counting of costs should be made explicit. How admissions from the emergency department are handled is one potential area of double counting, although the magnitude is limited in the oncology context. The costing of chemotherapy admissions, especially regarding private hospital admissions, MBS costs and PBS costs, is a larger area of potential double counting.

The censored nature of the data and the potential for clustering of costs using different AR-DRGs for similar activities at an institutional level should be considered in econometric analysis.

8.3.4 Recommendations for the PBS and the Australian health system

The incremental costs and benefits of later line treatments cannot be assessed correctly without an accurate understanding of both adverse events and the number of treatments provided. Currently, administrative data does not provide this information in a sufficiently comprehensive manner. If value-based pricing of oncology pharmaceuticals is to be implemented in Australia, more complete information is required. Cancer registries will be an important component of data infrastructure if the incremental costs and benefits of cancer treatments are to be accurately estimated. In order for value-based pricing to be introduced practical issues such as how and how often price re-negotiation would occur need to be considered. Following current international efforts to consider repricing of high cost pharmaceuticals should be considered.[298]

Risk sharing agreements and other instruments designed to protect the efficiency of public spending need to take into account the potential for further displacement as new treatments are listed for reimbursement. Instruments such as price volume arrangements will not ensure cost-effectiveness of displaced treatments as the volume of pharmaceuticals decreases with displacement and the cost-effectiveness deteriorates. Risk sharing agreements may need to consider adverse events which would require additional monitoring and incur associated costs.

Methods to calculate the incremental benefit of existing treatments in the Australian healthcare system need to be refined and require a larger number of participants than captured by the analysis used in this thesis.

8.3.5 Recommendations for treatments that may not be cost-effective at any price when displaced

This thesis suggests that lower prices for some pharmaceuticals will not return displaced treatments to their original cost-effectiveness. Therefore, the potential for displacement and

measures to ensure cost-effectiveness should be considered when pharmaceuticals are first listed. Decision-makers should consider not listing or defunding treatments that are not cost-effective at a price of zero when displaced (disinvestment).

The potential that some displaced treatments will not be cost-effective even with a price of zero highlights potential equity and effectiveness issues for the public health system. This implies that even if the pharmaceutical is entirely paid for by another entity, the costs of adverse events and pharmaceutical administration may exceed the value placed on the health benefit by a societal decision-maker.

The potential size of this problem needs to be more firmly established and acceptable policy options further canvassed. At one extreme, the financing of administration of treatments and the management of adverse events will continue to be subsidised by the Australian Federal Government and States at a higher cost-effectiveness ratio than other services. At the other extreme, the costs of adverse events and administration will need to be borne by the entity funding the pharmaceutical.

Increasing numbers of expensive oncology treatments represent a substantial challenge to preserving efficiency and equity within the Australian health system. New additions to the armamentarium need to have their effectiveness and cost-effectiveness demonstrated, but it is also necessary to ensure currently used treatments remain cost-effective.

Appendix A: Review of articles found in search for economic evaluations of multiple lines of therapy

The results of the full-text review for the articles found in the search undertaken in Chapter 3 for the economic evaluations of treatment sequences in carcinomas are tabulated below.

Table 81: Inclusion and exclusion of publications of literature search of treatment sequences in carcinomas

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Keyfitz (1977)[299]	1977	Exclusion	Not an economic analysis
Evans (1993)[300]	1993	Exclusion	Not an economic analysis
Butler et al. (1995)[301]	1995	Exclusion	Not an economic analysis
Evans et al. (1995)[302]	1995	Exclusion	Not an economic analysis
Glimelius et al. (1995)[303]	1995	Exclusion	Not an economic evaluation of multiple lines
Gulati and Bitran (1995)[304]	1995	Exclusion	Not an economic analysis
Jonsson et al. (1995)[305]	1995	Exclusion	Not an economic analysis
Palmer and Brandt (1996)[306]	1996	Exclusion	Not an economic evaluation of multiple lines
Schneiderman and Jecker (1996)[307]	1996	Exclusion	Not an economic analysis
Bishop and Macarounas-Kirchman (1997)[308]	1997	Exclusion	Not an economic evaluation of multiple lines
Collins (1997)[309]	1997	Exclusion	Not an economic analysis
Buijt et al. (1998)[310]	1998	Exclusion	Not solid tumour
Hillner (1998)[311]	1998	Exclusion	Not an economic analysis
Postma et al. (1998)[312]	1998	Exclusion	Not solid tumour
Waters (1998)[313]	1998	Exclusion	Not an economic evaluation of multiple lines
McLachlan et al. (1999)[16]	1999	Exclusion	Not an economic analysis
Balducci et al. (2000)[314]	2000	Exclusion	Not an economic analysis
Bennett and Stinson (2000)[315]	2000	Exclusion	Not an economic evaluation of multiple lines
Bunn and Kelly (2000)[316]	2000	Exclusion	Not an economic analysis
Elit et al. (2000)[317]	2000	Exclusion	Not an economic analysis
Will et al. (2000)[318]	2000	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Doyle et al. (2001)[319]	2001	Exclusion	Not an economic evaluation of multiple lines
Du and Goodwin (2001)[320]	2001	Exclusion	Not an economic analysis
Clegg et al. (2002)[321]	2002	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Dranitsaris et al. (2002)[322]	2002	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Monfardini (2002)[323]	2002	Exclusion	Not an economic analysis
Roberts et al. (2002)[324]	2002	Exclusion	Not an economic analysis
Rohde et al. (2002)[325]	2002	Exclusion	Not an economic analysis
Beil and Wein (2003a)[326]	2003	Exclusion	Not an economic analysis
Beil and Wein (2003b)[327]	2003	Exclusion	Not an economic analysis
Castro (2003)[328]	2003	Exclusion	Not an economic analysis
Cooper (2003)[329]	2003	Exclusion	Not an economic evaluation of multiple lines
Karnon (2003)[330]	2003	Exclusion	Not an economic analysis
Marino et al. (2003)[331]	2003	Exclusion	Not an economic evaluation of multiple lines
Chouaid et al. (2004)[332]	2004	Exclusion	Not an economic analysis
Iqbal et al. (2004)[333]	2004	Exclusion	Not an economic analysis
Jimeno et al. (2004)[334]	2004	Exclusion	Not an economic analysis
Knight et al. (2004)[335]	2004	Exclusion	Not solid tumour
Schrag (2004)[25]	2004	Exclusion	Not an economic analysis
Sculpher et al. (2005)[336]	2004	Exclusion	Not an economic analysis
Spiro et al. (2004)[337]	2004	Exclusion	Not an economic analysis
Vergnengre et al (2004)[338]	2004	Exclusion	Not an economic analysis
Drummond et al (2005)[339]	2005	Exclusion	Not an economic analysis
Manca et al. (2005)[340]	2005	Exclusion	Not an economic analysis
Manca and Palmer (2005)[341]	2005	Exclusion	Not an economic analysis
Willan et al. (2005)[342]	2005	Exclusion	Not an economic analysis
Bordeleau (2006)[343]	2006	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Molinier et al. (2006)[344]	2006	Exclusion	Not an economic analysis
Tassinari et al. (2006)[24]	2006	Exclusion	Not an economic analysis
Case et al. (2007)[345]	2007	Exclusion	Not an economic evaluation with choice in multiple lines of therapy- included in interesting group
Chouaid et al. (2007[346])	2007	Exclusion	Not an economic evaluation with choice in multiple lines of therapy- included in interesting group
Grusenmeyer et al. (2007)[347]	2007	Exclusion	Not an economic analysis
Karnon et al. (2007)[348]	2007	Exclusion	Not an economic evaluation of multiple lines
Klein and Gottfried (2007)[349]	2007	Exclusion	Not an economic analysis
Litwin et al. (2007)[350]	2007	Exclusion	Not an economic analysis
Chouaid et al. (2008)[351]	2008	Exclusion	Not an economic analysis
Ferro et al. (2008)[352]	2008	Exclusion	Not an economic analysis
Fox et al. (2008)[353]	2008	Exclusion	Not an economic analysis
Hecht (2008)[354]	2008	Exclusion	Not an economic analysis
Hind et al. (2008)[94]	2008	Inclusion	
Popov et al. (2008)[355]	2008	Exclusion	Not an economic analysis
Ramsey et al. (2008)[356]	2008	Exclusion	Not an economic analysis
Wong (2008)[357]	2008	Exclusion	Not an economic analysis
Yau et al. (2008)[358]	2008	Exclusion	Not an economic analysis
Berlinger and Flamm (2009)[359]	2009	Exclusion	Not an economic analysis
Boshoff and Posner (2009)[360]	2008	Exclusion	Not an economic analysis
Chouaid et al. (2009)[361]	2009	Exclusion	Not an economic analysis
Dahlberg et al. (2009)[362]	2009	Exclusion	Not an economic analysis
Fojo and Grady (2009)[363]	2009	Exclusion	Not an economic analysis
Goldberg et al. (2009)[364]	2009	Exclusion	Not an economic analysis
Hall et al. (2009)[365]	2009	Exclusion	Not an economic analysis
Lansdorp-Vogelaar et al. (2009)[366]	2009	Exclusion	Not an economic analysis
Miyazaki et al. (2009)[93]	2009	Inclusion	

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
NICE (2009)[90]	2009	Inclusion	
Shiroiwa et al. (2009)[95]	2009	Inclusion	
Tappenden et al. (2009)[367]	2009	Exclusion	Not an economic analysis
Wagner et al. (2009)[368]	2009	Exclusion	Not an economic analysis
Wong et al. (2009)[1]	2009	Inclusion	
Yahya and Ulm (2009)[369]	2009	Exclusion	Not an economic analysis
Yin and Yuan (2009)[370]	2009	Exclusion	Not an economic analysis
Yu et al. (2009)[295]	2009	Exclusion	Not an economic analysis
Prescrire Editorial Staff (2010)[371]	2010	Exclusion	Not an economic analysis
Carroll et al. (2010)[372]	2010	Exclusion	Not an economic analysis
Chilcott et al. (2010)[373]	2010	Exclusion	Not an economic analysis
Cooper et al. (2010)[374]	2010	Exclusion	Not an economic evaluation of multiple lines
Eng (2010)[375]	2010	Exclusion	Not an economic analysis
Goldberg et al. (2010)[376]	2010	Exclusion	Not an economic analysis
Kutikov et al. (2010)[377]	2010	Exclusion	Not an economic analysis
Lebeau et al. (2010)[378]	2010	Exclusion	Not an economic analysis
Manca et al. (2010)[379]	2010	Exclusion	Not an economic analysis
Oakley et al. (2010)[380]	2010	Exclusion	Not an economic analysis
Ochenduszko et al. (2010)[381]	2010	Exclusion	Not an economic analysis
Park et al. (2010)[382]	2010	Exclusion	Not an economic analysis
Paz-Ares et al. (2010)[383]	2010	Exclusion	Not an economic evaluation of multiple lines
Thompson Coon et al. (2010)[384]	2010	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Wong et al. (2010)[385]	2010	Exclusion	Not an economic analysis
Banz et al. (2011)[386]	2011	Exclusion	Not an economic analysis
Beveridge et al. (2011)[387]	2011	Exclusion	Not solid tumour
Cohn et al. (2011)[388]	2011	Exclusion	Not an economic evaluation of multiple lines
Hensley (2011)[389]	2011	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Hind et al. (2011)[390]	2011	Exclusion	Not an economic analysis
Ishak et al. (2011)[391]	2011	Exclusion	Not solid tumour
Isla et al. (2011)[392]	2011	Exclusion	Not an economic analysis
Nuijten et al. (2011)[393]	2011	Exclusion	Not an economic analysis
Tse et al. (2011)[394]	2011	Exclusion	Not an economic evaluation of multiple lines
Vergnenegre et al. (2011)[395]	2011	Exclusion	Not an economic evaluation of multiple lines
Vergnenegre et al. (2011)[396]	2011	Exclusion	Not an economic analysis
Wong et al. (2011)[397]	2011	Exclusion	Not an economic analysis
Yabroff et al. (2011)[398]	2011	Exclusion	Not an economic analysis
Almirall et al. (2012)[113]	2012	Exclusion	Not an economic analysis
Basu and Manca (2012)[399]	2012	Exclusion	Not an economic analysis
Beach et al. (2012)[400]	2012	Exclusion	Not an economic analysis
Bendell et al. (2012)[401]	2012	Exclusion	Not an economic analysis
Bongers et al. (2012)[402]	2012	Exclusion	Not an economic analysis
Borget et al. (2012)[40]	2012	Exclusion	Not an economic evaluation of multiple lines
Cadranel et al. (2012)[403]	2012	Exclusion	Not an economic analysis
Cartwright et al. (2012)[404]	2012	Exclusion	Not an economic analysis
Casciano et al. (2012)[405]	2012	Exclusion	Not an economic evaluation of multiple lines
Chaffee and van der Laan (2012)[406]	2012	Exclusion	Not an economic analysis
Chaffee and van der Laan (2012)[407]	2012	Exclusion	Not an economic analysis
Chouaid et al. (2012)[96]	2012	Inclusion	
De Souza et al. (2012)[408]	2012	Exclusion	Not an economic analysis
Diaz-Rubio et al. (2012)[409]	2012	Exclusion	Not an economic analysis
Dranitsaris et al. (2012)[410]	2012	Exclusion	Not an economic evaluation of multiple lines
Dyer et al. (2012)[411]	2012	Exclusion	Not an economic analysis
Fragoulakis et al. (2012)[146]	2012	Exclusion	Not an economic evaluation of multiple lines
Gaultney et al. (2012)[412]	2012	Exclusion	Not solid tumour
Handorf et al. (2012)[413]	2012	Exclusion	Not an economic evaluation of multiple lines

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Hatfield et al. (2012)[414]	2012	Exclusion	Not an economic analysis
Hedden et al. (2012)[415]	2012	Exclusion	Not an economic evaluation of multiple lines
Hornberger et al. (2012)[416]	2012	Exclusion	Not an economic evaluation of multiple lines
Kutikov et al. (2012)[417]	2012	Exclusion	Not an economic analysis
Le Caer et al. (2012)[99]	2012	Exclusion	Not an economic analysis
Manca et al. (2012)[97]	2012	Inclusion	
Mullins et al. (2012)[418]	2012	Exclusion	Not an economic evaluation of multiple lines
Nakayama et al. (2012)[419]	2012	Exclusion	Not an economic analysis
Nuijten et al. (2012)[420]	2012	Exclusion	Not an economic analysis
Parast et al. (2012)[421]	2012	Exclusion	Not an economic analysis
Perol et al. (2012)[422]	2012	Exclusion	Not an economic analysis
Popa et al. (2012)[423]	2012	Exclusion	Not an economic analysis
Rinaldi et al. (2012)[424]	2012	Exclusion	Not an economic analysis
Saramago et al. (2012)[425]	2012	Exclusion	Not an economic analysis
Saramago et al. (2012)[426]	2012	Exclusion	Not an economic analysis
Sookprasert et al. (2012)[427]	2012	Exclusion	Not an economic analysis
Sorenson (2012)[6]	2012	Exclusion	Not an economic analysis
Tappenden et al. (2012)[37]	2012	Exclusion	Not an economic analysis
Tilson et al. (2012)[428]	2012	Exclusion	Not an economic analysis
Vergnenegre et al. (2012)[429]	2012	Exclusion	Not an economic evaluation of multiple lines
Walleser et al. (2012)[430]	2012	Exclusion	Not an economic evaluation of multiple lines
Wang et al. (2012)[431]	2012	Exclusion	Not an economic analysis
Wang et al. (2012)[432]	2012	Exclusion	Not an economic analysis
Wong et al. (2012)[433]	2012	Exclusion	Not an economic analysis
Zeng et al. (2012)[434]	2012	Exclusion	Not an economic analysis
Bennouna et al. (2013)[435]	2013	Exclusion	Not an economic analysis
Bylicki et al. (2013)[436]	2013	Exclusion	Not an economic analysis
Chouaid et al. (2013)[437]	2013	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Chouaid et al. (2013)[88]	2013	Inclusion	
Dacosta Byfield et al. (2013)[187]	2013	Exclusion	Not an economic analysis
De Souza et al. (2013)[438]	2013	Exclusion	Not an economic analysis
Gaultney et al. (2013)[157]	2013	Exclusion	Not solid tumour
Gaultney and Uyl-de Groot (2013)[103]	2013	Exclusion	Not solid tumour
Hoch (2013)[26]	2013	Exclusion	Not an economic analysis
Hoyle et al. (2013)[137]	2013	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Hoyle et al. (2013)[41]	2013	Exclusion	Not an economic evaluation of multiple lines
Jakel et al. (2013)[83]	2013	Exclusion	Not an economic analysis
Joulain et al. (2013)[439]	2013	Exclusion	Not an economic analysis
Kaltenthaler et al. (2013)[440]	2013	Exclusion	Not an economic analysis
Kearns et al. (2013)[441]	2013	Exclusion	Not an economic analysis
Le Treut et al. (2013)[442]	2013	Exclusion	Not an economic analysis
Lester et al. (2013)[443]	2013	Exclusion	Not an economic analysis
Lichtenberg and Hostenkamp (2013)[444] published in Social Science and Medicne in 2015[445]	2013	Exclusion	Not solid tumour
Lord et al. (2013)[446]	2013	Exclusion	Not an economic analysis
Mazieres et al. (2013)[447]	2013	Exclusion	Not an economic analysis
Naviglio and Della Ragione (2013)[448]	2013	Exclusion	Not an economic analysis
Oliver and Chung (2013)[449]	2013	Exclusion	Not an economic analysis
Organisation for Economic Co-operation and Development (2013)[450]	2013	Exclusion	Not an economic analysis
Ortega et al. (2013)[451]	2013	Exclusion	Not an economic analysis
Rittmeyer et al. (2013)[452]	2013	Exclusion	Not an economic analysis
Scagliotti et al. (2013)[453]	2013	Exclusion	Not an economic analysis
Sonpavde et al. (2013)[454]	2013	Exclusion	Not an economic analysis
Stump et al. (2013)[455]	2013	Exclusion	Not an economic analysis
Tappenden et al. (2013)[98]	2013	Inclusion	

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Tie and Gibbs (2013)[179]	2013	Exclusion	Not an economic analysis
Tran et al. (2013)[456]	2013	Exclusion	Not an economic evaluation of multiple lines
Vergnenegre et al. (2013)[457]	2013	Exclusion	Not an economic analysis
Vergnenegre et al. (2013)[458]	2013	Exclusion	Not an economic analysis
Vergnenegre et al. (2013)[459]	2013	Exclusion	Not an economic analysis
Wang and Hutson (2013)[460]	2013	Exclusion	Not an economic analysis
Wong (2013)[461]	2013	Exclusion	Not an economic analysis
Wong et al. (2013)[462]	2013	Exclusion	Not an economic analysis
Abrams et al. (2014)[463]	2014	Exclusion	Not an economic analysis
Agarwal et al. (2014)[464]	2014	Exclusion	Not an economic analysis
Auliac et al. (2014)[465]	2014	Exclusion	Not an economic analysis
Bajaj et al. (2014)[466]	2014	Exclusion	Not an economic evaluation of multiple lines
Barlesi et al. (2014)[467]	2014	Exclusion	Not an economic analysis
Basu (2014)[468]	2014	Exclusion	Not an economic analysis
Batty et al. (2014)[469]	2014	Exclusion	Not solid tumour
Chan et al. (2014)[470]	2014	Exclusion	Not an economic analysis
Chouaid et al. (2014)[471]	2014	Exclusion	Not an economic analysis
Ciani et al. (2014)[472]	2014	Exclusion	Not an economic analysis
Cooper et al. (2014)[473]	2014	Exclusion	Not solid tumour
De Mello Sampayo et al. (2014)[108]	2014	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Diaby et al. (2014)[474]	2014	Exclusion	Not an economic analysis
Diaby et al. (2014)[475]	2014	Exclusion	Not an economic evaluation of multiple lines
Dotan et al. (2014)[476]	2014	Exclusion	Not an economic analysis
Dunbar et al. (2014)[477]	2014	Exclusion	Not an economic analysis
Einav et al. (2014)[478]	2014	Exclusion	Not an economic evaluation of multiple lines
Espinoza et al. (2014)[479]	2014	Exclusion	Not an economic analysis
Gavan et al. (2014)[480]	2014	Exclusion	Not solid tumour

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Gill et al. (2014)[481]	2014	Exclusion	Not an economic analysis
Goldstein et al. (2014)[482]	2014	Exclusion	Not an economic evaluation of multiple lines
Hendifar et al. (2014)[483]	2014	Exclusion	Not an economic analysis
Kaltenthaler et al. (2014)[484]	2014	Exclusion	Not an economic analysis
Klein et al. (2014)[485]	20142014	Exclusion	Not an economic analysis
Lange et al. (2014)[85]	2014	Exclusion	Not an economic analysis
Lerouge et al. (2014)[486]	2014	Exclusion	Not an economic analysis
Lichtenberg (2014)[487]	2014	Exclusion	Not an economic analysis
Matro et al. (2014)[488]	2014	Exclusion	Not an economic analysis
Messali et al. (2014)[489]	2014	Exclusion	Not an economic analysis
Nakahara and Kamae (2014)[490]	2014	Exclusion	Not an economic analysis
Ossandon et al. (2014)[491]	2014	Exclusion	Not an economic analysis
Parkinson et al. (2014)[492]	2014	Exclusion	Not an economic analysis
Pond et al. (2014)[493]	2014	Exclusion	Not an economic analysis
Rautenberg (2014)[494]	2014	Exclusion	Not an economic analysis
Rautenberg et al. (2014)[2]	2014	Included	
Russell et al. (2014)[495]	2014	Exclusion	Not an economic evaluation of multiple lines
Seal et al. (2014)[186]	2014	Exclusion	Not an economic analysis
Sermsri et al. (2014)[496]	2014	Exclusion	Not an economic analysis
Shankaran et al. (2014)[497]	2014	Exclusion	Not an economic evaluation of multiple lines
Shaya et al. (2014)[498]	2014	Exclusion	Not an economic evaluation of multiple lines
Smieliauskas et al. (2014)[499]	2014	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Strickler et al. (2014)[500]	2014	Exclusion	Not an economic analysis
Tappenden et al. (2014)[501]	2014	Exclusion	Not an economic analysis
Uyl-deGroot et al. (2014)[502]	2014	Exclusion	Not an economic analysis
Weber et al. (2014)[503]	2014	Exclusion	Not an economic analysis
Wen et al. (2014)[504]	2014	Exclusion	Not an economic evaluation of multiple lines

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Westerling et al. (2014)[505]	2014	Exclusion	Not an economic analysis
Zheng et al. (2014)[506]	2014	Exclusion	Not an economic evaluation of multiple lines
Austin et al. (2015)[507]	2015	Exclusion	Not an economic analysis
Bordonaro et al. (2015)[508]	2015	Exclusion	Not an economic analysis
Brosa et al. (2015)[509]	2015	Exclusion	Not an economic evaluation of multiple lines
Carrato et al. (2015)[510]	2015	Exclusion	Not an economic evaluation of multiple lines
Chouaid et al. (2015)[511]	2015	Exclusion	Not an economic analysis
Chouaid et al. (2015)[512]	2015	Exclusion	Not an economic evaluation of multiple lines
Chouaid et al. (2015)[513]	2015	Exclusion	Not an economic analysis
Chuang et al. (2015)[514]	2015	Exclusion	Not an economic analysis
Danese et al. (2015)[515]	2015	Exclusion	Not an economic evaluation of multiple lines
de Mello-Sampayo (2015)[516]	2015	Exclusion	Not solid tumour
Diaby et al. (2015)[517]	2015	Exclusion	Not an economic analysis
Edwards et al. (2015)[518]	2015	Exclusion	Not an economic evaluation of multiple lines
Faria et al. (2015)[519]	2015	Exclusion	Not an economic analysis
Fasola et al. (2015)[520]	2015	Exclusion	Not an economic analysis
Finek et al. (2015)[521]	2015	Exclusion	Not an economic evaluation of multiple lines
Fleeman et al. (2015)[522]	2015	Exclusion	Not an economic analysis
Gervais et al. (2015)[523]	2015	Exclusion	Not an economic analysis
Gharaibeh et al. (2015)[524]	2015	Exclusion	Not an economic evaluation of multiple lines
Goldstein et al. (2015)[525]	2015	Exclusion	Not an economic evaluation of multiple lines
Goldstein et al. (2015)[89]	2015	Included	
Goldstein et al. (2015)[526]	2015	Exclusion	Not an economic analysis
Goldstein et al. (2015)[527]	2015	Exclusion	Not an economic analysis
Goldstein et al. (2015)[528]	2015	Exclusion	Not an economic evaluation of multiple lines
Goldstein et al. (2015)[529]	2015	Exclusion	Not an economic evaluation of multiple lines
Hoffman-Censitis and Wong (2015)[530]	2015	Exclusion	Not an economic analysis
Howard et al. (2015)[27]	2015	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
ICECaP Working Group et al. (2015)[531]	2015	Exclusion	Not an economic evaluation of multiple lines
Kourlaba et al. (2015)[532]	2015	Exclusion	Not an economic evaluation of multiple lines
Kovacevic et al. (2015)[533]	2015	Exclusion	Not an economic evaluation of multiple lines
Lairson et al. (2015)[534]	2015	Exclusion	Not an economic evaluation of multiple lines
Lichtenberg (2015)[535]	2015	Exclusion	Not an economic analysis
Lein et al. (2015)[536]	2015	Exclusion	Not an economic evaluation with choice in multiple lines of therapy
Messori et al. (2015)[537]	2015	Exclusion	Not an economic analysis
Minion et al. (2015)[538]	2015	Exclusion	Not an economic analysis
Moro-Sibilot et al. (2015)[539]	2015	Exclusion	Not an economic analysis
Morrison et al. (2015)[540]	2015	Exclusion	Not an economic analysis
Pilkington et al. (2015)[274]	2015	Exclusion	Not an economic analysis
Pond et al. (2015)[541]	2015	Exclusion	Not an economic analysis
Rochau et al. (2015)[542]	2015	Exclusion	Not solid tumour
Rogowski et al. (2015)[543]	2015	Exclusion	Not an economic analysis
Ruggeri et al. (2015)[544]	2015	Exclusion	Not an economic analysis
Saltz (2015)[545]	2015	Exclusion	Not an economic analysis
Scherpereel et al. (2015)[546]	2015	Exclusion	Not an economic analysis
Sonpavde et al. (2015)[547]	2015	Exclusion	Not an economic analysis
Staton et al. (2015)[548]	2015	Exclusion	Not solid tumour
Tabrizian et al. (2015)[549]	2015	Exclusion	Not an economic analysis
Ting et al. (2015)[550]	2015	Exclusion	Not an economic evaluation of multiple lines
Toumi et al. (2015)[551]	2015	Exclusion	Not an economic analysis
Wade et al. (2015)[552]	2015	Exclusion	Not an economic evaluation of multiple lines
Walzer et al. (2015)[553]	2015	Exclusion	Not an economic analysis
Zhou et al. (2015)[554]	2015	Exclusion	Not an economic evaluation of multiple lines
Auliac et al. (2016)[555]	2016	Exclusion	Not an economic analysis
Chouaid et al. (2016)[556]	2016	Exclusion	Not an economic analysis

Reference	Year	Inclusion/Exclusion	Reason for inclusion or exclusion
Fournel et al. (2016)[557]	2016	Exclusion	Not an economic analysis
Geynisman et al. (2016)[558]	2016	Exclusion	Not an economic analysis
Goldstein et al. (2016)[559]	2016	Exclusion	Not an economic analysis
Goldstein et al. (2016)[560]	2016	Exclusion	Not an economic analysis
Goldstein et al. (2016)[561]	2016	Exclusion	Not an economic evaluation of multiple lines
Goldstein et al. (2016)[562]	2016	Exclusion	Not an economic evaluation of multiple lines
Jackson et al. (2016)[563]	2016	Exclusion	Not an economic analysis
Li et al. (2016)[564]	2016	Exclusion	Not an economic analysis
Quoix et al. (2016)[565]	2016	Exclusion	Not an economic analysis
Riesco-Martinez et al. (2016)[4]	2016	Included	
Schuler et al. (2016)[566]	2016	Exclusion	Not an economic analysis
Vergnenegre et al. (2016)[567]	2016	Exclusion	Not an economic evaluation of multiple lines
Willyard (2016)[568]	2016	Exclusion	Not an economic analysis
Wong et al. (2016)[569]	2016	Exclusion	Not economic evaluation
Yajima et al. (2016)[570]	2016	Exclusion	Not economic evaluation

Appendix B: Detailed data extraction for economic evaluations of multiple lines of therapy

The data extracted from the economic evaluations included in Section 3.1 are detailed below. The economic evaluations were divided into cancer types. Each economic evaluation has a Table listing the data extracted for the CHEERS checklist review (this information was summarised in Table 12 of Section 3.1). The economic evaluations that synthesised the treatment sequences from separate trials had a separate data extraction undertaken and this is detailed in a separate Table (data extraction for economic evaluations with synthesised alternatives). The nine colorectal cancer (CRC) economic evaluations are discussed in more detail with comparisons of the alternatives and treatment sequences undertaken.

Two of the included economic evaluations, Hind et al. (2008)[94] and NICE (2009)[90] were full health technology assessments (HTA) and did not correspond to the usual structure of an academic article. Hind et al. (2008)[94] included the economic evaluation as a chapter and the NICE review of breast cancer included the economic evaluation included as the first appendix. Some of the items in the CHEERS checklist were marked as not applicable for both publications because of these differences.

CRC economic evaluations

Nine economic evaluations were identified which examined treatment for CRC.[1,2,4,89,93-95,97,98] CRC treatment has advanced in recent years with more options becoming available.[203] There were three main chemotherapeutic agents used in metastatic CRC (irinotecan, oxaliplatin and 5-FU). One of these, 5-FU, is available in an intravenous form (5-FU) and an oral pro-drug form (capecitabine, also known by the trade name Xeloda).[571] These chemotherapy agents can be combined within a line of therapy as a protocol. These protocols often have abbreviations that are combinations of the component parts, for example, FOLFOX (a combination of 5-FU and oxaliplatin), XELOX (a combination of Xeloda and oxaliplatin) and FOLFIRI (a combination of 5-FU and irinotecan).

Antibody therapies (also known as monoclonal antibodies[1]) are also used for the treatment of CRC. These include anti-EGFR therapies (cetuximab and panitumumab) and an anti-angiogenesis agent (bevacizumab). There can be used alone or in combination with chemotherapy. Cetuximab was discussed in detail in Section 3.2: Cetuximab economic evaluations.

These six pharmaceutical agents (or a subset thereof) were the pharmaceuticals considered in the nine economic evaluations of CRC. There has been a recent addition to the pharmaceuticals used to treat CRC, regorafenib, which was approved by the FDA in the United States for the treatment of CRC in 2012[203] and was considered for subsidisation in Australia in 2014.[229] Regorafenib was not considered by any of the economic evaluations for CRC.

There were three approaches used to determine the potential alternative treatment sequences in CRC; all of the alternative treatment sequences sourced from a single RCT, each alternative treatment sequence sourced from a different trial or a modelling approach where each alternative treatment sequence was constructed using the evidence from multiple sources.

Two different approaches were taken to the construction of the alternatives treatment sequences with regard to use by the population of interest. The majority of those were the alternative mutually exclusive sequences were determined for an individual patient. That is, all alternatives are potentially given to the population of interest. The second considered the introduction of a new treatment in different groups, with the groups being stratified by the line of therapy. Although there were choices in multiple lines of therapy an individual patient would not be able to access all the different choices. An example of this is Shiroiwa et al. (2009).[95] Shiroiwa et al. (2009)[95] compared XELOX to FOLFOX4 in the first and second lines of therapy using a different Markov model in each line of therapy. Although it satisfies the inclusion criteria of the search strategy, an individual patient would not receive XELOX in the first and second lines of therapy.

In some economic evaluations there was lack of variation in the length of the treatment sequence and the pharmaceuticals received. Patients were expected to receive all treatments (it is only the order that is altered). This limited the economic evaluations estimation of the incremental benefit of introducing additional pharmaceuticals. This was important for the consideration of antibody therapy which is potentially expensive.[41] When all alternatives included antibody therapy, there is no information about the incremental cost-effectiveness of including antibody therapy in a treatment sequence. Only two economic evaluations included alternatives with and without antibody therapy.[1,89]

Table 82 shows the construction of the alternatives, the number of pharmaceuticals and the variation in chemotherapy and antibody therapy for the nine colorectal economic evaluations. The earliest economic evaluations are listed first. The number of pharmaceuticals considered

within an economic evaluation increased over time. There is a variable approach to the inclusion of antibody therapies, the majority of trials excluded them. However, more recent economic evaluations included antibody therapies. The setting for the most economic evaluations was either the UK or USA. There are no economic evaluations conducted in Australia included in this review of the literature.

Table 82: Construction of alternatives for treatment sequences in CRC

Economic evaluation	All alternatives accessible by population of interest	Number of pharmaceuticals considered (plus capecitabine)	Variation in chemotherapy received	Antibody therapy included	Variation in antibody therapy	Country
Hind et al. (2008)[94]	Yes	3	Yes	No	N/A	UK
Miyazaki et al. (2009)[93]	Yes	3	No	No	N/A	Japan
Shiroiwa et al. (2009)[95]	No	3 (4)	Yes	No	N/A	Japan
Wong et al. (2009)[1]	Yes	5	Yes	Yes	Yes	USA
Manca et al. (2012)[97]	Yes	3	Yes	No	N/A	UK
Tappenden et al. (2013)[98]	Yes	3 (4)	Yes	No	N/A	UK
Rautenberg et al. (2014)[2]	Yes	6 (7)	Yes	Yes	Yes	USA
Goldstein et al. (2015)[89]	Yes	4	No	Yes	Yes	USA
Riesco-Martinez et al. (2016)[4]	Yes	6	No	Yes	No	Canada

Abbreviations: CRC: colorectal cancer; UK: United Kingdom; US(A): United States of America

Table 83 shows the number of protocol options that were considered in each line of therapy of the CRC economic evaluations. Also shown is the total number of treatment sequence alternatives considered within the economic evaluations. The trial based economic evaluations had a smaller number of total alternatives reflecting the complexity and challenge of designing trials with multiple lines of therapy and large numbers of potential options. With six pharmaceuticals available a very large number of sequences was feasible, Rautenberg et al. (2014)[2] produced an analysis of 34 sequence alternatives.

Table 83: Number of alternatives in each line of therapy

Economic evaluation	Options in first line	Options in second line	Options in third line	Total alternatives
Hind et al. (2008)[94]	3	3	N/A	7
Miyazaki et al. (2009)[93]	2	2	N/A	2
Shiroiwa et al. (2009)[95]	2	2	N/A	2
Wong et al. (2009)[1]	5	2	2	9
Manca et al. (2012)[97]	3	3	N/A	5
Tappenden et al. (2013)[98]	6	7	N/A	22
Rautenberg et al. (2014)[2]	7	8	3	34
Goldstein et al. (2015)[89]	2	2	N/A	3
Riesco-Martinez et al. (2016)[4]	2	2	2	3

Note: Best supportive care was not included as a line of therapy
Abbreviation: N/A: not applicable

Colorectal economic evaluations that did not include the use of antibody therapy

Three of the economic evaluations used data from the two previously published RCTs as the basis of the clinical evidence and the selection of the alternatives.[68,72] These previously published RCTs were by Tournigand et al. (2004)[68] and the MRC FOCUS trial published by Seymour et al. (2007).[72] Both trials are discussed in detail in Chapter 6 and included in Appendix F.

Hind et al. (2008)[94]

Hind et al. (2008)[94] was published as a review in HTA in 2008. It involved a comprehensive review of three available chemotherapy treatments (irinotecan, oxaliplatin and raltitrexed) used in the treatment of CRC. RCTs were extracted and a meta-analysis conducted. The use of each of the agents in combination within first and second line therapy was considered as a potential alternative.

Hind et al. (2008)[94] undertook a literature review of existing economic evaluations and the weakness of the use of second line and other salvage therapy impacting on the results was highlighted. The potential for subsequent therapies to improve overall survival but the costs associated with the subsequent therapies not being included in the economic evaluation was discussed.

Hind et al. (2008)[94] included a discussion regarding the lack of information about the cost-effectiveness of treatment for CRC. Among the issues highlighted were the use of medians rather than means in analysis, the consideration of third line or salvage therapies, the absence of utility measurement within the trial and the use of PFS as an outcome measure. The relationship between PFS and overall survival was singled out as an important issue for modelling.

Among several recommendations for future economic evaluations, Hind et al. (2008)[94] suggested that preplanned sequences of therapies be considered to allow correct allocation of survival advantages to therapies and that mean rather than median values be used in the calculations of cost-effectiveness analysis.

As part of the review, an independent economic analysis was undertaken using the data from studies conducted by Tournigand et al. (2004)[68] and Seymour et al. (2007).[72] Although the data attributed to Seymour et al. (2007)[72] appeared to come from an earlier abstract and not the final published paper it was similar data to that considered in Chapter 6. A wide variety of costs were considered including the costs of adverse events. Both QALYs and life years were presented as health outcome measures. Seven treatment sequences were considered. Hind et al. (2008)[94] defined a treatment sequence as a preplanned administration of protocols to a patient given one after the other. The change from one protocol to the next is caused by failure of the preceding protocol.

Hind et al. (2008)[94] took a conservative approach and only modelled sequences that had been included within trials. Extrapolation of survival using a Weibull regression was undertaken. Comparisons of overall survival and progression free survival were presented.

Hind et al. (2008)[94] approach did not include post-progression costs associated with additional chemotherapy. However, there was a section highlighting the absence of these costs and the potential difference in costs between the sequences that may occur. Because of these concerns a traditional incremental analysis was not conducted but rather the costs of each alternative were compared to the least expensive alternative (which was considered the base case). A constant utility weight of 0.76 was used to convert life years into QALYs.

Hind et al. (2008)[94] made the conclusion that the current regime of cancer treatment recommended by NICE was the least expensive but potentially not the most cost-effective. With limitations, the more intensive treatment protocols may have been cost-effective.

Miyazaki et al. (2009)[93]

Miyazaki et al. (2009)[93] undertook a cost-minimisation analysis based on the RCT undertaken by Tournigand et al. (2004)[68] Miyazaki et al. (2009)[93] noted that because the outcomes were equal, it was appropriate to undertake a cost-minimisation exercise which concluded that the costs were different between the two alternative sequences.[93]

The economic evaluation included a Markov model with three health states, a pre-progression health state, a progressed health state and a death health state. The extrapolation of progression free survival (PFS) was undertaken to transform the median into a mean. The authors concluded that the use of FOLFIRI was cost-minimising for the Japanese health system. It was recognised that medical costs were higher for FOLFOX than FOLFIRI prior to the economic evaluation being undertaken. No modelling was undertaken for the post-treatment states. The analysis did not include any costs for adverse events.

Shiroiwa et al. (2009)[95]

Shiroiwa et al. (2009)[95] considered the use of capecitabine or 5-FU with oxaliplatin in the first and second line of therapy for CRC. Capecitabine is the oral form of 5-FU. 5-FU is delivered by infusion (and therefore was costlier to administer). The use of capecitabine instead of 5-FU was more convenient (and is associated with a higher utility weight in the economic evaluation) but did not alter the progression free survival or overall survival; it was argued the mechanism of action would result in fewer adverse events for capecitabine.[95]

The economic evaluation was conducted using two separate RCTs, each of which compared the protocol XELOX (oxaliplatin and capecitabine) to the protocol FOLFOX4 (oxaliplatin and 5-FU). One RCT recruited participants in the first line of therapy, while the other recruited participants in the second line of therapy and these trials were used as the basis of the economic evaluation. Utility weights were elicited from an online panel using time trade-off based on scenarios. The measure of effectiveness used in the economic evaluation was quality adjusted progression free days. A decision analytic model was constructed. The same model structure was used for both the first and second lines, but the parameters were altered from one to the other. The use of XELOX (or FOLFOX4) in one line of therapy is mutually exclusive with the use in the second line of therapy, so this economic evaluation demonstrates the potential for heterogeneity associated with using a protocol in different lines of therapy.

The use of oral therapy resulted in a higher utility weight, and the cost of capecitabine was less than the cost of 5-FU, consequently in both lines of therapy XELOX dominated FOLFOX4. As

expected the calculated PFS was similar. The magnitude of the benefit in the second line of therapy was lower than in the first line of therapy for both protocols.

Manca et al. (2012)[97]

Manca et al. (2012)[97] undertook a cost-effectiveness analysis using the mature data from Seymour and colleagues.[72] Manca et al. (2012)[97] used slightly different assumptions, patient populations and comparisons to Hind et al. (2008).[94] The model structure was different to Hind et al. (2008),[94] being a Markov model.

The completed MRC FOCUS trial included quality of life data which allowed Manca et al. (2012)[97] to conduct a cost-utility analysis compared to the assumption of a constant utility value of Hind et al. (2008).[94] Manca et al. (2012),[97] included non-trial treatments in the analysis (although they were only included in the costs).

Manca et al. (2012)[97] did conduct an incremental, cost-effective analysis and like Hind et al. (2008)[94] they found that the use of 5-FU alone was the least expensive option. However, given a threshold of £20,000, the combination therapy of oxaliplatin and 5-FU was cost-effective. All other alternatives were eliminated by extended dominance.

Tappenden et al. (2013)[98]

Tappenden et al. (2013)[98] conducted a whole disease modelling exercise based on of CRC. As part of this exercise, they evaluated 22 different treatment sequences (the maximum length of sequence was two lines of therapy). The treatment sequences were based upon the Seymour MRC FOCUS trial supplemented with a network meta-analysis of CRC chemotherapy agents.[572]

There were 22 options presented with combinations of 5-FU, capecitabine, oxaliplatin and irinotecan in the first and second lines of therapy. The majority of treatment sequences were dominated. The least expensive option was capecitabine in first and second line therapy, the two other non-dominated strategies were capecitabine and oxaliplatin in the first line and irinotecan in the second line; and capecitabine and oxaliplatin in the first line and capecitabine and irinotecan in the second line.

Colorectal economic evaluations including the use of antibody therapy

Wong et al. (2009)[1]

Wong et al. (2009)[1] considered the use of the antibody therapies which were becoming available for CRC. In the economic evaluation, up to three lines of therapy were modelled using information from a combination of phase 2 and phase 3 trials. A Markov model was

used; one feature of the model was that participants could move from one line of therapy to the next for two distinct reasons, either progression of the disease or because of unacceptable toxicity.

Wong et al. (2009)[1] restricted the choice of sequences to nine, based on "expectations in clinical practice" without a discussion of exactly how this was undertaken, and other alternatives rejected. Two of the nine treatment sequences had a sequence length of one; two treatment sequences had a sequence length of two and five treatment sequences had a sequence length of three. Because Wong et al. (2009)[1] involved sequences of different lengths, it allowed the calculation of the impact on an additional line of therapy by comparing the incremental costs and benefits of a sequence of one line of therapy to a sequence of two lines of therapy.

Quality of life was not measured although a background rate of death as well as treatment related mortality were included in the model. All participants who survived continued to receive treatment as described by the sequence. Therefore, if the treatment sequence length was three lines of therapy, the model assumed that all participants received three protocols unless death intervened. The implication of this is that unless death occurs, the number of treatments was equal for all members of the cohort.

An important feature of the heterogeneity of the treatment effect of the biological agent cetuximab is the presence or absence of the KRAS (Kristen rat sarcoma) mutation. Patients with a tumour that contains a mutant KRAS gene do not respond to cetuximab while those tumours containing the wild type (non-mutant) gene are more responsive to cetuximab (see Section 3.2). Although this was known in 2009 and while this is discussed in the Wong et al. paper.[1] the authors did not undertake any modelling of this source of heterogeneity.

Rautenberg et al. (2014)[2]

Rautenberg et al. (2014)[2] evaluated the costs and consequences of treatment sequences containing antibody therapies in CRC. The assumption was made that all patients received all treatments, that is, that all patients had tumours containing the wild type KRAS mutation that suggests benefit will be gained from the use of cetuximab or similar biological treatments.

This is a reasonable assumption to make because the purpose of the paper was to compare the costs of biological agents, but consequently, it does not address the use of biological agents in the mutant type KRAS tumours. Several reference studies were identified from the literature, and the median PFS from each was utilised. As some of these studies did not

correspond to the KRAS wild type population, there were implications for the validity of the approach (discussed in the review of cetuximab in Section 3.2). Costs were calculated for the pharmaceutical components of each line of therapy based on the expected median use of pharmaceuticals in each line of therapy. The results for each line of therapy were summed to produce the cost and survival for an entire treatment sequence. An assumption was made that participants within an alternative treatment sequence received all treatments.

Neither utility weights nor adverse events were included in the economic evaluation. There was no inclusion of adverse event costs. There was no transformation of the median data from the trials to an estimate of the mean. Palliative care (or best supportive care [BSC] as it was termed in the article) was included and was costed at 100 euros per month and included in all arms. The authors argue that the palliative care cost was likely to be an underestimate.

Goldstein et al. (2015)[89]

Goldstein et al. (2015)[89] conducted a cost-effectiveness analysis over two lines of therapy; the chemotherapy backbone was consistent in all three alternatives, FOLFOX in the first line of therapy and FOLFIRI in the second line of therapy. However, the use of antibody therapy (in this case bevacizumab) differed between the alternatives. In one alternative there was no use of antibody therapy, the second alternative was the use of antibody therapy in the first line of therapy and the third alternative was the continuing use of antibody therapy in the second line of therapy.

Two separate Markov models were constructed for two choices, the use of antibody therapy in the first line of therapy, and the continuing use of antibody therapy in the second line of therapy (this was based on using antibody therapy in first line, the alternative of using antibody therapy in the second line of therapy but not the first was not considered).

In both models the addition of antibody therapy far exceeded a threshold willingness to pay value of over USD $150 000 and the authors concluded that the cost-effectiveness ratio was high. The three alternatives were not considered as incremental to each other. Instead the two choices within each line were compared incrementally.

Riesco-Martinez et al. (2016)[4]

Riesco-Martinez et al. (2016)[4] compared three different strategies (alternatives) in which two types of antibody therapy were given over two to three lines of therapy in CRC. The efficacy of the different alternatives was similar, so the incremental cost-effectiveness was driven by the differences in costs.

One feature of the modelling undertaken in this economic evaluation was that, as well as death, modelled participants might not be eligible for further chemotherapy treatments. A Markov model was used to combine the expected survival benefits from the sequential use of treatments. A post-treatment survival was applied. The post-treatment period varied on the basis of how many prior therapies had been used. The post-treatment course decreased with an increasing number of therapies and was based on expert opinion.[4] The impact of this assumption was not tested in the sensitivity analyses.

Utility weights were estimated by asking clinicians to score scenarios on the EQ-5D scale and then applying tariffs. The base QALY weight fell with increasing lines of therapy, from 0.819 in the first line of therapy to 0.728 in the third line of therapy. There was little discussion about how the medians from the various trials that were used to determine the effectiveness was converted into means that are used in the Markov model.

A feature of this model is that all participants can receive all treatments, so it does not allow the ceasing of all treatment prior to mortality. All the alternatives included both relatively expensive antibody therapies. Of the three treatment combinations considered, the two lines of therapy alternative was extendedly dominated by one of the three lines of therapy alternatives.

CHEERS checklists for CRC economic evaluations

Table 84: CHEERS checklist for Hind et al. (2008)[94]

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	Front page	Yes	The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.	Discussed the pharmaceuticals involved. Noted the systematic review and economic evaluation
Abstract (item 2)	iii-iv	Yes		Because this was a health technology assessment including an economic evaluation rather than an economic evaluation the abstract details far more than the economic evaluation
Background (item 3)	Chapter 2	Yes		There was a detailed discussion of the background to the review
Target population (item 4)	61	Yes	Patients with advanced CRC	
Setting (item 5)	95	Yes	Not stated in set-up but England and Wales quoted in discussion	
Perspective (item 6)	95	Yes	NHS	Health system perspective
Comparators (item 7)	65	Yes	Based on trial reported treatment sequences	The number of alternative treatment sequences was limited by the approach taken
Time horizon (item 8)		Yes	Implied lifetime horizon	
Discount rate (item 9)	72	Yes	0%	
Choice of health outcomes (item 10)	64	Yes	Overall survival	Argument was made that discounting was not likely to be important given survival of cohort

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Measurement of effectiveness (item 11)	Chapter 3	Yes	Detailed analysis	Detailed analysis- several meta-analyses were conducted. There was also a substantial discussion about the importance of considering sequences. The actual results of the cost-effectiveness analysis were based upon results from trials
Preference based outcomes (item 12)	63	Yes	Did not use preference based outcomes as base case, included as an additional analysis	There was a discussion on page 63 about the lack of good quality of life information. The authors were very concerned about the nature of informational censoring
Estimation of resources (item 13)	68	Yes		A bottom-up costing approach was undertaken
Currency (item 14)	70	Yes	British pounds and the year was 2004	
Choice of model (15)	65	Yes	Extrapolation of overall survival and progression free survival	The reasoning why other modelling may have been inferior was discussed but the link to the decisions made by the study group was not explicit
Assumptions (16)	101	Yes		Well described limitations because of the methodological restrictions
Analytic methods (17)	Appendix 12	Yes	Weibull extrapolation of the survival curves was undertaken	Essentially the approach taken was partition modelling
Study parameter (18)	Chapter 4	Yes	Detailed referencing of the sources of the data	
Incremental (19)	91	No	Presented incremental cost relative to base treatment	Each treatment option was presented as a marginal cost and benefit compared to the base treatment for the cost-effectiveness conduct on Seymour et al. (2007)[72]
Characterising uncertainty (20)	72	Yes	Both a scenario analysis approach and a probabilistic approach were used	
Characterising heterogeneity (21)	104	Yes	Heterogeneity was acknowledged and was one of the reasons that a trial based approach was taken	
Discussion (22)	Chapter 7	Yes		

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Source of funding (23)	Page T	Yes		From the health technology assessment program in the United Kingdom
Conflict of interest (24)		No		There was no formal conflict of interest statement

Table 85: CHEERS checklist for Miyazaki et al. (2009)[93]

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	2433	Yes	Cost-minimization analysis of sequence changes between FOLFIRI and FOLFOX6 therapy for advanced colorectal cancer in Japan	Cost-minimisation and alternatives included in title
Abstract (2)	2433	Yes	All covered in the abstract	
Background (3)	2434	Yes	The reason why the study was important to Japan and recent trials discussed	Importance of achieving cost-minimising sequence discussed. Also discussed that there were no economic evaluations of these two sequences in the literature
Target population (4)	2009	Yes	Hypothetical cohort of 10 000 patients	
Setting (5)	2434	Partial	Japan healthcare system	Discussed in Japan but not a discussion of exactly what this included
Perspective (6)	2436	Yes	Healthcare payer	
Comparators (7)	2433-2434	Yes	Described as the treatments used to extend life	There was no discussion about alternative treatments that may have existed in this era
Time horizon (8)	2436	Yes	100 months	
Discount rate (9)	2433	Yes	3%	
Choice of health outcomes (10)	2434	Yes	Primarily a budget impact statement	Described as equally effective

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Measurement of effectiveness (11)	2435	Yes	Life years saved	Assumed no difference based on trial information
Preference based outcomes (12)	2438	N/A	Not included	An argument was made that previous research had suggested that utility measures did not differ between regimes
Estimation of resources (13)	2436-2437	Yes	Direct medical costs associated with administration	Did not include adverse events
Currency (14)	2436	Yes	2008 Japanese Yen	Identified as fiscal year 2008
Choice of model (15)	2434	Partial	Markov model	Why a Markov model was chosen was not discussed
Assumptions (16)	2435-2436	Yes	Reasonable discussion	
Analytic methods (17)	2435	No		Good description of the analytical methods used
Study parameter (18)	2435-2436	Yes	Good description of the study parameters included, including distributions	
Incremental (19)		N/A		Cost-minimisation, so no cost-effectiveness increment calculation
Characterising uncertainty (20)	2439	Yes	Monte Carlo simulation was used	Distributions described
Characterising heterogeneity (21)		No	There was no characterisation of heterogeneity	
Discussion (22)	2438	Yes	Discussed the limitations of the costs included	There was also a discussion about the lack of utility measurements
Source of funding (23)		No	No funding source was described	
Conflict of interest (24)	2440	Yes	A lack of conflict of interest was described by the authors	

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Table 86: CHEERS checklist for Shiroiwa et al. (2009)[95]

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	12	Yes	Cost-effectiveness analysis of XELOX for metastatic colorectal cancer based on the NO16966 and NO16967 trials	It was not entirely clear that the alternatives were in two different lines of therapy on the basis of the title
Abstract (2)	12	Yes	Structured abstract	
Background (3)	12-13	Yes		Covered size of population, the importance of CRC in Japan. Noted the change in the environment associated with CRC chemotherapy. The requirement for intravenous infusion of 5-FU was noted
Target population (4)		Yes	There were two populations, a first line and a second line population	Exactly who the second line population was is not discussed, especially the prior treatments that may have been received
Setting (5)	12	Partial	Japan	The key features of the Japanese health system were not discussed. The abstract noted that the health system was Japan, but this was not repeated in the methods
Perspective (6)	13	Yes	Healthcare payers	
Comparators (7)	13	Yes	The comparators were the same in each of the populations	XELOX versus FOLFOX
Time horizon (8)	N/A	No	Not stated	Appeared to be to first progression
Discount rate (9)	13	Yes	No discounting	No discounting was undertaken because of the short time frames involved
Choice of health outcomes (10)	13	Yes	Quality Adjusted Progression Free Days	It appears that the utility base did not alter between the different lines of therapy
Measurement of effectiveness (11)	14	Yes	Non-parametric methods were used on patient level data	
Preference based outcomes (12)	13-14	Yes	Time trade-off assessment	An example was given, notably there was a 0.06 difference in the utility weight between the oral versus IV preparation
Estimation of resources (13)	16	Yes	The derivation of the resources was described, but the individual costs were not.	Consideration of the potential differences between the Japanese population of interest and the trial population (European) was discussed and considered
Currency (14)	14	Yes	Euro (2007)	

CHEERS checklist (item number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Choice of model (15)		No		Minimal discussion about why the model was appropriate
Assumptions (16)		Partial		
Analytic methods (17)		Yes		Discussion about the methods used in determining cost and effect
Study parameter (18)		Yes		
Incremental (19)	16	Yes		The results suggested that XELOX was dominant in the two lines of therapy
Characterising uncertainty (20)	15-16	Yes	One-way and calculation of a probabilistic sensitivity analysis	
Characterising heterogeneity (21)		Partial		The consideration of the two different groups could be considered a discussion of heterogeneity, although this was actually displacement.
Discussion (22)	16	Yes		The finding of dominance limited the discussion
Source of funding (23)	17	Yes	The study was funded by Chugai Pharmaceutical Company Ltd	
Conflict of interest (24)	N/A	No		

Abbreviations: 5-FU: 5-fluorouracil; CRC: colorectal cancer; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; XELOX: a protocol consisting of oxaliplatin and capecitabine

Table 87: CHEERS checklist for Wong et al. (2009)[1]

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	2081	No	Cost implications of new treatments for advanced colorectal cancer	Pointed out disease and costs, did not point out was an economic evaluation
Abstract (2)	2081	Yes	Identified objective, data sources, outcomes and some policy recommendations	Comprehensive abstract

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Background (3)	2081-2082	Yes	Discussion of recent increase in the number of pharmaceutical agents and the uncertainty associated with using them in multiple lines of therapy	
Target population (4)	2083 & 2084	Yes	70-year-old man in US, 75kg and 69 inches tall	Based on median age of diagnosis of cancer, no alternatives were used no reference was provided.
Setting (5)	2083	Yes	United States	Slightly more implicit than would ideally be the case
Perspective (6)	2082	Yes	Third party payer	
Comparators (7)	2082-2083	Yes	Nine alternatives explored	Selected to reflect sequential advances in care, no references provided. Acknowledgment that there are multiple other potential alternatives
Time horizon (8)	2083	No	Lifetime	Not stated, assumed to be lifetime given text describing that the objective was to measure overall survival
Discount rate (9)	2085	Yes	3%	
Choice of health outcomes (10)	2083	Yes	Life Years	
Measurement of effectiveness (11)	2084	No	A series of trials were used	How the methods were used to include the studies were not included, no method of synthesis was used, justification that the study chosen was sufficient was not included.
Preference based outcomes (12)		N/A	N/A	The outcome measure was life years, it was stated that "it is reasonable to use life expectancy rather than quality adjusted life expectancy" (page 2087). The assertion is also made that this results in a conservative (lower) estimate for ICER because preference weights less than one. While this is mathematically correct choosing a measure with a lower cost per outcome is not necessary "conservative."
Estimation of resources (13)	2083	Yes	Pharmaceutical costs only, no vial wastage, no supportive medications and no costs related to management of toxicity	Minimal costs included
Currency (14)	2083	Yes	2008 USD	All prices were calculated from 2008

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Choice of model (15)	2082	Partial	Markov model	Markov model used, reason not discussed why Markov was the most appropriate model structure. A diagram of the model structure was included.
Assumptions (16)	2083-2085	Yes	Assumptions were well documented	Well documented
Analytic methods (17)		No	Little analytical detail included, no method of dealing with heterogeneity was included	
Study parameter (18)	2084	Yes	Studies described and methods of calculating costs described	
Incremental (19)	2086, Figure 3	Yes	Several alternatives were eliminated by extended dominance	
Characterising uncertainty (20)	Figure 4, Table 5,6 and 7, 2065-2087	Yes		
Characterising heterogeneity (21)		No	There was no discussion of heterogeneity	
Discussion (22)	2087-2088	Yes		The limitations were well discussed
Source of funding (23)	2090	Yes		
Conflict of interest (24)	2090	Yes		

Symbol: kg: kilogram
Abbreviations: N/A: not applicable; US(A): United States of America; USD: United States of America dollars

Table 88: Data extraction for economic evaluations with synthesised alternatives, Wong et al. (2009)[1]

Approach	Where in paper	Result and explanation	Comment
Choice of alternatives in each line of therapy	Table 1	Both chemotherapy and antibody therapy	
Choice of number of lines of therapy	2082	One, two or three lines of therapy	
Justification for aggregation into alternatives	2083	Chosen to reflect the sequential advancements in treatment	
Number of alternatives	Table 1	Nine	
Method of assessing effectiveness for each line of therapy	Table 3	Index trial method, using the trial with the largest trial population	The same trials were used for second and third line populations
How was the median survival time usually reported in trials dealt with	2084	DEALE- declining exponential approximation of life expectancy	
Method of combining lines of therapy	Figure 1, 2082	Markov model	
How transitioned from one line of therapy to another	Figure 1, 2082	Toxicity Progression	
Alternatives options to next therapy	2082	Death	
Post-progression survival included	2084-2085	Yes, called supportive care	
Post-progression survival the same for all alternatives	2085	Yes, six months	
How was total survival calculated		Total survival was calculated through the Markov model, essentially adding progression free survivals together, although there was a potential adjustment for toxicity	

Abbreviation: DEALE: Declining Exponential Approximation of Life Expectancy

Table 89: CHEERS checklist for Manca et al. (2012)[97]

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	22	Yes	The cost-effectiveness of different chemotherapy strategies for patients with poor prognosis advanced colorectal cancer (MRC FOCUS)	The titles noted cost-effectiveness and that they were different strategies
Abstract (2)	22	Yes	Structured abstract	
Background (3)	22-23	Yes		Good description of the treatment of CRC in the UK, the recent developments in the treatments and the requirement for decision-making about adoption of new technologies
Target population (4)	22 and 26	Partial	Total of 2135 patients were accrued to the FOCUS trial, at 61 centres, between May 2001 and December 2003. Their characteristics and full details of the treatment received, and clinical outcomes are given in the main clinical report	The population was implied but important features such as performance status were not made clear
Setting (5)	22	Yes	UK	The trial and the evaluation were both conducted in the UK population
Perspective (6)	23	Yes	NHS Perspective	
Comparators (7)	23	Yes	*Strategy A:* the standard approach of sequential single agent MdG regimen using FU until evidence of treatment failure, followed by single agent irinotecan; *Strategy B-ir:* first line MdG regimen until treatment failure, followed by doublet therapy with MdG and irinotecan (IrMdG regimen); *Strategy B-ox:* first line MdG regimen until treatment failure, followed by doublet therapy with MdG and oxaliplatin (OxMdG regimen); *Strategy C-ir:* first line doublet therapy with the IrMdG regimen; and	The five comparators were the same as were used in the MRC FOCUS study. The text specifically comments on the data and inclusion of post-progression chemotherapy

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
			Strategy C-ox: first line doublet therapy with the OxMdG regimen.	
Time horizon (8)	24	Yes	10 years	
Discount rate (9)	23	Yes	3.5%	
Choice of health outcomes (10)	22	Yes	Survival	
Measurement of effectiveness (11)	22	Yes	Survival	
Preference based outcomes (12)	23	Yes	EQ-5D	Was conducted within the trial
Estimation of resources (13)	24	Yes	Listed and mentioned supplementary appendix	
Currency (14)	23	Yes	UK sterling 2009	
Choice of model (15)	23	Yes	Markov modelling	The text stated that the structure of the model was chosen to reflect the natural history of the disease
Assumptions (16)	24-25	Yes		Combined with analytical assumptions
Analytic methods (17)	24-25	Yes		Detailed description of the statistical methods that were used in the analysis
Study parameter (18)	25	Yes	Additional information was included in the appendix	There was a very detailed description of parameters.
Incremental (19)	29	Yes	Strategy A and Strategy C-ir	
Characterising uncertainty (20)	27-28	Yes	PSA and one-way sensitivity analysis	Strategy C-ir has a greater than 50% chance of being cost-effective at a threshold of 30 000 pounds
Characterising heterogeneity (21)		No		

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Discussion (22)		Yes		Good discussion, comparison to the value-add over Hind et al. (2008).[94]
Source of funding (23)	30	Yes	Principal trial funding was from the UK MRC	
Conflict of interest (24)	N/A	No	Not listed or discussed	

Abbreviations: EQ-5D: European Quality of life-5 Dimensions; FOCUS (trial): fluorouracil: oxaliplatin: CPT11: use and sequencing; MRC: Medical Research Council; PSA: probabilistic sensitivity analysis; UK: United Kingdom

Table 90: CHEERS checklist for Tappenden et al. (2013)[98]

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	542	Yes	Using whole disease modelling to inform resource allocation decisions: economic evaluation of a clinical guideline for colorectal cancer using a single model	Included a whole of disease model
Abstract (2)	542	Yes		Focus was on the whole of disease modelling, as appropriate
Background (3)	542-543	Yes		The choice of CRC is used as an example
Target population (4)	545	Yes	Whole population/hypothetical birth cohort	Because of the inclusion of screening the whole of disease modelling was over the whole population
Setting (5)	545	Yes	UK	The discussion of the whole of disease modelling made the setting clearer than the other economic evaluations considered
Perspective (6)	545	Yes	NHS/Personal Social Services	
Comparators (7)	Table 2, 546-546	Yes		There were a lot of comparators, there is a short description in the text and the table has a list of comparators

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Time horizon (8)	545	Yes	Lifetime model	
Discount rate (9)	545	Yes	3.5%	
Choice of health outcomes (10)	545	Yes	Survival	
Measurement of effectiveness (11)		Yes	Meta-analysis undertaken	
Preference based outcomes (12)	547	Yes	QALY	
Estimation of resources (13)	In appendix	Yes		
Currency (14)	545	Yes	2011 UK Prices	
Choice of model (15)	545	Partial		Simulation of experience, probabilistic
Assumptions (16)	547-548	Yes		
Analytic methods (17)	547-548	Yes		
Study parameter (18)	In appendix	Yes		Obviously too detailed to include all of the parameters in paper, therefore the majority were included in the appendix
Incremental (19)	Table 2, 550	Yes		
Characterising uncertainty (20)	547	Yes	PSA	
Characterising heterogeneity (21)	545	Yes		Included high, intermediate and high-risk patients
Discussion (22)	549-552	Yes		The discussion included a description of the metastatic treatment
Source of funding (23)	552	Yes	Funded by National Institute for Health Research	

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Conflict of interest (24)	552	Yes	No conflict of interest	

Abbreviations: NHS: National Health Service; PSA: probabilistic sensitivity analysis; QALY: quality adjusted life years; UK: United Kingdom

Table 91: Data extraction for economic evaluations with synthesised alternatives, Tappenden et al. (2013)[98]

Approach	Where in paper	Result and explanation	Comment
Choice of alternatives in each line of therapy	Table 2, 550		
Choice of number of lines of therapy	Not discussed		
Justification for aggregation into alternatives	Not discussed		
Number of alternatives	Table 2, 550	22	
Method of assessing effectiveness for each line of therapy	546-547	The results from Seymour et al. (2007)[72] were used as the base case and then results were altered by a meta-analysis	
How was the median survival time usually reported in trials dealt with		Means were calculated from Seymour et al. (2007)[72] and then adjusted	
Method of combining lines of therapy		Essentially top down	
How transitioned from one line of therapy to another		Not discussed	
Alternatives options to next therapy		No	
Post-progression survival included	546-547	Yes	

Approach	Where in paper	Result and explanation	Comment
Post-progression survival the same for all alternatives		No	The post-progression survival was calculated by subtracting from overall survival the two progression free survivals
How was total survival calculated	546-547		The post-progression survival was calculated by subtracting from overall survival the two progression free survivals

Table 92: CHEERS checklist for Rautenberg et al. (2014)[2]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	99	Yes	Economic outcomes of sequences which include monoclonal antibodies against vascular endothelial growth factor and/or epidermal growth factor receptor for the treatment of unresectable metastatic colorectal cancer	It was only restricted to life years saved, but it was considered that economic outcomes
Abstract (2)	99	Yes	Structured abstract	
Background (3)	99-100	Yes		
Target population (4)		No	Implied to be metastatic CRC	
Setting (5)		No		
Perspective (6)	101	Yes	German statutory health insurance company	
Comparators (7)		Yes		
Time horizon (8)	101	Yes	Implied to be lifelong	Not explicitly stated
Discount rate (9)		No		
Choice of health outcomes (10)	101	Yes	Median progression free survivals were added together	The separately additive model was used
Measurement of effectiveness (11)	101	No	From pivotal trials referenced in the efficacy sections of the summary of product characteristics for bevacizumab, cetuximab and panitumumab.	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Preference based outcomes (12)		N/A	Did not include a preference measure	
Estimation of resources (13)	Table 2 and page 101	Yes		Adverse event costs were not included
Currency (14)	102	Yes	Euro 2012 (German)	
Choice of model (15)		No		Summation of median survival
Assumptions (16)	101-102	Partial		
Analytic methods (17)		No		
Study parameter (18)		Yes		
Incremental (19)		No		There was no inclusion of an incremental cost-effectiveness
Characterising uncertainty (20)	108	Yes	One-way sensitivity analysis	
Characterising heterogeneity (21)		No	There was no discussion about heterogeneity	One important area of heterogeneity that was not included was genetic heterogeneity with regard to KRAS status
Discussion (22)	106-109	Yes		
Source of funding (23)	109	Yes		
Conflict of interest (24)	109	Yes		

Abbreviation: KRAS: Kristen rat sarcoma

Table 93: Data extraction for economic evaluations with synthesised alternatives, Rautenberg et al. (2014)[2]

Approach	Where in paper	Result and explanation	Comment
Choice of alternatives in each line of therapy	Table 3	From summary of product characteristics	
Choice of number of lines of therapy	101	Only to third line	Suggested by the clinical evidence
Justification for aggregation into alternatives	101	Combined into plausible treatment sequences	
Number of alternatives	Table 5	34	
Method of assessing effectiveness for each line of therapy	100-101	Pivotal trial approach, there were identified by the regulatory trials identified in summary of product characteristics	
How was the median survival time usually reported in trials dealt with	Not reported	No change was made the medians were added together	
Method of combining lines of therapy	101	Plausible alternatives. That was a combination of licensed indications, feasibility of combinations and expert opinion. The combinations were verified by clinical experts.	
How transitioned from one line of therapy to another		Time-based	
Alternatives options to next therapy	Not reported	There were no alternatives to progression	
Post-progression survival included		Yes	
Post-progression survival the same for all alternatives		Yes	1.8 months was the time for the best supportive care time
How was total survival calculated	101	Addition of progression free survival in all lines of therapy	Used the medians

Table 94: CHEERS checklist for Goldstein et al. (2015)[89]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1112	Yes	First- and second-line bevacizumab in addition to chemotherapy for metastatic colorectal cancer: a United States-based cost-effectiveness analysis	Included cost-effectiveness
Abstract (2)	1112	Yes		Makes clear that two Markov models were produced
Background (3)	1112-1113	Yes		The potential reasons for the high cost-effectiveness of bevacizumab was highlighted
Target population (4)	1113	No		It did give some details of the population of the trials
Setting (5)	1113	Yes		The details of what a US payer covers was not discussed
Perspective (6)	1113	Yes	US Payer	
Comparators (7)	1113, Figure 1, Figure 2	Yes		
Time horizon (8)	1113	Yes	Lifetime	
Discount rate (9)	1113	Yes	3%	
Choice of health outcomes (10)	1113	Yes	Survival	
Measurement of effectiveness (11)	1113	Yes		Based on trials N01966 and ML18147
Preference based outcomes (12)	1113	Yes	Two states only for utility	
Estimation of resources (13)	1113-1114, Table 1	Yes		
Currency (14)	1113	Yes	2013 US dollars	
Choice of model (15)	1113	No	Markov model	Did not discuss why the Markov model was the most appropriate method
Assumptions (16)	1113-1114	Yes		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Analytic methods (17)	1113-1114	Yes		
Study parameter (18)	Table 1	Yes		Parameters
Incremental (19)	Table 2	Yes		Separate analyses were presented for first line and second line analysis
Characterising uncertainty (20)	1115-1116, Figure 3, Figure 4	Yes		The results were sensitive to assumptions around overall survival
Characterising heterogeneity (21)		No		
Discussion (22)	1116-1117	Yes		
Source of funding (23)		No		
Conflict of interest (24)	On website	Yes	Two of the authors have disclosures	

Table 95: CHEERS checklist for Riesco-Martinez et al. (2016)[4]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	Cost-Effectiveness Analysis of Different Sequences of the Use of Epidermal Growth Factor Receptor Inhibitors for Wild-Type KRAS Unresectable Metastatic Colorectal Cancer	Noted both cost-effectiveness and the fact that sequences are involved
Abstract (2)	1	Yes	Structured abstract	Worth noting that this was restricted to wild type cancer types
Background (3)	2	Yes		The potential problems with delaying or using treatments early is discussed
Target population (4)	1	Yes	Unresectable wild type CRC	
Setting (5)	N/A	No		Canada was the setting but not discussed

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Perspective (6)	8	Yes	Universal Healthcare System	
Comparators (7)	2	Yes	3 different strategies were considered. All included the use of an anti-EGFR treatment and bevacizumab.	There are multiple strategies that are not considered
Time horizon (8)	1	Yes	5 years	
Discount rate (9)	1	Yes	5%	
Choice of health outcomes (10)	3	Partial	Median PFS in months	
Measurement of effectiveness (11)	2-3	Yes	Choice of index trial	
Preference based outcomes (12)	7	Yes	Measurement of health status by oncologists and then translation into utility	
Estimation of resources (13)	Table 1	Yes	Discussion of resources in the text	
Currency (14)	1	Yes	2012 Canadian Dollars	
Choice of model (15)	2	Partial	Markov model	The use of other models was not discussed
Assumptions (16)	8	Yes		
Analytic methods (17)		No		The assumptions about how the medians were turned to means within the decision analysis were not discussed
Study parameter (18)	Table 1	Yes		
Incremental (19)	Table 2	Yes	One sequence was dominated	
Characterising uncertainty (20)	8	Yes	One-way and probabilistic sensitivity analysis	
Characterising heterogeneity (21)	N/A	No		The genetic heterogeneity was eliminated by being restricted to KRAS wild type
Discussion (22)	8-10	Yes		
Source of funding (23)	Online	Yes	MiMedx funded	This was in the disclosures that was online

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Conflict of interest (24)	10	Yes	Disclosures were noted to be online	

Table 96: Data extraction for economic evaluations with synthesised alternatives, Riesco-Martinez et al. (2016)[4]

Approach	Where in paper	Result and explanation	Comment
Choice of alternatives in each line of therapy	2 and Figure 1	Treatment sequence including both antibody-based treatments	
Choice of number of lines of therapy	2 and Figure 1	There were two or three lines of therapy, for alternative C, there was best supportive care in the third line followed by a period of post-progression survival	
Justification for aggregation into alternatives	1	Treatment sequence including both antibody-based treatments	
Number of alternatives	1	3	
Method of assessing effectiveness for each line of therapy	2-3	Systematic review, but how these were combined was not made clear	
How was the median survival time usually reported in trials dealt with	Figure 1	Transformation in Markov model	
Method of combining lines of therapy	Figure 1	Markov model	
How transitioned from one line of therapy to another	3	Progression	
Alternatives options to next therapy	Figure 1	Ineligible for further therapy	
Post-progression survival included	Figure 1	Yes	
Post-progression survival the same for all alternatives	Table 1	No, the post-progression survival differed according to the number of lines of therapy	

Approach	Where in paper	Result and explanation	Comment
How was total survival calculated	Figure 1	Markov model transitioning from one line of therapy to the next	

Breast cancer economic evaluations

Table 97: CHEERS checklist for NICE (2009)[90]

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	51	Yes	A cost-utility analysis of chemotherapy sequences for the treatment of patients with advanced breast cancer	
Abstract (2)	N/A	N/A		Because it is situated as an appendix there is not a standard abstract
Background (3)	51	Yes		It was noted that previous economic evaluations did not include more than one line of therapy
Target population (4)	52	Yes	Patients with metastatic breast cancer who have received prior anthracycline therapy	
Setting (5)	52	Yes	NHS	Although given that it is a NICE document, the setting is the NHS
Perspective (6)	52	Yes	NHS	Assumed to be a health services perspective
Comparators (7)	53	Yes	A series of six protocols in different lines of therapy were considered, these results in 17 strategies	
Time horizon (8)	54	Yes	Lifetime model	
Discount rate (9)	66	Yes	No discounting	It was decided that there would be no discounting based on the short overall survival time
Choice of health outcomes (10)	61	Yes	Survival for first, second and third line treatment	The model structure was essentially an additive model
Measurement of effectiveness (11)	61	Yes	Indirect analysis for first line undertaken	

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Preference based outcomes (12)	62	Yes	Utilities based on a solitary study	
Estimation of resources (13)	63-66	Yes	Very detailed discussion	
Currency (14)		Yes	2006-2007 UK pounds	
Choice of model (15)	54-55	Yes	The use of decision tree was not discussed	
Assumptions (16)	58-60	Yes		Very detailed description of assumptions
Analytic methods (17)	66	Yes		
Study parameter (18)	67-68	Yes		
Incremental (19)	71	Yes		There were significant numbers of dominated treatments
Characterising uncertainty (20)	66-68	Yes	Several scenarios were discussed, and a probabilistic sensitivity analysis was undertaken	
Characterising heterogeneity (21)		No	Heterogeneity was not discussed	Heterogeneity of treatment response was explicitly considered in the decision tree
Discussion (22)	73-74	Yes		
Source of funding (23)	xix	Yes	London School of Economics	
Conflict of interest (24)	89	Yes		Although not obvious if the nominated individuals were involved in the economic evaluations

Table 98: Data extraction for economic evaluations with synthesised alternatives, NICE (2009)[90]

Approach	Where in paper	Result and explanation	Comment
Choice of alternatives in each line of therapy	Page 53, Table A1.1	"Standard chemotherapy regimens," six were chosen	It was not discussed how these were chosen
Choice of number of lines of therapy	Page 53, Table A1.1	No justification given	
Justification for aggregation into alternatives	Page 54, Table A1.2	No repeating of treatments	

Approach	Where in paper	Result and explanation	Comment
Number of alternatives	Page 54, Table A1.2	17	
Method of assessing effectiveness for each line of therapy		Meta-analysis of trials in the line of therapy, divided patients into responders and non-responders	
How was the median survival time usually reported in trials dealt with	Page 59	Assumed exponential curve, technically used time to progression	
Method of combining lines of therapy	Figure A1.1 Page 55-56	Decision Analysis	
How transitioned from one line of therapy to another	Figure A1.1 Page 55-56	Progression Toxicity	Both progression and toxicity made the participant transition to the next line of therapy. Technically the patients transitioning because of toxicity have not progressed
Alternatives options to next therapy	Figure A1.1 Page 55-56	Toxic death	
Post-Progression Survival included	Page 55	Yes	
Post-Progression Survival the same for all alternatives	Page 61	5 months, Yes	
How was total survival calculated	Page 61	Summation of all lines of therapy plus 5 months' post-progression survival	

NSCLC economic evaluations

Table 99: CHEERS checklist for Chouaid et al. (2012)

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	Cost-effectiveness of erlotinib versus chemotherapy for first-line treatment of non-small cell lung cancer (NSCLC) in fit	The title did not mention the fact that two treatments were received

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
			elderly patients participating in a prospective phase 2 study (GFPC 0504)	
Abstract (2)	1	Yes		
Background (3)	1-2	Yes		Brief
Target population (4)	2	Yes	Fit, elderly patients with advanced lung cancer	Definition of elderly and fit was not obvious from the text
Setting (5)	2	No		Not obvious which elements of the healthcare system were included
Perspective (6)	2	Yes	French Healthcare System	
Comparators (7)	2	Yes	Two different strategies	Based on trial
Time horizon (8)	2-3	Yes	To death or last censoring	
Discount rate (9)		No	Implicitly zero	The way the costs and benefits were constructed suggested that the discount rate was zero
Choice of health outcomes (10)	2	Yes	Survival	
Measurement of effectiveness (11)	2-3	Yes	Single study	
Preference based outcomes (12)	2	Yes	QALY	
Estimation of resources (13)	2	No		There appears to be problems with the cost estimations, there are missing elements from the table
Currency (14)	2	Yes	2011 French Euros	
Choice of model (15)	2	Yes	Partition modelling	Trial based economic
Assumptions (16)	2-3	Yes		
Analytic methods (17)	2	Yes		

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Study parameter (18)	3	Yes		Direct estimation in the trial, utilities estimated using normal distribution
Incremental (19)	5	Yes		
Characterising uncertainty (20)	3	Yes	Both univariate and PSA were conducted	
Characterising heterogeneity (21)		No	Heterogeneity was not included	It is now known the one treatment (erlotinib) that is was involved in this study has a treatment response that is determined by the patient's genetic makeup
Discussion (22)	4-5	Yes		
Source of funding (23)	5	Yes		
Conflict of interest (24)		No		

Table 100: CHEERS checklist for Chouaid et al. (2013)

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	103	No	Cost analysis of erlotinib versus chemotherapy for first-line treatment of non-small-cell lung cancer in frail elderly patients participating in a prospective phase 2 study (GFPC 0505)	The title does not specify that there was an economic evaluation
Abstract (2)	103	Yes		Cost-effectiveness was mentioned in the abstract
Background (3)	103-104	Yes		
Target population (4)	104	No	"fit elderly patients with advanced NSCLC"	Although there was a reference there is a lack of detail about the exact population

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Setting (5)		No		
Perspective (6)	104	Yes	French Health Payers perspective	
Comparators (7)	104	Yes		It was derived from the trial comparators
Time horizon (8)	104	Yes	Implied to be lifetime	Statistical analysis was
Discount rate (9)		No	Implied to be zero	There was no discussion of discounting
Choice of health outcomes (10)	104	Yes	Survival	
Measurement of effectiveness (11)	104	Yes	Trial based survival outcomes	
Preference based outcomes (12)	104	Yes	Utility outcomes from single trial	
Estimation of resources (13)	104	Yes	From trial	
Currency (14)	104	Yes	2011 Euro	
Choice of model (15)	104	Yes	Partition model based on trial	No adjustment made
Assumptions (16)	104-105	Yes		Each component was assessed independently
Analytic methods (17)	104-105	Yes		
Study parameter (18)	104	Yes		Utilities were the only one were published data was used
Incremental (19)	Table 4 on 104	Yes		
Characterising uncertainty (20)	104	Yes	Both one-way scenario analysis and probabilistic sensitivity analysis	
Characterising heterogeneity (21)		No		

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Discussion (22)	105-106	Yes		
Source of funding (23)	106	Yes		
Conflict of interest (24)	107	Yes		

Appendix C: Cetuximab cost-effectiveness analysis

The data extraction for each of the recovered literature and the CHEERS checklist for the economic evaluations for Section 3.2 is contained in this Appendix. The economic evaluations are briefly described, the CHEERS checklist is undertaken and a comparison Table for each set of evaluations (later line, first line and sequence) is included.

Economic evaluations of later lines of therapy

Norum (2006)[140]

This was the earliest publication identified as a cost-effectiveness analysis of cetuximab. Norum (2006)[140] reported the results of an incremental analysis which compared the third line therapy of irinotecan and cetuximab versus no chemotherapy. The population of interest was the EGFR expressing population (i.e. not a wild type KRAS population).

The RCT used for measurement of effectiveness in the economic evaluation was the Cunningham trial of 2004 (BOND).[130] This was a trial of cetuximab in one arm compared to cetuximab and irinotecan in the other arm. The use of data from this trial to construct a comparison of cetuximab and irinotecan versus no treatment potentially underestimated the survival gain. Additionally, the use of median survival to represent mean survival is a potential weakness.

An assumption was made that no costs were associated with both post-progression treatment and the no treatment arm. It was argued that only incremental costs were considered. The incremental cost-effectiveness of moving from no treatment to treatment with cetuximab and irinotecan in the third line of therapy results in a cost-effectiveness ratio of nearly AUD (2011) $500 000 per life year gained. There was no attempt within the paper to assess quality of life.

Annemans et al. (2007)[141]

Annemans et al. (2007)[141] reported the use of cetuximab plus irinotecan versus current care in EGFR (i.e. not a wild type KRAS population) expressing metastatic colorectal cancer (CRC) tumours in patients treated in Belgium. Two different continuation strategies were generated from an RCT of cetuximab and irinotecan versus cetuximab based on discontinuing treatment at 6 weeks or 12 weeks if there was a lack of response. The comparator was a series of

matched controls (n=66) derived from standard practice. The lack of randomisation was a weakness.

The costs associated with extra chemotherapy were captured in the analysis. The non-cetuximab control group had much higher costs associated with hospitalisation, additional chemotherapy and laboratory tests. Despite longer survival the cetuximab groups had lower non-cetuximab costs (7 123 euros for the 6-week cetuximab group versus 13 450 euros for the current care), approximately 50% of total costs in one case and 20% in the other. This cost difference resulted in the small incremental difference reported in the study. If the chemotherapy costs were removed from all three arms, the incremental cost-effectiveness of moving from no treatment to cetuximab (plus irinotecan) increases from AUD (2011) $70 000 to $100 000 per life year gained. Comparison between this economic evaluation and Norum (2006)[140] is illustrative. It demonstrates that including other therapies for which there is no evidence of benefit impacts significantly on the results of an economic evaluation. It has the impact of increasing costs of the comparator arm and decreasing the cost-effectiveness ratio.

Starling et al. (2007)[142]

This economic evaluation was undertaken using trial-based information. The effectiveness information was obtained from the arms of two separate RCTs. The effectiveness of the cetuximab plus irinotecan arm was taken from Cunningham 2004 (BOND) and was compared to the BSC care arm of a 1998 publication. A parametric approach was used to extend the censored data from Cunningham (2004) to calculate average life expectancy. The relative survival benefit reported by Cunningham (1998) between no treatment and irinotecan (1.71) was assumed to be the same as the relative difference between cetuximab and no treatment in the 2004 publication. Accordingly, the mean survival of the cetuximab-only arm was adjusted for this.

The costs of chemotherapy were included for patients in the BSC arm. These costs were not included in the cetuximab plus irinotecan arm. The cost of chemotherapy was assumed to be AUD (2011) $4 000 (£1 680). The removal of the incremental difference in the use of additional chemotherapy did not make a large difference to the incremental cost-effectiveness, as opposed to Annemans et al. (2007).[141]

Tappenden et al. (2007)[136]

This HTA assessment discussed the cost-effectiveness of cetuximab plus irinotecan in second or subsequent lines of therapy after the use of irinotecan. It was assumed that the tumours

were EGFR expressing cancers. In this study, the model used was the same as that discussed in Starling et al. (2007)[142] but Tappenden et al. (2007)[136] used a different series of utility weights. This resulted in a different cost-effectiveness result from that reported by Starling et al. (2007).[142] The impact of the new utility values was to decrease the incremental gain in QALYs between alternatives. This had the impact of increasing the cost-effectiveness ratio. Again, it was assumed that there was increased chemotherapy use in the no cetuximab alternative but not in the cetuximab alternative.

Several different alternatives were used to calculate survival in the BSC alternative. The costs associated with the BSC alternative were dependent on the length of survival. The difference in the costs for the cetuximab alternative and the no cetuximab alternative for best supportive care was an important source of uncertainty in the calculation of cost-effectiveness ratios. While the cost-effectiveness ratio was always high, the inclusion of post-progression chemotherapy in one arm but not the other reduced the size of the incremental cost-effectiveness ratio

An additional feature of this economic evaluation is the inclusion of a decision stopping rule based on a post hoc analysis of survival. This decision rule shares many similarities with that used in Annemans et al. (2007).[141] Within the results presented in this Appendix and in Section 3.2 (for example in Figure 11) the cost-effectiveness analysis which included the decision rule is referred to as Tappenden A. The cost-effectiveness analysis without the inclusion of the decision stopping rule is referred to as Tappenden B.

Mittmann et al. (2009)[129]

Mittmann et al. (2009)[129] was a cost-effectiveness analysis based on data collected during the C.O.17 trial. It compared the use of cetuximab to best supportive care. The trial included patients with EGFR expressing tumours but subsequently the KRAS status of the tumours for those who had tissue available was assessed and the cost-effectiveness of treatment based on KRAS status was also assessed as a post hoc analysis.

Information on resource use was collected prospectively; information on pharmaceutical use was included but appeared to be restricted to those pharmaceuticals obviously associated with administration of cetuximab and treatment of adverse events. In the table of disaggregated costs an amount of CAD (2007) $100 was allocated for concomitant medications for both arms of the study. Additional chemotherapy was not considered. Resource use was costed from the perspective of the Canadian health service.

The use of either the KRAS or EGFR tests to define the population of interest was not considered within the framework of the incremental cost-effectiveness analysis.

Health Quality Ontario (2010)[3]

The Ontario medical services advisory secretariat conducted an economic evaluation aimed at assessing the value of the KRAS test in guiding therapy for anti-EGFR therapies.[3] This economic evaluation was designed to assess testing versus not testing for the KRAS mutation; the authors stated explicitly that the evaluation was not designed to test the cost-effectiveness of pharmaceutical treatments alone.

The economic question was to determine the cost-effectiveness of KRAS testing for the third line of therapy with anti-EGFR therapy. However, one of the options included was best supportive care- which included "those measures designed to provide palliation of symptoms and improve quality of life." The costs and consequences from Mittmann et al. (2009)[129] were included in the model. The third line of therapy specifically excluded the use of chemotherapy

A Markov model was produced, and adverse events were included. The total cost attributed to best supportive care was CAD (2009) $1 404. Several alternatives were excluded by extended dominance. The incremental cost-effectiveness was low compared to the other cost-effectiveness analyses. One reason for this difference was the lack of an incremental cost increase associated with increased post-progression survival.

Shiroiwa et al. (2010)[143]

Shiroiwa et al. (2010)[143] conducted a cost-effectiveness analysis of cetuximab with and without testing of KRAS status. Only direct medical costs were included. KRAS testing dominated no KRAS testing but compared to no treatment the cost-effectiveness ratio was high. It was assumed that no other chemotherapy was used.

Blank et al. (2011)[145]

Blank et al. (2011)[145] conducted a cost-effectiveness analysis of cetuximab use in the last line of therapy with and without testing for the KRAS gene. Several detection methods for KRAS were considered. A set cost per month of palliative care was used and there was no consideration of further chemotherapy.

Fragoulakis et al. (2012)[146]

Fragoulakis et al. (2012)[146] conducted a cost-minimisation economic evaluation of later line therapy comparing cetuximab to panitumumab in wild type KRAS patients.[146] It was conducted

from the perspectives of the health systems in Greece and the UK.[146] It concluded that panitumumab was less costly. There was no inclusion of chemotherapy costs in later lines of therapy. Because of the limited information and the construction of the cost-minimisation, it has not been included in the Table below.

Vijayaraghaven et al. (2012)[147]

Vijayaraghaven et al. (2012)[147] conducted a cost-effectiveness analysis of cetuximab or panitumumab using a Markov modelling approach. The alternatives included testing patients and giving treatment based on the results versus giving all patients EGFR and chemotherapy. It was centred on the issue of KRAS testing and therefore there was no non-EGFR option. No additional chemotherapy was considered in any of the arms.

Hoyle et al. (2013)[137]

Hoyle et al. (2013)[137] conducted a systematic review and economic evaluation of cetuximab with and without additional chemotherapy. The main difference between Hoyle et al. (2013)[137] and Tappenden et al. (2007)[136] was Tappenden et al. (2007)[136] did not include a KRAS wild type cancer group. Therefore, Tappenden et al. (2007)[136] was inapplicable for the more contemporary use of cetuximab.

Chapter 5 in this HTA included an assessment of the industry submissions to NICE about cetuximab. This assessment modelled the alternative of irinotecan compared to cetuximab and irinotecan in the second line of therapy. However, the consideration of best supportive care involves a set cost per month.

Chapter 6 within this HTA presented the independent economic assessment of third line therapy for cetuximab. The use of cetuximab was either as a monotherapy or in combination with irinotecan. Again, the assumption was made that all patients would not receive any other chemotherapy. This thesis has used Hoyle A and Hoyle B refer to the industry submission and the independent assessment respectively.

Table 101: Economic Evaluations of cetuximab later lines of therapy

Study	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007)[136]	Mittmann et al. (2009)[129]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Blank et al. (2011)[145]	Vijayaraghaven et al. (2012)[147]	Hoyle B (2013)[137]
Year of publication	2006	2007	2007	2007	2009	2010	2010	2011	2012	2013
Place in therapy	Last Line	Last Line	Last line	Second and later lines	Last line	Third line	Last line	Last Line	Second and later lines	Second and later lines
Economic evaluation type	Cost-effectiveness	Cost-utility	Cost-effectiveness/Cost-utility	Cost-utility	Cost-utility	Cost-utility	Cost-utility	Cost-utility	Cost-effectiveness	Cost-utility
Population	Third line treatment-resistant population	Second or subsequent line after failure of irinotecan	Third line treatment resistance population	Second or subsequent line after failure of irinotecan	Third line treatment resistance population	Third line treatment resistance population	Second or subsequent line after failure of irinotecan	Third line treatment resistance population	Second or subsequent line after failing chemotherapy	Third line treatment population
Cetuximab treatment	Cetuximab	Cetuximab plus irinotecan	Cetuximab plus irinotecan	Cetuximab plus irinotecan	Cetuximab (no testing) Cetuximab (testing)	Cetuximab (no testing) Cetuximab (testing) Cetuximab plus irinotecan (testing) Cetuximab plus irinotecan (no testing)	Cetuximab (no testing) Cetuximab (testing)	Cetuximab (no testing) Cetuximab (KRAS testing) Cetuximab (KRAS and BRAF)	Cetuximab (no testing) Cetuximab (KRAS) Cetuximab plus irinotecan (testing) Cetuximab plus irinotecan (no testing)	Cetuximab (KRAS) Cetuximab plus irinotecan (KRAS)

Study	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007)[136]	Mittmann et al. (2009)[129]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Blank et al. (2011)[145]	Vijayaraghaven et al. (2012)[147]	Hoyle B (2013)[137]
Alternatives	BSC	BSC	BSC	BSC	BSC	Panitumumab (testing) Panitumumab (no testing) BSC	BSC	BSC	Panitumumab (testing) Panitumumab (no testing)	BSC
KRAS testing included	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Perspective	Society	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer	Health Services Payer
Country	Norway	Belgium	UK	UK	Canada	Canada	Japan	Swiss	USA Germany	UK
Outcomes	From survey of literature	From trial	From trial	From trial	From trial	From modelling	From modelling	From modelling	From modelling	From trial-adjusted
Method of modelling	Direct Calculation	Direct Calculation	Direct calculation	Partition modelling	Direct calculation	Markov model	Markov model	Markov model	Markov model-microsimulation	Partition modelling
Specific trial used	BOND	BOND	BOND	BOND	CO.17	Indirectly from CO.17	CO.17	CO.17	De Roock (2008) Keratitis (2008)	A mixture of different trials
Method of extrapolation	Nil	Nil	"Standard parametric approaches"	Weibull	Nil	State transition probabilities from CO.17	State transition probabilities from	State transition probabilities from CO.17	State transition probabilities	Weibull and adjusted

Study	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007)[136]	Mittmann et al. (2009)[129]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Blank et al. (2011)[145]	Vijayaraghaven et al. (2012)[147]	Hoyle B (2013)[137]
							CO.17 and assumption			
Pharmaceutical use	Expert	From trial	From trial	From trial	From trial	Expert	Expert	Expert	Expert	Expert
Adverse events	Nil	Costs	Costs only	Costs only for hospitalisations	Costs and indirect through MAUI	Costs and indirect through MAUI	Not included	Not included	Costs	Costs
Outcome	Life years gained	Life years gained	Life years gained	QALY	QALY	QALY	QALY	QALY	Life years gained	QALY
Time horizon	N/A	Not stated	2.5 years	Not stated	1.6 years (trial based)	Not stated	2.5 years	Not stated	Not stated	10 years
Assumed to be lifelong	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Discounting	Nil	Nil	3.5%	Nil	Nil	5%	3%	3%	Not stated	3.5%
Sensitivity analysis	Yes, demonstrated	Yes	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated
Source of utility	N/A	N/A	Standard utility applied to all time points 0.746	0.8 stable 0.6 progressive	Within trial- MAUI (HUI3)	From MAUI-(HUI3)	0.7 for progression free	0.72 and increasing for cetuximab 0.71 and decreasing for BSC 0.5 for progression	N/A	Adjusted other measures 0.69 for progression, highly for cetuximab

Study	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007)[136]	Mittmann et al. (2009)[129]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Blank et al. (2011)[145]	Vijayaraghaven et al. (2012)[147]	Hoyle B (2013)[137]
Total QALY for cetuximab	N/A	N/A	0.6803	0.55	0.4 (All) 0.51 (KRAS)	1.05 (C – KRAS) 1.04 (C- All) 1.25 (C+I – KRAS) 1.39 (C+I – All)	0.49 (KRAS) 0.48 (All)	0.947 (All) 0.936 (KRAS) 0.834 (KRAS-BRAF)	N/A	0.61 (Cet) 0.97 (Cet+I)
Total Cost of cetuximab arm in AUD $ (2011/12)	$70 403	$47 191	$57 382	$45 352	$36 853 (All) $48 774 (KRAS)	$75 752 (C-All) $47 166 (C-KRAS) $115 430 (C+I, All) $60 224 (C + I, KRAS)	$54 345 (All) $45 029 (KRAS)	$82 234 (All) $75 213 (KRAS) $73 958 (KRAS + BRAF)	$25 580 to $46 935	$68 394 (Cet) $131 810 (Cet+I)
Acquisition cost Cetuximab/total cost	N/A	50%	53%	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Incremental QALY	N/A	N/A	N/A	0.14	0.08 (All) 0.18 (KRAS)	0.2992 (C-All) 0.3082 (C-KRAS) 0.6452 (C+ I-All) 0.5141 (C+ I-KRAS)	0.12 (All) 0.13 (KRAS)	0.504 (All) 0.493 (KRAS) 0.491 (KRAS + BRAF)	N/A	0.25 (Cet) 0.61 (Cet+I)
Incremental Cetuximab	$422 417 (LYS, no treatment)	$70 280 (LYS, not	$110 736 (LYS, no treatment)	$198 827 (QALY, no treatment)	$391 523 (All)	$85,563-$141 215	$262 767 (KRAS)	133, 373 to 146 354		$217 991 (Cet) $193 300

Study	Norum (2006)[140]	Annemans et al. (2007)[141]	Starling et al. (2007)[142]	Tappenden et al. (2007)[136]	Mittmann et al. (2009)[129]	Health Quality Ontario (2010)[3]	Shiroiwa et al. (2010)[143]	Blank et al. (2011)[145]	Vijayaraghaven et al. (2012)[147]	Hoyle B (2013)[137]
cost-effectiveness		treatment)			$244 053 (KRAS)	(QALY, no treatment	$363 767 (All)	(QALY, no treatment)		(Cet +I)
Advice	Promising but expensive	Confirmed cost-effectiveness of treatment	ICER is relatively high	ICER is high	ICER is high	KRAS testing dominates no testing	KRAS testing dominates, cetuximab not cost-effective	Economically favourable to identify patients with KRAS and BRAF mutations	Identifying patients with KRAS mutations was cost saving	Represent poor value for money

Abbreviations: AUD: Australian dollar; BRAF: BRAF gene mutation; Cet: cetuximab; Cet+I: cetuximab and irinotecan; ICER: incremental cost-effectiveness ratio; KRAS: Kristen rat sarcoma; LYS: life year saved; N/A: not applicable; QALY: quality adjusted life years

Table 102: CHEERS checklist for Norum (2006)

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	532	Yes	Cetuximab in the treatment of metastatic colorectal cancer: a model-based cost-effectiveness analysis	
Abstract (2)	532	Yes		
Background (3)	532	Yes		
Target population (4)	533-534	Yes	EGFR positive population	
Setting (5)	534	Yes	Norway	
Perspective (6)	533-534	Yes	Societal	Not directly stated
Comparators (7)	Figure 1	Yes	Chemotherapy – irinotecan and cetuximab versus no treatment	
Time horizon (8)		No		
Discount rate (9)		No		
Choice of health outcomes (10)	533	Yes	Life year saved	
Measurement of effectiveness (11)	533	Yes	Median survival was used	Median differences were used
Preference based outcomes (12)		No	Life years were the outcome so a preference based outcome was not required	
Estimation of resources (13)	Table 2	Yes		
Currency (14)	533	Yes	Norwegian krona converted to Euro	
Choice of model (15)		No	Direct calculation, alternative modelling was not considered	Model was not considered
Assumptions (16)	533-535	Yes		
Analytic methods (17)	533-535	Yes		
Study parameter (18)	Table 3	Yes		
Incremental (19)	Table 2	Yes		

CHEERS checklist (item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Characterising uncertainty (20)	Table 3	Yes	Described as multivariate but conducted multiple one-way sensitivity analysis	
Characterising heterogeneity (21)		No		
Discussion (22)	536-537	Yes		
Source of funding (23)	537	Yes	Norwegian Cancer Union	
Conflict of interest (24)		No		

Table 103: CHEERS checklist for Annemans et al. (2007)[141]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	419	Yes	Cost-effectiveness of cetuximab in combination with irinotecan compared with current care in metastatic colorectal cancer after failure on irinotecan--a Belgian analysis	
Abstract (2)	419	Yes		
Background (3)	419	Yes		
Target population (4)		No	It was the population was not described as EGFR positive, although that was implied. The population was the BOND trial but exactly who was included in this population was not specified.	
Setting (5)	420	Yes	Belgium	
Perspective (6)	420	Yes	Belgium healthcare system	
Comparators (7)	420	Yes		
Time horizon (8)		No		
Discount rate (9)		No		
Choice of health outcomes (10)		No		
Measurement of effectiveness (11)	420	Yes	Life years gained	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Preference based outcomes (12)		No		
Estimation of resources (13)	Table 3, Table 4, 421-422	Yes		
Currency (14)	420	Yes	Euro	
Choice of model (15)		No	Direct calculation	
Assumptions (16)	420-422	Yes		
Analytic methods (17)	420-422	Yes		
Study parameter (18)	Table 4, Table 5	Yes	The resources were not disaggregated	
Incremental (19)	Table 5	Yes		
Characterising uncertainty (20)	Table 6	Yes	A series of one way and two way sensitivity analysis were conducted.	
Characterising heterogeneity (21)		No		
Discussion (22)	423-424	Yes		
Source of funding (23)		No		
Conflict of interest (24)		No		

Table 104: CHEERS checklist for Starling et al. (2007)[142]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	206	Yes	Cost-effectiveness analysis of cetuximab/irinotecan vs active/best supportive care for the treatment of metastatic colorectal cancer patients who have failed previous chemotherapy treatment	
Abstract (2)	206	Yes		
Background (3)	206-207	Yes		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Target population (4)		No	Patients who fail second line chemotherapy, presumably EGFR expressing patients, but this was not actually stated	
Setting (5)		No		
Perspective (6)	207	Yes	Third party payer	NHS
Comparators (7)	207	Yes		
Time horizon (8)		Yes	2.5 years	
Discount rate (9)	209	Yes		
Choice of health outcomes (10)		Yes		
Measurement of effectiveness (11)		Yes		
Preference based outcomes (12)		Yes		
Estimation of resources (13)		Yes		
Currency (14)		Yes		
Choice of model (15)		No		
Assumptions (16)		Yes		
Analytic methods (17)		Yes		
Study parameter (18)		Yes		
Incremental (19)		Yes		
Characterising uncertainty (20)		Yes		
Characterising heterogeneity (21)		No		
Discussion (22)		Yes		
Source of funding (23)		No		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Conflict of interest (24)		Yes		

The assessment of the CHEERS checklist was based on the title, abstract and title being sourced from the title page, abstract and the first chapter. The remainder was taken from chapter 4, from the independent economic assessment beginning on page 51 for bevacizumab and page 60 for cetuximab.

Table 105: CHEERS checklist for Tappenden et al. (2007)[136]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer	
Abstract (2)	iii	Yes		
Background (3)	Chapter 1	Yes		
Target population (4)	60	Yes		
Setting (5)	77	Yes	Discusses cost to NHS but limited in the description of exactly what the setting includes	
Perspective (6)	42	Yes	Perspective of the NHS, including on direct costs and health effects	
Comparators (7)	61	Yes	Cetuximab and irinotecan after failure of irinotecan-containing cytotoxic therapy Best supportive care in the same population	
Time horizon (8)	42	Yes	Lifetime horizon	
Discount rate (9)	44	Yes	Discounted at 3.5%	
Choice of health outcomes (10)	61	Yes	Life years gained QALY gained	
Measurement of effectiveness (11)	61	Yes	Weibull survival function	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Preference based outcomes (12)	63	Yes	Only two states were used, pre and post-progression	
Estimation of resources (13)	63-65	Yes		
Currency (14)	63	Yes		
Choice of model (15)		No		
Assumptions (16)	62-64	Yes		
Analytic methods (17)	62	Yes		
Study parameter (18)	Table 42, Table 43	Yes		
Incremental (19)	Table 47	Yes		
Characterising uncertainty (20)	Table 48, Table 49, Figure 15, Figure 16, Figure 17, Figure 18	Yes	Scenario analysis and probabilistic sensitivity analysis conducted. Cost-effectiveness acceptability curves were included.	
Characterising heterogeneity (21)		No		
Discussion (22)	82-85	Yes	Future research was suggested to determine the impact of cetuximab in combination with irinotecan.	
Source of funding (23)	95	Yes		
Conflict of interest (24)		No		

Table 106: CHEERS checklist for Mittmann et al. (2009)[129]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1182	Yes	"Prospective Cost-Effectiveness Analysis of Cetuximab in Metastatic Colorectal Cancer: Evaluation of National Cancer Institute of Canada Clinical Trials Group CO.17 Trial"	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Abstract (2)	1182-1183	Yes	Structured abstract	
Background (3)	1183	Yes	Cetuximab and best supportive care versus best supportive care Subgroup analysis on KRAS wild type	
Target population (4)	1184	Yes	Population of the CO.17 trial	Recruitment criteria was not described fully
Setting (5)	N/A	No	Australian and Canadian patients used	It was not discussed how the differences in settings were managed
Perspective (6)	1184	Yes	Canadian healthcare payer	
Comparators (7)				
Time horizon (8)	1185	Yes	Trial based	
Discount rate (9)	1185	Yes	0% discount rate	The argument was made that discounting was not used because median survival time was less than a year
Choice of health outcomes (10)	1183	Yes	Both life years saved and QALY	
Measurement of effectiveness (11)	1184	Yes	Restricted mean survival was used to estimate overall survival.	
Preference based outcomes (12)	1185	Yes	HUI3	Within trial- last observation was carried forward. Mean area under the curve was calculated on a per patient basis. Cetuximab was associated with an increasing utility value, BSC was associated with a relatively stable utility value.
Estimation of resources (13)	1184	Yes		Only trial-related information was included, potential for substantial missing information
Currency (14)	1184	Yes	2007 Canadian dollars	
Choice of model (15)		No		The choice of model was not justified

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Assumptions (16)	1184-1186	Partial		The assumptions around effectiveness and QALYs were well documented, the assumptions around cost, especially the completeness of the data were less so
Analytic methods (17)	1185	Yes		
Study parameter (18)	1185	Yes		
Incremental (19)	1188	Yes		
Characterising uncertainty (20)	1185	Yes	One-way sensitivity analysis conducted, PSA conducted- although called bootstrapping	
Characterising heterogeneity (21)	1185	Yes	KRAS wild type versus all recruited	
Discussion (22)	1189-1191	Yes		
Source of funding (23)	1192	Yes		
Conflict of interest (24)		No		

The majority of the checklist was taken from the economic analysis section that began on page 30 of the report.

Table 107: CHEERS checklist for Health Quality Ontario (2010)[3]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	KRAS Testing for Anti-EGFR Therapy in Advanced Colorectal Cancer: An Evidence-Based and Economic Analysis	
Abstract (2)		N/A	There was a structured executive summary	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Background (3)	12-13	Yes	Detailed background including how testing is undertaken and the importance of licensing	
Target population (4)	30	Yes	Third line treatment population with CRC	
Setting (5)	13	Yes		
Perspective (6)	32	Yes		
Comparators (7)	32	Yes	Best supportive care Cetuximab treatment without KRAS testing Cetuximab treatment with KRAS testing Cetuximab and irinotecan treatment without KRAS testing Cetuximab and irinotecan treatment with KRAS testing Panitumumab without KRAS testing Panitumumab with KRAS testing	
Time horizon (8)	32	Yes	Explicitly life time horizon	
Discount rate (9)	30	Yes	Five per cent was applied	
Choice of health outcomes (10)	30	Yes	QALY	
Measurement of effectiveness (11)	34	Yes	Index trials were used to generate transition probabilities for the Markov model	
Preference based outcomes (12)	34-35	Yes	Literature source listed, why that source was preferred over others was not discussed	
Estimation of resources (13)	33	Yes		
Currency (14)	33	Yes	2009 Canadian dollars	
Choice of model (15)	32	Partial	Markov structure. Three state Markov model.	
Assumptions (16)	32-35	Yes		
Analytic methods (17)	32-35	Yes		
Study parameter (18)	32-35	Yes		
Incremental (19)	Table 23	Yes		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Characterising uncertainty (20)		Partial	Probabilistic sensitivity analysis undertaken but the reporting was not complete	
Characterising heterogeneity (21)		No		
Discussion (22)		N/A		
Source of funding (23)		N/A		
Conflict of interest (24)		N/A		

Table 108: CHEERS checklist for Shiroiwa et al. (2010)[143]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	375	Yes	Cost-Effectiveness Analysis of KRAS Testing and Cetuximab as Last-Line Therapy for Colorectal Cancer	
Abstract (2)	375	Yes		
Background (3)	375-376	Yes		
Target population (4)	376	Yes	Japanese patients with metastatic CRC who have failed 5-FU, irinotecan and oxaliplatin	
Setting (5)	376	No	Japan but not a description of the Japanese setting	
Perspective (6)	378	Yes	Health payers perspective	
Comparators (7)	375	Yes	All patients receive cetuximab All patients receive BSC KRAS testing with wild type receiving	
Time horizon (8)	377	Yes	Time horizon of 2.5 years	
Discount rate (9)	375	Yes	3%	
Choice of health outcomes (10)	377	Yes	Life years gained	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Measurement of effectiveness (11)	377	Yes	CO.17 trial	
Preference based outcomes (12)	377	Yes	HUI3- based on the results of the CO.17 trial	
Estimation of resources (13)	378-379	Yes	Based on a standard treatment model designed by the authors	
Currency (14)	378	Yes	Japanese yen and United States dollars	
Choice of model (15)	377	Partial	Three state Markov model. It was argued pre and post-progression states were different but not why the model was superior	
Assumptions (16)	377-378	Yes		
Analytic methods (17)	377	Yes		
Study parameter (18)	377	Yes		
Incremental (19)	Table III	Yes		
Characterising uncertainty (20)	379	Yes	One-way and probabilistic sensitivity analysis conducted	
Characterising heterogeneity (21)	Table III	Yes	KRAS status as a measure of heterogeneity was included	
Discussion (22)	380-381	Yes	Discussion of dominance	
Source of funding (23)	383	Yes	Supported by Roche Diagnostics	
Conflict of interest (24)	N/A	No		

Table 109: CHEERS checklist for Blank et al. (2011)[145]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	6338	Yes	KRAS and BRAF mutation analysis in metastatic colorectal cancer: a cost-effectiveness analysis from a Swiss perspective	
Abstract (2)	6338	Yes	Structured abstract	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Background (3)	6338-6339	Yes		
Target population (4)	6339	Yes	Hypothetical cohort of chemotherapy-refractory metastatic CRC patients	
Setting (5)	6339	No	Switzerland	
Perspective (6)	6339	Yes	Switzerland health	
Comparators (7)	6339	Yes	KRAS and BRAF testing with cetuximab KRAS testing with cetuximab No cetuximab/Best supportive care	
Time horizon (8)	6339	Yes	K	
Discount rate (9)	6339	Yes	Discount rate of 3%	
Choice of health outcomes (10)	6339-6340	Yes	QALYS and overall survival	
Measurement of effectiveness (11)	6340	Yes	Extrapolation from median survival	
Preference based outcomes (12)	6340	Yes	Preference based HUI from CO.17	
Estimation of resources (13)	6341-6342	Yes		
Currency (14)	6339	Yes	Euros 2010	
Choice of model (15)	6339	Partial	Markov model. The Markov model was based on prior work	
Assumptions (16)	6340-6343	Yes		
Analytic methods (17)	6340-6343	Yes		
Study parameter (18)	6340-6343	Yes		
Incremental (19)	Table 3	Yes		
Characterising uncertainty (20)	6343	Yes		
Characterising heterogeneity (21)		No		
Discussion (22)	6344-6345	Yes		
Source of funding (23)	6345	Yes	Supported by educational grant	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Conflict of interest (24)	6345	Yes	No conflict of interest	

Table 110: CHEERS checklist for Fragoulakis et al. (2012)[146]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	2132	Yes	Cost-Minimization Analysis of the Treatment of Patients With Metastatic Colorectal Cancer in Greece	
Abstract (2)	2132	Yes	Structured abstract	
Background (3)	2132-2133	Yes	Conduct an economic evaluation between panitumumab and cetuximab because there was limited information about the relative cost	
Target population (4)	2132	Yes	EGFR expressing KRAS wild type metastatic CRC patients	
Setting (5)		No	The funding system was described	
Perspective (6)	2135	Yes	NHS perspective & Social security sickness fund perspective	
Comparators (7)	2132	Yes	Cetuximab Panitumumab	
Time horizon (8)	2134	Yes	5 months- median progression free survival time	
Discount rate (9)		No		
Choice of health outcomes (10)		N/A		
Measurement of effectiveness (11)		N/A		
Preference based outcomes (12)		N/A		
Estimation of resources (13)		Yes		
Currency (14)	2136	Yes	2011 Euro - Greece	
Choice of model (15)		No		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Assumptions (16)		Partial		
Analytic methods (17)	2136-2137	Yes		
Study parameter (18)				
Incremental (19)		N/A		
Characterising uncertainty (20)		Yes		
Characterising heterogeneity (21)		No	There was no heterogeneity	
Discussion (22)		Yes		
Source of funding (23)	2141	Yes		
Conflict of interest (24)	2141	Yes		

Table 111: CHEERS checklist for Vijayaraghaven et al. (2012)[147]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	438	Yes	Cost-effectiveness of KRAS testing in metastatic colorectal cancer patients in the United States and Germany	
Abstract (2)	438	Yes	Abstract was not structured	
Background (3)	438-439	Yes		
Target population (4)	439	Yes	Metastatic colorectal carcinoma patients who had failed one line of therapy (at least)	
Setting (5)	440	Partial	Germany and the United States. The article did comment on the different treatments that might be received in each country	
Perspective (6)	440	Yes	Healthcare system perspective	
Comparators (7)	439	Yes	Cetuximab and chemotherapy with KRAS testing Cetuximab and chemotherapy without KRAS testing Cetuximab with KRAS testing	There was no non-antibody therapy alternative

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
			Cetuximab without KRAS testing Panitumumab with KRAS testing Panitumumab without KRAS testing	
Time horizon (8)	439	Yes	Lifetime model	
Discount rate (9)		No		
Choice of health outcomes (10)	439	Yes	Life expectancy	
Measurement of effectiveness (11)	Table 1	Yes	Listed the median survivals used in the model	
Preference based outcomes (12)		N/A		
Estimation of resources (13)	Table 2	Yes		Several inputs were on the basis of expert opinion
Currency (14)	440, Table 3	Yes	2009 United States dollars and 2009 German Euros	
Choice of model (15)	439 Figure 1	Partial	Markov simulation model Undertaken in Treeage	
Assumptions (16)	439-441	Yes		
Analytic methods (17)	439-441	Partial	Several features of the modelled methods were not described	How the model moved from medians to means was not described
Study parameter (18)	Table 1	Yes		
Incremental (19)	Table 3	Yes	Several options were dominated	The lack of no- antibody alternative notable in the results
Characterising uncertainty (20)	441	Yes	One-way sensitivity analysis, tornado diagram and a threshold analysis were undertaken	
Characterising heterogeneity (21)		No		
Discussion (22)	442-444	Yes		
Source of funding (23)	444	Yes	Roche molecular systems	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Conflict of interest (24)	444	Yes		

The page numbers for the checklist for Hoyle et al. (2013)[41] were based on the Value in Health article

Table 112: CHEERS checklist for Hoyle et al. (2013)[137]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	Cost-Effectiveness of Cetuximab, Cetuximab Plus irinotecan, and Panitumumab for Third and Further Lines of Treatment for KRAS Wild-Type Patients with Metastatic Colorectal Cancer	
Abstract (2)	1	Yes	Structured abstract	
Background (3)	1-2	Yes		
Target population (4)	1	Yes	Third line treatment for wild type KRAS patients with metastatic CRC	
Setting (5)	1	No	Not described	
Perspective (6)	1	Yes	UK National Health Service	
Comparators (7)	1	Yes	Best supportive care Cetuximab Cetuximab and irinotecan Panitumumab	
Time horizon (8)		No	Implied that it is lifelong	
Discount rate (9)	8	Yes	Argued to be zero because of the short time frame	
Choice of health outcomes (10)	2	Yes	Overall survival	
Measurement of effectiveness (11)	2	Yes	Literature review, indirect comparison	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Preference based outcomes (12)	3	Yes	Used the HUI-3 but capped the utility value by an aged general population	
Estimation of resources (13)	2-4	Yes		
Currency (14)		Yes	British pounds	
Choice of model (15)	2	Yes	The model structure was chosen between simple and was informed by a review of the literature- partitioned survival model	
Assumptions (16)	2-4	Yes		
Analytic methods (17)	2-4	Yes		
Study parameter (18)	2-4	Yes		
Incremental (19)	6	Yes	The panitumumab alternative was dominated	
Characterising uncertainty (20)	6	Yes	One-way sensitivity analysis was reported in an appendix Probabilistic sensitivity analysis was present on page 6	
Characterising heterogeneity (21)		No		
Discussion (22)	6-7	Yes	There was some discussion in the results section	
Source of funding (23)	8	Yes		
Conflict of interest (24)	8	Yes		

Economic evaluations of cetuximab as first line of therapy

Asseburg et al. (2011)[144]

Asseburg et al. (2011)[144] reported the cost-effectiveness of cetuximab as first line therapy in a very select population- those with no KRAS mutation and metastatic disease limited to the liver. This population has disease which was potentially downgradable and subsequently amenable to surgery.

Second and third line chemotherapy were included as costs according to current treatment patterns in the country of interest, Germany. This was included in all arms and therefore was not a driver of the incremental analysis. The alternative arm was the use of another monoclonal antibody- bevacizumab. The cost-effectiveness of these two options (including antibody therapy) over more traditional therapy (not including antibody therapy) was not included.

There was a disagreement in terms of the QHES checklist; Lange assessed the subgroup analysis as being prespecified, however, in this thesis it was assessed as being a retrospective analysis subgroup analysis of an earlier trial (Van Custom) within this thesis.

Lawrence et al. (2013)[148]

Lawrence et al. (2013)[148] conducted a cost-utility analysis comparing the use of three monoclonal antibodies (cetuximab, bevacizumab and panitumumab) in the first line of therapy for metastatic CRC. The alternative of no monoclonal antibodies was included. Additional chemotherapy costs were included in all alternatives; they were the same in three arms and decreased in the panitumumab arm.

Barone et al. (2014)

Although it met the inclusion criteria it was very difficult to assess the methodology and quality of Barone et al. (2014).[149] Barone et al. (2014)[149] conducted a cost-effectiveness of KRAS testing in high-risk patients prior to metastatic disease with the anticipation of using anti-EGFR therapy.

Despite presenting a cost-effectiveness analysis including costs and benefits and an incremental analysis, this study contained little discussion of the methods used. Reference was made to another paper regarding the methods, but the second paper was in Italian and therefore not able to be assessed for the purposes of this thesis. Barone et al. (2014)[149] found a much lower cost-effectiveness ratio than other studies.

Westwood et al. (2014)[86]

Westwood et al. (2014)[86] was a health technology assessment of the cost-effectiveness of KRAS testing. The systematic review included in the HTA is discussed above. A cost-effectiveness analysis was conducted for different methods of KRAS mutation testing for deciding between standard chemotherapy (FOLFOX or FOLFIRI) or chemotherapy with cetuximab. The population considered were adults with metastatic CRC restricted to the liver whose disease could be resectable or potentially resectable.[86] The model considered up to three lines of therapy. The conclusion was that no test was more effective or cost-effective compared to the others. The data extraction from this economic evaluation was restricted because of removal of information for commercial in confidence reasons.

Graham et al. (2015)[150]

Graham et al. (2015)[150] was a formal cost-minimisation evaluation between cetuximab and panitumumab in the first line treatment of wild type RAS metastatic CRC. The chemotherapy backbone given in combination with the anti-EGFR agent differed, being FOLFOX for panitumumab and FOLFIRI for cetuximab. Included costs were for RAS testing, pharmaceutical acquisition, pharmaceutical administration and for adverse events.

Additional lines of therapy and chemotherapy costs were not considered in the analysis.

Wen et al. (2015)[151]

Wen et al. (2015)[151] examined the cost-effectiveness of the screening process for detecting wild type RAS (as opposed to KRAS testing) based on a trial conducted in China.[151] Based on the testing, those detected with mutant genes with wild type were treated with cetuximab (and FOLFIRI) or alternatively bevacizumab (and FOLFIRI). There were four alternatives, two alternative pharmaceuticals for two alternative testing regimes. There was no discussion of those who tested positive (who presumably differ between the alternative testing regimes).

Second line therapy costs were included in the costs. The survival in the second line did not depend of the treatment received. The attributed costs in the second line were relatively high, in some cases exceeding the estimated costs in the first line. While the model was identified as being most sensitive to the costs of treatment in the first line, the model was also sensitive to the costs of treatment in the second line.

Table 113: CHEERS checklist for Asseburg et al. (2011)[144]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	482	Yes	Cost-Effectiveness of Targeted Therapy With Cetuximab in Patients With K-ras Wild-Type Colorectal Cancer Presenting With Initially Unresectable Metastases Limited to the Liver in a German Setting	
Abstract (2)	482	Yes	Structured abstract	
Background (3)	482-483	Yes		
Target population (4)	483	Yes	First line treatment of patients with metastatic CRC with KRAS wild type who were initial unresectable	
Setting (5)	483	No	Germany	
Perspective (6)	486	Yes	Germany health insurance	
Comparators (7)	483	Yes	Chemotherapy with cetuximab Chemotherapy with bevacizumab	
Time horizon (8)	484	Yes	10 years	
Discount rate (9)	486	Yes	5% for costs and outcomes	
Choice of health outcomes (10)	485	Yes	Life years	
Measurement of effectiveness (11)	484	Yes		
Preference based outcomes (12)		N/A		
Estimation of resources (13)	Table 2	Yes		
Currency (14)	Table 2	Yes	Euro (Germany) 2010	
Choice of model (15)	485	Partial	Did not explain the choice of model	
Assumptions (16)	484-486	Yes		
Analytic methods (17)	484-485	Yes		
Study parameter (18)	484-486	Yes		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Incremental (19)	Table 5	Yes		
Characterising uncertainty (20)	Table IV	Yes	One-way sensitivity analysis and probabilistic sensitivity analysis	
Characterising heterogeneity (21)		No		
Discussion (22)	491-495	Yes		
Source of funding (23)	495	Yes	Merch Serono	
Conflict of interest (24)		No		

Table 114: CHEERS checklist for Lawrence et al. (2013)[148]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1387	Yes	Economic analysis of bevacizumab, cetuximab, and panitumumab with fluoropyrimidine-based chemotherapy in the first-line treatment of KRAS wild-type metastatic colorectal cancer (mCRC)	
Abstract (2)	1387	Yes	Structured abstract	
Background (3)	1388	Yes		
Target population (4)	1388-1389	Yes	KRAS wild type metastatic CRC patients with no previous treatment	
Setting (5)	1387	No	Canada	
Perspective (6)	1390	Yes	Canadian healthcare system perspective	
Comparators (7)	1388	Yes	Bevacizumab with chemotherapy Cetuximab with chemotherapy Panitumumab with chemotherapy Chemotherapy alone	
Time horizon (8)	1387	Yes	10 years	
Discount rate (9)	Table 2	Yes	5% costs and benefits	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Choice of health outcomes (10)	1388	Yes	Survival adjusted to QALYs	
Measurement of effectiveness (11)	1388-1389	Yes	Indirect comparison	
Preference based outcomes (12)	1392	Yes	UK oncology nurses and the use of a visual analogue scale	
Estimation of resources (13)	Table 2	Yes		
Currency (14)	1390	Yes	2011 Canadian dollars	
Choice of model (15)	1388	Partial	Markov model was used, an explanation of why this was the preferred model was not discussed	
Assumptions (16)	1388-1392	Yes		
Analytic methods (17)	1388-1392	Yes		
Study parameter (18)	1388-1392	Yes		
Incremental (19)	Table 3	Yes		
Characterising uncertainty (20)	1394	Yes	One-way sensitivity analysis	
Characterising heterogeneity (21)		No		
Discussion (22)	1394-1397	Yes		
Source of funding (23)	1397	Yes		
Conflict of interest (24)	1397	Yes		

Table 115: CHEERS checklist for Barone et al. (2014)[149]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1	Yes	KRAS early testing: consensus initiative and cost-effectiveness evaluation for metastatic colorectal patients in an Italian setting	
Abstract (2)	1	Yes	Unstructured abstract	
Background (3)	1	Yes	Discussion about KRAS status as marker of resistance to anti-EGFR treatment. Discussion about liver limited metastatic disease	
Target population (4)		Yes	High-risk non-metastatic disease, with anticipation of metastatic treatment	
Setting (5)		No	Italy	
Perspective (6)		No		
Comparators (7)		Yes	Cetuximab and FOLFOX FOLFOX Bevacizumab and FOLFOX Cetuximab and FOLFIRI FOLFIRI	Gaining the KRAS status at time of metastasis would not allow time prior to the requirement of starting treatment
Time horizon (8)		No		
Discount rate (9)		No		
Choice of health outcomes (10)	Table 3	Yes	QALY	
Measurement of effectiveness (11)		No		
Preference based outcomes (12)		No		
Estimation of resources (13)		No		
Currency (14)	8	Yes	2012 Euro	
Choice of model (15)		No	A previous designed model was adapted and used by NICE, SMC and other HTAs. The model has been adapted for non-metastatic patients who were at high-risk of metastatic disease.	There was not a model diagram or discussion of the structure

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Assumptions (16)		No		
Analytic methods (17)		No		
Study parameter (18)		No		
Incremental (19)	Table 3	Yes		
Characterising uncertainty (20)		No		
Characterising heterogeneity (21)		No		
Discussion (22)		Partial	A very good discussion about the cost trade-off with increased numbers of tests required if testing occurs prior to metastatic disease.	Limitations of the model were not discussed
Source of funding (23)	1	Yes	Merck Sereno	
Conflict of interest (24)	1	Yes	No other interests declared	

Westwood et al. (2014)[86] was a health technology assessment report. Chapter 4 included the assessment of cost-effectiveness. Several the results of variables had been removed for commercial in confidence purposes, and this had an impact on the checklist.

Table 116: CHEERS checklist for Westwood et al. (2014)[86]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	Cover page	Yes	KRAS mutation testing of tumours in adults with metastatic colorectal cancer: a systematic review and cost-effectiveness analysis	
Abstract (2)	XVII XIX to XXII	Yes	There was a plain English summary and a structured abstract	
Background (3)	Chapter 2	Yes	Chapter 2 contained the background	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Target population (4)	Chapter 2	Yes	Target was adults with CRC in which metastasis were confined to the liver and unresectable, and may become resectable after treatment	
Setting (5)		Yes	NHS	
Perspective (6)		Yes	Health system	
Comparators (7)		Yes	Comparison of different tests	
Time horizon (8)	Page 42	Yes	Twenty-three years	
Discount rate (9)	Page 52	Yes	A discount rate of 3.5% was used	
Choice of health outcomes (10)		Yes	Quality adjusted life years	
Measurement of effectiveness (11)		No	Several the measurements of modelled effectiveness had been removed.	These had been removed for commercial in confidence purposes
Preference based outcomes (12)		Yes		
Estimation of resources (13)		No	Various resource costs were missing	These were missing for commercial in confidence reasons
Currency (14)		Yes		
Choice of model (15)	Page 41-42	Yes	A decision analytic approach was used, linking test performance to outcomes. The test performance was a decision tree and the clinical outcomes a Markov model	
Assumptions (16)	Chapter 4	Yes		
Analytic methods (17)	Chapter 4	Yes		
Study parameter (18)		Yes		
Incremental (19)	Table 22	Yes		
Characterising uncertainty (20)	52	Yes	A PSA of 5 000 iterations was used	
Characterising heterogeneity (21)		Yes		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Discussion (22)	Chapter 5	Yes		
Source of funding (23)	XXII	Yes	Funding for this study was provided by the health technology assessment programme of the National Institute for Health Research	
Conflict of interest (24)		No		

Table 117: CHEERS checklist for Graham et al. (2015)[150]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	619	Yes	Cost-minimization analysis of panitumumab compared with cetuximab for first-line treatment of patients with wild-type RAS metastatic colorectal cancer	
Abstract (2)	619	Yes	Structured abstract	
Background (3)	619-620	Yes		
Target population (4)	619	Yes	RAS wild type patients with metastatic CRC without prior treatment for metastatic disease	
Setting (5)	620	No		
Perspective (6)	620	Yes	United States third party payer	
Comparators (7)	621	Yes	Panitumumab and chemotherapy Cetuximab and chemotherapy	
Time horizon (8)	621	Yes	Average progression free survival in first line of therapy	
Discount rate (9)		No	Undiscounted	
Choice of health outcomes (10)		N/A		
Measurement of effectiveness (11)		N/A		
Preference based outcomes (12)		N/A		

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Estimation of resources (13)		Table 1		
Currency (14)	619	Yes	2014 United States dollars	
Choice of model (15)		Partial	Not argued why other methods would not be superior- especially around determination of average use	
Assumptions (16)	619-621	Yes		
Analytic methods (17)	619-621	Yes		
Study parameter (18)	619-621	Yes		
Incremental (19)		N/A		
Characterising uncertainty (20)		No		
Characterising heterogeneity (21)		No		
Discussion (22)	624-625	Yes		
Source of funding (23)	627	Yes		
Conflict of interest (24)	627	Yes		

Table 118: CHEERS checklist for Wen et al. (2015)[151]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Title (1)	1577	Yes	Cost-effectiveness of RAS screening before monoclonal antibodies therapy in metastatic colorectal cancer based on FIRE3 Study	
Abstract (2)	1577	Yes	Unstructured abstract	
Background (3)	1577-1578	Yes		The importance of the FIRE-3 study for this economic evaluation was highlighted
Target population (4)	1582	Yes	KRAS wild type Stage IV metastatic CRC	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Setting (5)	1579	Partial	Was defined as Chinese perspective	
Perspective (6)	1579	Yes	Was defined as Chinese perspective	Appeared to be the Chinese health system payer perspective
Comparators (7)	Figure 1	Yes	Two alternative treatment strategies and two alternative screening strategies. Screening with KRAS or RAS and treatment with bevacizumab or cetuximab	
Time horizon (8)	1583	Yes	Ten-year time horizon	
Discount rate (9)	1583	Yes	3% discount rate was used	
Choice of health outcomes (10)	1583	Yes	Life months saved	
Measurement of effectiveness (11)	1578	Yes	Based on extrapolation of the FIRE-3 study results	
Preference based outcomes (12)	1583	Yes	Utility weights based on previously published studies. Quality adjusted life months	
Estimation of resources (13)	1579	Partial	The broad cost categories were discussed but the details were missing	
Currency (14)	1583	Yes	2014 was the base year, USD was the base currency	
Choice of model (15)	1583	Partial	The benefits of the Markov model were not discussed	
Assumptions (16)	1582-1583	Partial	The assumptions about the non-RAS participants did not seem to be included in the RAS alternative	
Analytic methods (17)	1582-1583 Figure 1	Yes		
Study parameter (18)		No	The ranges used in the evaluations were not present	
Incremental (19)	1579 Figure 2	Yes		
Characterising uncertainty (20)	Figure 4 and Figure 5	Yes	One-way and probabilistic sensitivity analysis	
Characterising heterogeneity (21)		No	Apart from the KRAS and RAS there was no heterogeneity in the model	

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result	Comment
Discussion (22)	1581-1582	Yes	The fact that the results were not based on patient level data and this is a potential weakness was acknowledged	
Source of funding (23)	1583	Yes	No funding	
Conflict of interest (24)	1583	Yes	No conflict of interest	

Table 119: Economic evaluations of cetuximab as the first line of therapy

Study	Asseburg et al. (2011)[144]	Lawrence et al. (2013)[148]	Barone et al. (2014)[149]
Year of publication	2011	2013	2014
Place in therapy	First line	First line	First line
Type	Journal	Journal	Journal
Economic evaluation type	Cost-effectiveness	Cost-utility	Cost-utility
Exact population	Metastatic CRC limited to the liver with no KRAS mutation	First line treatment with no KRAS mutation	First line treatment with no KRAS mutation in patients with previous resection
Cetuximab treatment	Cetuximab with FOLFIRI	Cetuximab with FOLFIRI	Cetuximab with FOLFIRI Cetuximab with FOLFOX
Alternatives	Bevacizumab with FOLFOX	Bevacizumab with FOLFOX Panitumumab with FOLFOX BSC	Bevacizumab with FOLFOX FOLFOX FOLFIRI
KRAS testing included	Yes	Yes	Yes
Perspective	Health Services Payer	Health Services Payer	Health Services Payer
Country	Germany	Canada	Italy
Outcomes	Indirect analysis of trials	State transition probabilities	Not directly included
Method of modelling	Decision analysis including healed state	Markov Model	Not directly included
Specific trial used	CRYSTAL	CRYSTAL	Not directly included

Study	Asseburg et al. (2011)[144]	Lawrence et al. (2013)[148]	Barone et al. (2014)[149]
Method of extrapolation	Weibull	Least squares	Not directly included
Pharmaceutical Use	Expert	Expert	Expert
Adverse events	Costs- note very high rate of perforation in bevacizumab group	Costs only	Not directly included
Outcome	Life years gained	QALY	QALY
Time Horizon	5 years	10 years	Not stated
Assumed to be lifelong	No- there existed a healed state	Yes	Not stated
Discounting	5%	5%	Not stated
Sensitivity analysis	Yes, demonstrated	Yes, demonstrated	No
Source of utility	N/A	0.95 pre-progression 0.575 post-progression Petrou & Campbell (1997)[45]	Not stated
Total QALY for cetuximab	N/A	1.86	2.92
Total Cost of cetuximab arm in AUD$ (2011/12)	$193 375	$206 741	$57 801
Acquisition cost cetuximab/Total Cost	N/A	N/A	N/A
Incremental QALY	N/A	0.51	0.91
Incremental cetuximab cost-effectiveness	$29 537 (over bevacizumab)	$313 908 (over BSC)	$25 603 (Over BSC)
Advice	Cost-effective intervention	Bevacizumab is cost-effective compared to cetuximab	Cost-effective

Economic evaluations involving treatment sequences

Wong et al. (2009),[1] Rautenberg et al. (2014)[2] and Riesco-Martinez et al. (2016)[4] were all discussed and had a quality review in Section 3.1 and Appendix B.

Wong et al. (2009)[1]

Wong et al. (2009)[1] constructed a treatment sequence from individual lines of therapy. Best supportive care was counted as a line of therapy and up to four lines of therapy were given. No KRAS stratification was included. A Markov model was used, progression and toxicity were included as reasons to change therapy. It did not appear that progression or toxicity would result in withdrawal of treatment and therefore, death excepted, all patients received all the modelled therapies.

Cetuximab was only included in the third line of therapy and therefore there was no modelling of cetuximab in different lines of therapy. Therefore, Wong et al. (2009)[1] could be considered in the group of later lines of therapy, where cetuximab is assessed as an incremental therapy in the third line of therapy.

Wong et al. (2009)[1] is also discussed in Economic evaluations of multiple lines of therapy in oncology.

Behl et al. (2012)[125]

Behl et al. (2012)[125] constructed a multi-sequence treatment model were the arms differed in the inclusion of cetuximab and the screening tests required for access to anti-EGFR treatment. The screening tests were for KRAS and BRAF mutations. Four alternatives were compared; no EGFR treatment (without screening), EGFR treatment with KRAS mutation screening, EGFR treatment with KRAS and BRAF mutation screening or EGFR treatment without screening. All the alternatives included treatment using chemotherapy, bevacizumab, radiotherapy and best supportive care.

A Markov model was constructed that included multiple treatments. There was no adjustment for the protocols occurring in different lines of therapy. That is, there was no adjustment of the transition probabilities based on an ordering of the potentially available treatments. The model also included the possibility of conversion of CRC to a potentially resectable form. The improvements in outcomes were based on improvement in resections. The incremental cost-effectiveness ratio for treatments with EGFR compared to treatment without EGFR treatments were high (greater than USD $600 000).

Rautenberg et al. (2014)[2]

Rautenberg et al. (2014)[2] included costs and outcomes of the different lines of therapy, all including monoclonal antibodies, including cetuximab (as well as panitumumab and bevacizumab). It was not clear how the issue of KRAS mutation was dealt with as data from both selected and unselected trials with respect to KRAS were used in the modelling. The introduction suggested that cetuximab was indicated for the treatment of KRAS wild type patients.

Median survival times were used, and key references were used to estimate the progression free survival for alternative protocols in each line of therapy. This approach assumes that all participants will receive all lines of therapy. In this case this assumption implies that no deaths or toxicity will occur in an initial line of therapy and thus limit the use of subsequent therapies. While there can be differences in the effectiveness in different lines of therapy, the biological plausibility of these may be questionable. For example, panitumumab (another anti-EGFR agent) is estimated to be more effective in the third line of therapy (8 months) rather than in the second line of therapy (5.9 months). Similarly, cetuximab and irinotecan were compared in the second line (4 months) to the third line (5.4 months).

No incremental analysis was conducted as part of the paper so one was constructed using the results included. The results were ordered in terms of when the anti-EGFR treatments were used, in the first line, in the second line and in the third line. The most effective regime was using anti-EGFR therapies in the third line (partly explained by the superior performance of panitumumab in the third line).

It is worth pointing out that the trial used for the construction of the second line estimate for cetuximab was Sobrero et al. (2008)[120] (EPIC) and the four months of survival refers to treatment of an unselected population with regards to KRAS. For third line use of cetuximab, an observational cohort from Denmark was used.[121] The possibility that selection bias has produced some of the differences between these two groups must be considered. However, in both cases the use of an unselected population with respect to KRAS status is inappropriate. Retrospective analysis of the EPIC trial found that PFS was longer in the wild type group but only 25% of participants provided tissue for KRAS testing.[19] To complicate matters further the wild type estimates from C.O.17 were also used in the evaluation of cetuximab in the third line.

The combination of unselected and selected population with regard to KRAS status and the combination of observational and RCT data without adjustment must be considered as weaknesses in the modelling. Rautenberg et al. (2014)[2] is also discussed in Economic evaluations of multiple lines of therapy in oncology.

Riesco-Martinez et al. (2016)[4]

Riesco-Martinez et al. (2016)[4] compared a variety of different alternatives in which all patients received an EGFR (either panitumumab or cetuximab) and bevacizumab. The EGFR treatment was either given in the first line of therapy or the third line of therapy. The median progression free survival was derived was different trials and suggested that the progression free survival from treatment with cetuximab was longer in the first line of therapy than in the third line of therapy.

Riesco-Martinez et al. (2016)[4] is also discussed in Economic evaluations of multiple lines of therapy in oncology.

Table 120: CHEERS checklist for Behl et al. (2012)[125]

CHEERS checklist (Item Number)	Location in paper (page)	Satisfactory or not	Actual result
Title (1)	1785	Yes	Cost-Effectiveness Analysis of Screening for KRAS and BRAF Mutations in Metastatic Colorectal Cancer
Abstract (2)	1785	Yes	Structured abstract
Background (3)	1785-1786	Yes	Discussion of the background of the potential for down-staging
Target population (4)	1786	Yes	Metastatic colorectal cancer
Setting (5)	1786	Yes	United States
Perspective (6)		No	Appears to be health system based on costs
Comparators (7)	1786	Yes	Four alternatives were compared. no anti-EGFR treatment anti-EGFR treatment without screening anti-EGFR treatment with KRAS screening anti-EGFR treatment with KRAS and BRAF screening
Time horizon (8)	1789	Yes	Ten years
Discount rate (9)	1789	Yes	3%
Choice of health outcomes (10)	1786	Yes	
Measurement of effectiveness (11)		No	From randomised controlled trials but which ones was not described
Preference based outcomes (12)	N/A	No	
Estimation of resources (13)	1789	Yes	Table 1
Currency (14)	1789	Yes	2010 United States dollars
Choice of model (15)	Figure 1	Partial	Markov modelling
Assumptions (16)	1788-1789	Yes	
Analytic methods (17)	1787-1788	Yes	
Study parameter (18)	Table 1	No	Several parameters were missing especially around the effectiveness
Incremental (19)	Table 2 Figure 2	Yes	
Characterising uncertainty (20)	Figure 3 Figure 4	Yes	One-way and probabilistic sensitivity analysis
Characterising heterogeneity (21)	N/A	No	
Discussion (22)	1792-1793	Yes	An important component of the discussion was the implications of not including utility weights.
Source of funding (23)	1794-1795	Yes	
Conflict of interest (24)	1795	Yes	

Table 121: Economic evaluations of cetuximab involving treatment sequences

Study	Wong et al. (2009)[1]	Behl et al. (2012)[125]	Rautenberg et al. (2014)[2]	Riesco-Martinez et al. (2016)[4]
Year of publication	2009	2012	2014	2016
Place in therapy	Entire treatment sequence	Entire treatment sequence	Entire treatment sequence	Entire treatment sequence
Type	Journal	Journal	Journal	Journal
Economic evaluation type	Cost-effectiveness	Cost-effectiveness	Cost-effectiveness	Cost-utility analysis
Exact population	All patients with metastatic CRC	All patients with metastatic CRC	All patients with metastatic CRC	Unresectable wild type KRAS metastatic CRC
Cetuximab treatment	Cetuximab in third line Cetuximab and irinotecan in third line	Cetuximab (no testing) Cetuximab (KRAS testing) Cetuximab (KRAS and BRAF)	Cetuximab in all lines of therapy	EGFR in first line EGFR in third line with chemotherapy EGFR in third line without chemotherapy
Alternatives	No others in third line	BSC- which included all other therapies	All lines of therapy had a monoclonal antibody included	No alternatives without
KRAS testing included	No	Yes	No	No
Perspective	Health Services Payer	Health Services Payer	Health Services Payer	Health Services payer
Country	USA	USA	Germany	Canada
Outcomes	Trial	Trial	Trial	Trail
Method of modelling	Markov model	Microsimulation of Markov model	Additive	Markov model
Specific trial used	Cunningham 2004	Nil	Multiple	Multiple
Method of extrapolation	Modelling	Modelling	Additive	Modelling
Pharmaceutical Use calculations	Expert	Expert	Expert	Obtained from pharmacy
Adverse events	No	No	No	Yes
Outcome	Months of life	Years of life	Years of life	QALY
Time Horizon	No stated	10 years	N/A	5 years

Study	Wong et al. (2009)[1]	Behl et al. (2012)[125]	Rautenberg et al. (2014)[2]	Riesco-Martinez et al. (2016)[4]
Assumed to be lifelong	Yes	Yes	No	No
Discounting	3%	No	No	5%
Sensitivity analysis	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated	Yes, demonstrated
Source of utility	N/A	N/A	N/A	Primary data collection
Total QALY for cetuximab	N/A	N/A	N/A	N/A
Total Cost of cetuximab arm in 2011/12 $AUS	$171 149 to $329 031	$87,455-$100 679	$54 437 (Cet + I in second line)	$165 662 (EGFR in third line)
Acquisition cost cetuximab/Total Cost	N/A	N/A	N/A	N/A
Incremental QALY	N/A	N/A	N/A	N/A
Incremental cetuximab cost-effectiveness	$54 856	Approx. $1 000 000	$225 955 per year in third line	N/A
Advice	Treatment with the most effective regime comes with high incremental costs	ICER above generally accepted cost-effectiveness ratio	Reasonable trade-off	Delaying use of anti-EGFR treatment was the most cost-effective strategy

Abbreviations: Cet+I: cetuximab and irinotecan; CRC: colorectal cancer; EGFR: epithelial growth factor receptor; KRAS: Kristen rat sarcoma; QALY: quality adjusted life years; N/A: not applicable; US(A): United States of America

Appendix D: Econometric output

The results of 14 models are presented using ordinary least squares regression (both with an unaltered cost and a logged cost as the dependent variable. Four models are present with random effects and fixed effects modelling techniques.

Table 122: Model specifications for the econometric analysis

	Model specification
Model number	**Independent variables**
1	Lines of therapy, death, year, centre, month, comorbidity, age, cancer
2	Model 1 with interaction between month and comorbidity
3	Model 1 with year of recruitment
4	Model 2 with year of recruitment
5	Model 1 with months to fourth power
6	Model 1 with months to fifth power
7	Model 3 with month to fourth power
8	Model 2 with month to fourth power
9	Model 4 with month to fourth power
10	Model 3 with month to fifth power
11	Model 2 with month to fifth power
12	Model 4 with month to fifth power
13	Model 1 with lagged cost for one period
14	Model 9 with lagged costs for one period

Table 123: Unaltered costs ordinary least squares models 1 to 7

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Second line of therapy	$1 469 ($981 to $1 958)	$1 493 ($1 006 to $1 980)	$1 575 ($1 086 to $2 064)	$1 593 ($1 106 to $2 081)	$1 676 ($1 191 to $2 160)	$1 676 ($1 192 to $2 160)	$1 735 ($1 252 to $2 219)
Third line of therapy	$2 108 ($1 156 to $3 059)	$2 098 ($1 144 to $3 052)	$2 224 ($1 277 to $3 171)	$2 211 ($1 260 to $3 161)	$2 078 ($1 111 to $3 044)	$2 060 ($1 089 to $3 032)	$2 144 ($1 180 to $3 109)
Fourth line of therapy	$2 954 ($200 to $5 708)	$2 781 ($61 to $5 501)	$3 048 ($314 to $5 782)	$2 879 ($176 to $5 582)	$1 840 (-$622 to $4 303)	$1 837 (-$632 to $4 307)	$1 894 (-$560 to $4 349)
Fifth line of therapy	$5 240 (-$3 328 to $13 808)	$4 476 (-$3 941 to $12 892)	$4 988 (-$3 578 to $13 555)	$4 272 (-$4 147 to $12 690)	$2 787 (-$5 402 to $10 977)	$2 849 (-$5 337 to $11 035)	$2 634 (-$5 555 to $10 824)
Months	-$110 (-$130 to -$89)	-$142 (-$168 to -$115)	-$106 (-$126 to -$86)	-$137 (-$163 to -$110)	-$810 (-$1 014 to -$606)	-$923 (-$1 276 to -$570)	-$779 (-$991 to -$568)
Months squared	-	-	-	-	$39 ($22 to $55)	$54 ($13 to $95)	$37 ($20 to $53)
Months cubed	-	-	-	-	-$1 (-$1 to $0)	-$2 (-$3 to $0)	-$1 (-$1 to $0)
Months to the power of 4	-	-	-	-	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)
Months to the power of 5	-	-	-	-	-	$0 ($0 to $0)	-
Death	$2 060 ($1 207 to $2 912)	$2 090 ($1 237 to $2 942)	$2 291 ($1 424 to $3 157)	$2 309 ($1 442 to $3 177)	$2 321 ($1 465 to $3 177)	$2 318 ($1 462 to $3 174)	$2 462 ($1 591 to $3 334)
Death month	$2 182 (-$54 to $4 418)	$2 059 (-$149 to $4 268)	$2 157 (-$74 to $4 388)	$2 041 (-$163 to $4 246)	$2 011 (-$179 to $4 201)	$2 023 (-$168 to $4 214)	$2 002 (-$187 to $4 191)
Comorbidity	$175 ($109 to $240)	$54 (-$55 to $163)	$190 ($123 to $256)	$74 (-$37 to $185)	$235 ($170 to $299)	$235 ($171 to $300)	$243 ($177 to $308)
2007	$303 (-$1 379 to $1 985)	$537 (-$1 138 to $2 213)	$134 (-$1 543 to $1 811)	$364 (-$1 308 to $2 035)	$1 571 (-$106 to $3 248)	$1 596 (-$83 to $3 275)	$1 432 (-$250 to $3 113)

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
2008	$485 (-$1 177 to $2 147)	$718 (-$940 to $2 377)	$323 (-$1 337 to $1 984)	$552 (-$1 106 to $2 210)	$1 705 ($45 to $3 365)	$1 713 ($52 to $3 373)	$1 577 (-$88 to $3 242)
2009	$992 (-$551 to $2 534)	$1 124 (-$410 to $2 657)	$801 (-$744 to $2 346)	$934 (-$603 to $2 472)	$1 652 ($125 to $3 178)	$1 676 ($144 to $3 207)	$1 513 (-$25 to $3 050)
2010	$720 (-$828 to $2 267)	$914 (-$623 to $2 451)	$79 (-$1 499 to $1 658)	$290 (-$1 283 to $1 863)	$1 973 ($435 to $3 511)	$1 990 ($450 to $3 529)	$1 532 (-$65 to $3 129)
2011	$311 (-$1 339 to $1 962)	$535 (-$1 110 to $2 181)	-$779 (-$2 525 to $968)	-$522 (-$2 271 to $1 227)	$2 012 ($340 to $3 684)	$1 994 ($323 to $3 665)	$1 288 (-$520 to $3 096)
2012	-$1 136 (-$2 840 to $568)	-$1 139 (-$2 827 to $550)	-$2 297 (-$4 116 to -$478)	-$2 252 (-$4 059 to -$445)	-$683 (-$2 365 to $999)	-$608 (-$2 302 to $1 085)	-$1 413 (-$3 222 to $396)
2013	$621 (-$1 346 to $2 588)	$182 (-$1 779 to $2 143)	-$625 (-$2 716 to $1 466)	-$992 (-$3 068 to $1 084)	-$219 (-$2 183 to $1 745)	-$166 (-$2 125 to $1 794)	-$1 011 (-$3 124 to $1 103)
2014	$2 077 (-$1 017 to $5 172)	$1 102 (-$2 004 to $4 207)	$665 (-$2 535 to $3 866)	-$206 (-$3 403 to $2 991)	$365 (-$2 689 to $3 419)	$177 (-$2 895 to $3 248)	-$552 (-$3 747 to $2 643)
Age 45 to 64	-$459 (-$1 129 to $211)	-$414 (-$1 089 to $261)	-$406 (-$1 069 to $257)	-$366 (-$1 035 to $303)	-$344 (-$1 017 to $328)	-$353 (-$1 026 to $319)	-$311 (-$978 to $356)
Age 65+	-$1 327 (-$2 105 to -$549)	-$1 245 (-$2 031 to -$459)	-$1 359 (-$2 138 to -$580)	-$1 279 (-$2 067 to -$492)	-$1 298 (-$2 074 to -$522)	-$1 313 (-$2 091 to -$536)	-$1 318 (-$2 096 to -$539)
Centre A	-$237 (-$1 631 to $1 156)	-$321 (-$1 721 to $1 079)	-$529 (-$1 935 to $876)	-$597 (-$2 008 to $815)	-$218 (-$1 604 to $1 168)	-$215 (-$1 599 to $1 168)	-$397 (-$1 792 to $998)
Centre B	$3 657 ($1 902 to $5 413)	$3 569 ($1 805 to $5 334)	$3 561 ($1 806 to $5 315)	$3 481 ($1 718 to $5 243)	$3 608 ($1 850 to $5 366)	$3 606 ($1 848 to $5 364)	$3 547 ($1 791 to $5 303)
Centre C	$2 820 ($1 636 to $4 005)	$2 791 ($1 603 to $3 978)	$2 446 ($1 257 to $3 636)	$2 434 ($1 240 to $3 628)	$2 745 ($1 592 to $3 899)	$2 744 ($1 593 to $3 895)	$2 513 ($1 353 to $3 672)
Centre D	$822 (-$421 to $2 066)	$652 (-$602 to $1 905)	$528 (-$710 to $1 766)	$378 (-$869 to $1 625)	$583 (-$634 to $1 801)	$582 (-$633 to $1 797)	$403 (-$809 to $1 615)
Centre E	$1 493 ($123 to $2 863)	$1 381 ($13 to $2 749)	$908 (-$497 to $2 314)	$826 (-$578 to $2 229)	$1 235 (-$114 to $2 583)	$1 233 (-$113 to $2 580)	$874 (-$506 to $2 255)
Centre F	$3 027 ($1 803 to $4 250)	$2 966 ($1 741 to $4 191)	$2 531 ($1 294 to $3 769)	$2 494 ($1 254 to $3 733)	$2 814 ($1 616 to $4 011)	$2 813 ($1 618 to $4 009)	$2 506 ($1 296 to $3 715)

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Centre G	$1 969 ($616 to $3 322)	$1 819 ($470 to $3 169)	$1 632 ($256 to $3 008)	$1 503 ($132 to $2 875)	$1 669 ($344 to $2 994)	$1 671 ($348 to $2 994)	$1 464 ($116 to $2 812)
Centre H	$680 (-$507 to $1 868)	$643 (-$546 to $1 833)	$391 (-$800 to $1 582)	$367 (-$826 to $1 561)	$592 (-$566 to $1 749)	$593 (-$562 to $1 748)	$413 (-$748 to $1 574)
Centre I	$1 097 (-$220 to $2 415)	$1 007 (-$312 to $2 325)	$923 (-$391 to $2 237)	$844 (-$471 to $2 158)	$972 (-$312 to $2 257)	$970 (-$312 to $2 252)	$867 (-$416 to $2 150)
Centre J	$1 228 (-$43 to $2 499)	$1 104 (-$174 to $2 382)	$1 166 (-$100 to $2 431)	$1 050 (-$222 to $2 322)	$1 039 (-$205 to $2 282)	$1 048 (-$191 to $2 288)	$1 004 (-$236 to $2 245)
Centre K	$1 317 ($3 to $2 631)	$1 264 (-$47 to $2 575)	$1 048 (-$281 to $2 376)	$1 008 (-$319 to $2 335)	$1 254 (-$24 to $2 532)	$1 252 (-$23 to $2 528)	$1 086 (-$212 to $2 385)
CRC	$1 640 ($1 191 to $2 089)	$1 562 ($1 109 to $2 015)	$1 567 ($1 123 to $2 011)	$1 495 ($1 048 to $1 943)	$1 656 ($1 213 to $2 099)	$1 654 ($1 211 to $2 097)	$1 610 ($1 172 to $2 048)
NSCLC	$950 ($239 to $1 661)	$974 ($263 to $1 686)	$893 ($180 to $1 606)	$918 ($204 to $1 633)	$731 ($33 to $1 429)	$741 ($38 to $1 444)	$701 (-$1 to $1 402)
Month and comorbidity interaction	$0 (-$4 to $5)	$7 ($3 to $12)	-	$7 ($2 to $12)	-	-	-
2010 cohort	$687 ($109 to $1 266)	-	$1 034 ($466 to $1 603)	$993 ($422 to $1 563)	-	-	$654 ($69 to $1 238)
Lagged cost	-	-	-	-	-	-	-
Constant	$1 917 (-$61 to $3 896)	$2 252 ($291 to $4 212)	$2 194 ($210 to $4 177)	$2 500 ($536 to $4 464)	$3 638 ($1 654 to $5 621)	$3 837 ($1 789 to $5 885)	$3 743 ($1 760 to $5 725)
Observations	4 373	4 373	4 373	4 373	4 373	4 373	4 373

Note: The identities of the centres have been deliberated obscured, the lagged costs are expressed in natural units (not dollars)

Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Table 124: Unaltered costs ordinary least squares models 8 to 14

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
Second line of therapy	$1 676 ($1 191 to $2 160)	$1 735 ($1 252 to $2 219)	$1 737 ($1 253 to $2 221)	$1 676 ($1 192 to $2 160)	$1 737 ($1 253 to $2 221)	$1 406 ($912 to $1 900)	$1 601 ($1 107 to $2 095)
Third line of therapy	$2 078 ($1 111 to $3 044)	$2 144 ($1 180 to $3 109)	$2 126 ($1 157 to $3 095)	$2 060 ($1 088 to $3 032)	$2 126 ($1 157 to $3 095)	$1 889 ($924 to $2 855)	$1 958 ($977 to $2 938)
Fourth line of therapy	$1 839 (-$625 to $4 304)	$1 894 (-$562 to $4 350)	$1 892 (-$569 to $4 353)	$1 838 (-$632 to $4 309)	$1 894 (-$569 to $4 356)	$2 619 (-$109 to $5 347)	$1 853 (-$628 to $4 333)
Fifth line of therapy	$2 780 (-$5 407 to $10 966)	$2 632 (-$5 555 to $10 818)	$2 698 (-$5 488 to $10 885)	$2 858 (-$5 329 to $11 044)	$2 713 (-$5 473 to $10 900)	$4 231 (-$4 525 to $12 987)	$2 381 (-$6 092 to $10 855)
Months	-$810 (-$1 012 to -$607)	-$779 (-$989 to -$569)	-$900 (-$1 257 to -$543)	-$924 (-$1 277 to -$571)	-$902 (-$1 259 to -$544)	-$82 (-$103 to -$62)	-$546 (-$782 to -$311)
Months squared	$39 ($23 to $55)	$37 ($20 to $53)	$53 ($12 to $94)	$54 ($12 to $95)	$53 ($12 to $95)	-	$23 ($5 to $41)
Months cubed	-$1 (-$1 to $0)	-$1 (-$1 to $0)	-$2 (-$3 to $0)	-$2 (-$3 to $0)	-$2 (-$4 to $0)	-	$0 (-$1 to $0)
Months to the power of 4	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)	-	$0 ($0 to $0)
Months to the power of 5	-	-	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)	-	-
Death	$2 321 ($1 465 to $3 177)	$2 462 ($1 591 to $3 334)	$2 461 ($1 589 to $3 332)	$2 318 ($1 462 to $3 174)	$2 460 ($1 589 to $3 331)	$1 878 ($1 029 to $2 727)	$2 253 ($1 383 to $3 123)
Death month	$2 009 (-$169 to $4 188)	$2 002 (-$175 to $4 179)	$2 015 (-$175 to $4 205)	$2 025 (-$153 to $4 204)	$2 018 (-$159 to $4 196)	$2 050 (-$165 to $4 265)	$1 981 (-$192 to $4 153)
Comorbidity	$233 ($126 to $341)	$242 ($134 to $351)	$243 ($178 to $309)	$237 ($129 to $345)	$247 ($138 to $355)	$179 ($115 to $244)	$240 ($131 to $348)
2007	$1 573 (-$108 to $3 254)	$1 432 (-$254 to $3 118)	$1 456 (-$227 to $3 140)	$1 594 (-$89 to $3 277)	$1 453 (-$235 to $3 141)	$635 (-$1 439 to $2 709)	$1 332 (-$761 to $3 425)

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
2008	$1 707 ($43 to $3 371)	$1 577 (-$92 to $3 247)	$1 584 (-$82 to $3 249)	$1 711 ($46 to $3 375)	$1 580 (-$90 to $3 250)	$669 (-$1 397 to $2 734)	$1 413 (-$681 to $3 507)
2009	$1 653 ($123 to $3 183)	$1 513 (-$28 to $3 054)	$1 537 (-$5 to $3 078)	$1 675 ($140 to $3 209)	$1 535 (-$10 to $3 079)	$1 008 (-$948 to $2 964)	$1 300 (-$667 to $3 268)
2010	$1 974 ($434 to $3 515)	$1 533 (-$68 to $3 134)	$1 544 (-$54 to $3 143)	$1 988 ($446 to $3 531)	$1 542 (-$60 to $3 144)	$954 (-$1 009 to $2 918)	$1 327 (-$694 to $3 349)
2011	$2 013 ($339 to $3 687)	$1 288 (-$524 to $3 100)	$1 259 (-$547 to $3 065)	$1 993 ($319 to $3 666)	$1 256 (-$554 to $3 066)	$561 (-$1 482 to $2 604)	$1 017 (-$1 174 to $3 208)
2012	-$684 (-$2 366 to $998)	-$1 413 (-$3 222 to $395)	-$1 343 (-$3 163 to $478)	-$607 (-$2 301 to $1 086)	-$1 341 (-$3 161 to $479)	-$964 (-$3 054 to $1 126)	-$1 323 (-$3 519 to $873)
2013	-$224 (-$2 193 to $1 745)	-$1 012 (-$3 125 to $1 100)	-$964 (-$3 075 to $1 148)	-$160 (-$2 124 to $1 805)	-$954 (-$3 064 to $1 157)	$474 (-$1 836 to $2 785)	-$946 (-$3 416 to $1 525)
2014	$353 (-$2 708 to $3 414)	-$556 (-$3 748 to $2 636)	-$766 (-$3 974 to $2 442)	$188 (-$2 887 to $3 264)	-$746 (-$3 950 to $2 458)	$1 688 (-$1 589 to $4 965)	-$544 (-$3 979 to $2 890)
Age 45 to 64	-$344 (-$1 019 to $331)	-$311 (-$981 to $358)	-$321 (-$988 to $346)	-$354 (-$1 029 to $321)	-$322 (-$991 to $348)	-$494 (-$1 168 to $181)	-$357 (-$1 037 to $323)
Age 65+	-$1 297 (-$2 079 to -$516)	-$1 317 (-$2 101 to -$534)	-$1 334 (-$2 113 to -$555)	-$1 315 (-$2 098 to -$532)	-$1 336 (-$2 122 to -$551)	-$1 182 (-$1 978 to -$385)	-$1 179 (-$1 987 to -$371)
Centre A	-$219 (-$1 604 to $1 166)	-$398 (-$1 791 to $996)	-$397 (-$1 790 to $996)	-$214 (-$1 596 to $1 168)	-$395 (-$1 785 to $996)	-$78 (-$1 529 to $1 374)	-$192 (-$1 649 to $1 266)
Centre B	$3 607 ($1 849 to $5 364)	$3 547 ($1 791 to $5 302)	$3 544 ($1 788 to $5 300)	$3 607 ($1 851 to $5 364)	$3 546 ($1 792 to $5 301)	$3 664 ($1 815 to $5 512)	$3 656 ($1 812 to $5 500)
Centre C	$2 745 ($1 593 to $3 898)	$2 513 ($1 354 to $3 671)	$2 508 ($1 351 to $3 666)	$2 745 ($1 594 to $3 895)	$2 509 ($1 352 to $3 665)	$2 428 ($1 194 to $3 662)	$2 203 ($981 to $3 425)
Centre D	$581 (-$639 to $1 801)	$402 (-$812 to $1 616)	$399 (-$811 to $1 610)	$584 (-$633 to $1 802)	$403 (-$808 to $1 615)	$792 (-$510 to $2 094)	$468 (-$817 to $1 754)
Centre E	$1 233 (-$110 to $2 577)	$874 (-$501 to $2 249)	$868 (-$511 to $2 247)	$1 235 (-$106 to $2 576)	$870 (-$503 to $2 244)	$1 400 (-$28 to $2 828)	$915 (-$533 to $2 363)
Centre F	$2 813 ($1 618 to $4 008)	$2 506 ($1 298 to $3 713)	$2 502 ($1 294 to $3 709)	$2 814 ($1 621 to $4 007)	$2 503 ($1 297 to $3 708)	$2 673 ($1 389 to $3 956)	$2 267 ($989 to $3 544)

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
Centre G	$1 668 ($350 to $2 986)	$1 463 ($123 to $2 804)	$1 463 ($117 to $2 809)	$1 673 ($358 to $2 988)	$1 466 ($128 to $2 804)	$1 758 ($344 to $3 171)	$1 397 (-$22 to $2 816)
Centre H	$591 (-$565 to $1 747)	$413 (-$747 to $1 572)	$412 (-$747 to $1 571)	$594 (-$559 to $1 747)	$413 (-$744 to $1 570)	$629 (-$611 to $1 868)	$413 (-$814 to $1 641)
Centre I	$971 (-$310 to $2 252)	$867 (-$413 to $2 146)	$863 (-$417 to $2 144)	$971 (-$307 to $2 250)	$866 (-$411 to $2 142)	$868 (-$468 to $2 204)	$716 (-$605 to $2 038)
Centre J	$1 037 (-$206 to $2 280)	$1 004 (-$236 to $2 244)	$1 014 (-$222 to $2 251)	$1 050 (-$189 to $2 289)	$1 017 (-$218 to $2 253)	$1 124 (-$199 to $2 448)	$993 (-$313 to $2 299)
Centre K	$1 253 (-$20 to $2 527)	$1 086 (-$208 to $2 380)	$1 082 (-$213 to $2 377)	$1 253 (-$18 to $2 524)	$1 083 (-$208 to $2 374)	$971 (-$298 to $2 241)	$784 (-$473 to $2 041)
CRC	$1 655 ($1 208 to $2 102)	$1 610 ($1 167 to $2 052)	$1 608 ($1 169 to $2 046)	$1 656 ($1 208 to $2 103)	$1 610 ($1 168 to $2 052)	$1 510 ($1 048 to $1 971)	$1 514 ($1 057 to $1 971)
NSCLC	$732 ($31 to $1 433)	$701 (-$3 to $1 405)	$711 ($5 to $1 416)	$740 ($35 to $1 445)	$710 ($2 to $1 417)	$651 ($84 to $1 219)	$473 (-$93 to $1 040)
Month and comorbidity interaction	$0 (-$4 to $5)	$0 (-$5 to $5)	-	$0 (-$5 to $4)	$0 (-$5 to $4)	-	-$1 (-$5 to $4)
2010 cohort	-	$654 ($68 to $1 239)	$662 ($78 to $1 246)	-	$663 ($78 to $1 247)	-	$701 ($108 to $1 293)
Lagged cost	-	-	-	-	-	.114 (.071 to .157)	.094 (.052 to .137)
Constant	$3 640 ($1 660 to $5 621)	$3 743 ($1 765 to $5 722)	$3 957 ($1 911 to $6 004)	$3 835 ($1 790 to $5 880)	$3 954 ($1 911 to $5 997)	$1 025 (-$1 321 to $3 372)	$2 643 ($213 to $5 072)
Observations	4 373	4 373	4 373	4 373	4 373	4 145	4 145

Note: The identities of the centres have been deliberated obscured, the lagged costs are expressed in natural units (not dollars)
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Table 125: Logged costs ordinary least squares models 1 to 7

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Second line of therapy	.754 (.628 to .880)	.765 (.640 to .891)	.784 (.658 to .910)	.794 (.668 to .920)	.846 (.723 to .970)	.845 (.722 to .969)	.859 (.735 to .983)
Third line of therapy	.926 (.678 to 1.174)	.919 (.671 to 1.168)	.955 (.709 to 1.20)	.947 (.70 to 1.193)	.910 (.666 to 1.154)	.898 (.653 to 1.143)	.922 (.679 to 1.166)
Fourth line of therapy	1.127 (.525 to 1.729)	1.053 (.464 to 1.642)	1.150 (.555 to 1.745)	1.077 (.493 to 1.660)	.637 (.046 to 1.228)	.633 (.035 to 1.232)	.647 (.058 to 1.237)
Fifth line of therapy	1.235 (-.388 to 2.859)	.918 (-.606 to 2.443)	1.166 (-.460 to 2.791)	.861 (-.667 to 2.388)	.201 (-1.223 to 1.624)	.239 (-1.185 to 1.663)	.168 (-1.255 to 1.591)
Months	-.043 (-.048 to -.037)	-.056 (-.063 to -.049)	-.042 (-.047 to -.036)	-.055 (-.062 to -.047)	-.290 (-.330 to -.251)	-.366 (-.431 to -.301)	-.284 (-.325 to -.244)
Months squared	-	-	-	-	.013 (.009 to .016)	.023 (.015 to .031)	.012 (.009 to .016)
Months cubed	-	-	-	-	.0 (.0 to .0)	-.001 (-.001 to .0)	.0 (.0 to .0)
Months to the power of 4	-	-	-	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
Months to the power of 5	-	-	-	-	-	.0 (.0 to .0)	-
Death	.231 (.025 to .436)	.244 (.040 to .449)	.293 (.084 to .501)	.303 (.096 to .510)	.342 (.139 to .546)	.340 (.137 to .544)	.371 (.165 to .578)
Death month	.275 (-.164 to .714)	.221 (-.214 to .657)	.266 (-.171 to .703)	.214 (-.220 to .648)	.209 (-.219 to .637)	.217 (-.212 to .646)	.206 (-.222 to .633)
Comorbidity	.044 (.029 to .059)	-.004 (-.027 to .018)	.048 (.033 to .063)	.001 (-.022 to .024)	.070 (.055 to .085)	.070 (.055 to .085)	.072 (.056 to .087)
2007	-.267 (-.830 to .296)	-.170 (-.722 to .383)	-.316 (-.877 to .244)	-.219 (-.770 to .332)	.210 (-.303 to .723)	.226 (-.285 to .737)	.180 (-.334 to .694)

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
2008	-.280 (-.821 to .261)	-.189 (-.719 to .342)	-.325 (-.865 to .215)	-.233 (-.763 to .296)	.194 (-.294 to .682)	.199 (-.287 to .685)	.167 (-.322 to .656)
2009	.130 (-.388 to .648)	.180 (-.325 to .686)	.078 (-.438 to .595)	.130 (-.374 to .634)	.373 (-.091 to .838)	.389 (-.074 to .851)	.345 (-.121 to .811)
2010	.027 (-.494 to .548)	.102 (-.407 to .611)	-.143 (-.672 to .385)	-.062 (-.579 to .456)	.491 (.021 to .961)	.502 (.034 to .969)	.402 (-.080 to .885)
2011	-.284 (-.827 to .259)	-.195 (-.727 to .338)	-.575 (-1.138 to -.012)	-.473 (-1.026 to .080)	.395 (-.102 to .892)	.380 (-.114 to .875)	.248 (-.276 to .772)
2012	-.781 (-1.372 to -.190)	-.806 (-1.385 to -.228)	-1.094 (-1.709 to -.479)	-1.102 (-1.705 to -.499)	-.613 (-1.153 to -.073)	-.563 (-1.101 to -.025)	-.762 (-1.328 to -.196)
2013	-.068 (-.695 to .558)	-.263 (-.885 to .360)	-.407 (-1.057 to .243)	-.579 (-1.223 to .066)	-.516 (-1.094 to .061)	-.478 (-1.053 to .097)	-.678 (-1.280 to -.077)
2014	.471 (-.302 to 1.245)	.066 (-.715 to .846)	.090 (-.710 to .889)	-.285 (-1.088 to .519)	-.375 (-1.105 to .355)	-.502 (-1.242 to .239)	-.561 (-1.320 to .197)
Age 45 to 64	-.191 (-.326 to -.056)	-.171 (-.307 to -.036)	-.175 (-.309 to -.040)	-.157 (-.292 to -.022)	-.147 (-.275 to -.020)	-.153 (-.280 to -.025)	-.140 (-.267 to -.012)
Age 65+	-.528 (-.690 to -.366)	-.493 (-.656 to -.331)	-.535 (-.697 to -.374)	-.502 (-.663 to -.340)	-.524 (-.677 to -.370)	-.532 (-.686 to -.379)	-.527 (-.680 to -.374)
Centre A	-.217 (-.590 to .156)	-.253 (-.629 to .123)	-.295 (-.669 to .079)	-.326 (-.703 to .052)	-.205 (-.566 to .157)	-.202 (-.562 to .158)	-.241 (-.605 to .123)
Centre B	.994 (.672 to 1.316)	.956 (.628 to 1.283)	.968 (.646 to 1.290)	.932 (.605 to 1.260)	.962 (.646 to 1.277)	.961 (.646 to 1.275)	.950 (.634 to 1.265)
Centre C	.926 (.653 to 1.198)	.912 (.634 to 1.189)	.827 (.550 to 1.103)	.818 (.537 to 1.099)	.896 (.639 to 1.153)	.895 (.641 to 1.150)	.849 (.588 to 1.111)
Centre D	.174 (-.117 to .466)	.105 (-.192 to .403)	.096 (-.198 to .389)	.033 (-.267 to .332)	.073 (-.203 to .348)	.073 (-.20 to .347)	.036 (-.242 to .315)
Centre E	.182 (-.169 to .533)	.134 (-.220 to .489)	.025 (-.334 to .383)	-.014 (-.376 to .348)	.067 (-.267 to .401)	.069 (-.263 to .401)	-.007 (-.349 to .336)
Centre F	.978 (.699 to 1.257)	.952 (.669 to 1.236)	.844 (.559 to 1.129)	.825 (.536 to 1.114)	.884 (.621 to 1.147)	.886 (.624 to 1.147)	.821 (.551 to 1.091)

Model	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Centre G	.636 (.314 to .958)	.571 (.244 to .897)	.544 (.218 to .871)	.486 (.155 to .816)	.503 (.197 to .809)	.505 (.201 to .809)	.461 (.150 to .772)
Centre H	.145 (-.149 to .439)	.132 (-.166 to .429)	.075 (-.220 to .370)	.065 (-.234 to .363)	.116 (-.161 to .392)	.116 (-.158 to .391)	.082 (-.196 to .361)
Centre I	.144 (-.188 to .477)	.105 (-.230 to .441)	.098 (-.235 to .431)	.063 (-.273 to .399)	.098 (-.216 to .412)	.098 (-.215 to .410)	.077 (-.239 to .393)
Centre J	.215 (-.097 to .528)	.163 (-.155 to .482)	.199 (-.113 to .511)	.149 (-.168 to .467)	.139 (-.156 to .434)	.146 (-.147 to .440)	.132 (-.163 to .427)
Centre K	.178 (-.124 to .479)	.154 (-.151 to .460)	.106 (-.198 to .409)	.087 (-.221 to .394)	.144 (-.139 to .428)	.144 (-.137 to .426)	.110 (-.176 to .397)
CRC	.338 (.237 to .440)	.302 (.20 to .405)	.319 (.216 to .422)	.285 (.181 to .388)	.345 (.248 to .443)	.344 (.247 to .442)	.336 (.237 to .435)
NSCLC	.236 (.080 to .392)	.243 (.087 to .398)	.220 (.064 to .377)	.227 (.072 to .383)	.142 (-.010 to .294)	.150 (-.002 to .301)	.136 (-.016 to .288)
Month and comorbidity interaction	.0 (-.001 to .001)	.003 (.002 to .004)	-	.003 (.002 to .004)	-	-	-
2010 cohort	.147 (.011 to .284)	-	.277 (.136 to .417)	.262 (.123 to .402)	-	-	.133 (-.003 to .268)
Lagged cost	-	-	-	-	-	-	-
Constant	7.374 (6.786 to 7.963)	7.513 (6.932 to 8.094)	7.446 (6.858 to 8.033)	7.577 (6.997 to 8.157)	7.996 (7.462 to 8.531)	8.128 (7.592 to 8.664)	8.017 (7.482 to 8.552)
Observations	4 201	4 201	4 201	4 201	4 201	4 201	4 201

Note: The identities of the centres have been deliberated obscured
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Table 126: Logged costs ordinary least squares models 8 to 14

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
Second line of therapy	.847 (.723 to .970)	.860 (.736 to .984)	.859 (.735 to .983)	.845 (.722 to .969)	.859 (.735 to .983)	.504 (.378 to .629)	.596 (.469 to .722)
Third line of therapy	.910 (.666 to 1.154)	.922 (.679 to 1.165)	.911 (.667 to 1.155)	.898 (.653 to 1.143)	.911 (.667 to 1.155)	.527 (.286 to .767)	.582 (.341 to .822)
Fourth line of therapy	.635 (.044 to 1.226)	.645 (.056 to 1.235)	.644 (.048 to 1.241)	.633 (.034 to 1.232)	.644 (.047 to 1.241)	.685 (.094 to 1.275)	.462 (-.129 to 1.052)
Fifth line of therapy	.186 (-1.240 to 1.613)	.155 (-1.272 to 1.581)	.206 (-1.218 to 1.630)	.236 (-1.192 to 1.664)	.204 (-1.225 to 1.632)	.460 (-1.234 to 2.155)	-.084 (-1.639 to 1.470)
Months	-.290 (-.329 to -.250)	-.284 (-.324 to -.243)	-.362 (-.427 to -.296)	-.366 (-.432 to -.30)	-.362 (-.428 to -.295)	-.024 (-.029 to -.018)	-.194 (-.243 to -.145)
Months squared	.013 (.009 to .016)	.012 (.009 to .016)	.023 (.015 to .031)	.023 (.014 to .031)	.023 (.014 to .031)	-	.009 (.005 to .012)
Months cubed	.0 (.0 to .0)	.0 (.0 to .0)	-.001 (-.001 to .0)	-.001 (-.001 to .0)	-.001 (-.001 to .0)	-	.0 (.0 to .0)
Months to the power of 4	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	-	.0 (.0 to .0)
Months to the power of 5	-	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	-	-
Death	.343 (.139 to .546)	.372 (.165 to .578)	.371 (.164 to .577)	.341 (.137 to .544)	.371 (.164 to .577)	.166 (-.040 to .373)	.261 (.052 to .469)
Death month	.206 (-.223 to .635)	.203 (-.225 to .631)	.214 (-.214 to .643)	.217 (-.214 to .647)	.214 (-.216 to .643)	.199 (-.228 to .627)	.173 (-.249 to .595)
Comorbidity	.067 (.044 to .090)	.069 (.045 to .092)	.072 (.057 to .087)	.070 (.046 to .093)	.071 (.048 to .095)	.032 (.018 to .047)	.048 (.024 to .071)
2007	.214 (-.299 to .727)	.183 (-.331 to .698)	.194 (-.317 to .706)	.226 (-.285 to .738)	.195 (-.318 to .708)	.104 (-.621 to .829)	.330 (-.364 to 1.025)

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
2008	.197 (-.291 to .685)	.170 (-.319 to .660)	.171 (-.316 to .658)	.199 (-.287 to .686)	.171 (-.316 to .659)	-.004 (-.710 to .701)	.238 (-.436 to .912)
2009	.375 (-.089 to .840)	.347 (-.119 to .812)	.359 (-.105 to .823)	.389 (-.074 to .852)	.359 (-.104 to .823)	.286 (-.402 to .974)	.401 (-.254 to 1.057)
2010	.493 (.023 to .963)	.404 (-.078 to .887)	.409 (-.071 to .889)	.502 (.034 to .970)	.409 (-.071 to .889)	.228 (-.462 to .917)	.429 (-.239 to 1.097)
2011	.397 (-.099 to .894)	.250 (-.274 to .774)	.226 (-.296 to .747)	.381 (-.114 to .876)	.226 (-.296 to .748)	.10 (-.606 to .806)	.376 (-.322 to 1.073)
2012	-.615 (-1.155 to -.076)	-.764 (-1.330 to -.198)	-.718 (-1.282 to -.154)	-.563 (-1.102 to -.025)	-.718 (-1.283 to -.154)	-.248 (-.990 to .494)	-.303 (-1.031 to .425)
2013	-.527 (-1.111 to .057)	-.688 (-1.295 to -.081)	-.647 (-1.245 to -.048)	-.480 (-1.061 to .101)	-.648 (-1.253 to -.044)	.250 (-.521 to 1.022)	-.146 (-.918 to .626)
2014	-.397 (-1.136 to .343)	-.582 (-1.349 to .184)	-.701 (-1.470 to .069)	-.506 (-1.254 to .242)	-.704 (-1.480 to .073)	.608 (-.248 to 1.464)	-.006 (-.898 to .887)
Age 45 to 64	-.147 (-.274 to -.019)	-.139 (-.267 to -.011)	-.145 (-.272 to -.017)	-.152 (-.280 to -.025)	-.145 (-.272 to -.017)	-.159 (-.292 to -.025)	-.131 (-.263 to .001)
Age 65+	-.521 (-.676 to -.367)	-.525 (-.679 to -.371)	-.536 (-.689 to -.383)	-.532 (-.686 to -.377)	-.536 (-.690 to -.382)	-.373 (-.531 to -.214)	-.390 (-.547 to -.233)
Centre A	-.207 (-.569 to .155)	-.243 (-.608 to .121)	-.240 (-.602 to .122)	-.203 (-.563 to .158)	-.241 (-.603 to .122)	-.152 (-.515 to .210)	-.173 (-.538 to .193)
Centre B	.960 (.643 to 1.276)	.947 (.631 to 1.264)	.948 (.634 to 1.262)	.960 (.645 to 1.275)	.947 (.632 to 1.262)	.729 (.421 to 1.037)	.755 (.443 to 1.066)
Centre C	.895 (.638 to 1.153)	.849 (.587 to 1.111)	.846 (.587 to 1.106)	.895 (.640 to 1.150)	.846 (.586 to 1.106)	.618 (.357 to .878)	.614 (.350 to .878)
Centre D	.069 (-.209 to .346)	.033 (-.247 to .313)	.035 (-.241 to .311)	.072 (-.203 to .348)	.034 (-.244 to .312)	.105 (-.174 to .384)	.027 (-.254 to .308)
Centre E	.064 (-.270 to .399)	-.009 (-.352 to .335)	-.008 (-.349 to .332)	.068 (-.264 to .401)	-.009 (-.350 to .332)	.105 (-.228 to .439)	-.003 (-.345 to .339)
Centre F	.883 (.619 to 1.147)	.820 (.549 to 1.090)	.819 (.551 to 1.087)	.885 (.624 to 1.147)	.819 (.551 to 1.088)	.631 (.365 to .897)	.577 (.305 to .849)

Model	Model 8	Model 9	Model 10	Model 11	Model 12	Model 13	Model 14
Centre G	.50 (.191 to .808)	.457 (.145 to .770)	.461 (.152 to .770)	.504 (.199 to .810)	.460 (.150 to .771)	.413 (.101 to .724)	.336 (.019 to .653)
Centre H	.115 (-.162 to .392)	.082 (-.197 to .361)	.081 (-.195 to .358)	.116 (-.159 to .391)	.081 (-.195 to .358)	.168 (-.112 to .448)	.137 (-.141 to .416)
Centre I	.096 (-.219 to .411)	.075 (-.241 to .391)	.076 (-.238 to .389)	.097 (-.216 to .410)	.075 (-.239 to .389)	.068 (-.252 to .389)	.035 (-.284 to .355)
Centre J	.136 (-.161 to .433)	.129 (-.168 to .426)	.140 (-.154 to .433)	.146 (-.150 to .441)	.139 (-.156 to .434)	.106 (-.20 to .411)	.067 (-.237 to .372)
Centre K	.143 (-.141 to .427)	.109 (-.178 to .396)	.109 (-.176 to .393)	.144 (-.138 to .426)	.109 (-.176 to .394)	.122 (-.164 to .408)	.087 (-.199 to .374)
CRC	.343 (.244 to .442)	.334 (.233 to .434)	.335 (.236 to .433)	.344 (.244 to .443)	.334 (.234 to .435)	.221 (.118 to .325)	.237 (.132 to .341)
NSCLC	.143 (-.009 to .295)	.137 (-.015 to .289)	.143 (-.008 to .294)	.150 (-.002 to .301)	.143 (-.008 to .295)	.152 (-.003 to .307)	.101 (-.053 to .256)
Month and comorbidity interaction	.0 (-.001 to .001)	.0 (-.001 to .001)	-	.0 (-.001 to .001)	.0 (-.001 to .001)	-	.0 (-.001 to .001)
2010 cohort	-	.133 (-.003 to .268)	.139 (.003 to .275)	-	.139 (.003 to .275)	-	.093 (-.042 to .229)
Lagged cost	-	-	-	-	-	.339 (.299 to .378)	.291 (.250 to .332)
Constant	8.002 (7.466 to 8.537)	8.022 (7.485 to 8.558)	8.153 (7.617 to 8.689)	8.129 (7.593 to 8.665)	8.153 (7.617 to 8.690)	4.564 (3.774 to 5.354)	5.469 (4.692 to 6.247)
Observations	4 201	4 201	4 201	4 201	4 201	3 861	3 861

Note: The identities of the centres have been deliberated obscured

Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Table 127: Coefficients for fixed and random effects with unaltered costs as the dependent variable

Model	Fixed effects				Random effects			
	Model 1	Model 5	Model 7	Model 12	Model 1	Model 5	Model 7	Model 12
Second line of therapy	$2 088 ($1 187 to $2 988)	$2 089 ($1 217 to $2 960)	$2 089 ($1 217 to $2 960)	$2 068 ($1 199 to $2 937)	$1 582 ($887 to $2 277)	$1 749 ($1 090 to $2 408)	$1 785 ($1 131 to $2 439)	$1 788 ($1 134 to $2 442)
Third line of therapy	$3 167 ($1 981 to $4 353)	$2 720 ($1 478 to $3 962)	$2 720 ($1 478 to $3 962)	$2 685 ($1 456 to $3 915)	$2 450 ($1 402 to $3 497)	$2 263 ($1 174 to $3 353)	$2 302 ($1 221 to $3 383)	$2 292 ($1 209 to $3 374)
Fourth line of therapy	$4 922 ($2 527 to $7 317)	$3 463 ($1 101 to $5 825)	$3 463 ($1 101 to $5 825)	$3 443 ($1 038 to $5 847)	$3 564 ($873 to $6 254)	$2 249 ($4 to $4 494)	$2 284 ($89 to $4 478)	$2 294 ($73 to $4 516)
Fifth line of therapy	$7 351 ($4 155 to $10 547)	$4 674 ($2 202 to $7 145)	$4 674 ($2 202 to $7 145)	$4 944 ($2 661 to $7 227)	$5 659 ($1 513 to $9 805)	$3 151 ($1 252 to $5 051)	$3 078 ($1 169 to $4 987)	$3 166 ($1 269 to $5 063)
Months	-$173 (-$239 to -$107)	-$871 (-$1 075 to -$667)	-$871 (-$1 075 to -$667)	-$1 032 (-$1 379 to -$685)	-$123 (-$160 to -$87)	-$806 (-$1 000 to -$611)	-$791 (-$986 to -$595)	-$893 (-$1 220 to -$566)
Months squared	-	$38 ($23 to $54)	$38 ($23 to $54)	$58 ($16 to $101)	-	$38 ($23 to $53)	$38 ($23 to $53)	$52 ($13 to $91)
Months cubed	-	-$1 (-$1 to $0)	-$1 (-$1 to $0)	-$2 (-$4 to $0)	-	-$1 (-$1 to $0)	-$1 (-$1 to $0)	-$1 (-$3 to $0)
Months to the power of 4	-	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)	-	$0 ($0 to $0)	$0 ($0 to $0)	$0 ($0 to $0)
Months to the power of 5	-	-	-	$0 ($0 to $0)	-	-	-	$0 ($0 to $0)
Death	$1 667 ($681 to $2 653)	$1 786 ($781 to $2 791)	$1 786 ($781 to $2 791)	$1 781 ($775 to $2 788)	$2 328 ($1 450 to $3 206)	$2 478 ($1 608 to $3 348)	$2 552 ($1 673 to $3 431)	$2 552 ($1 671 to $3 434)
Death month	$2 481 ($190 to $4 772)	$2 062 (-$172 to $4 296)	0	-				
Comorbidity	$115 (-$91 to $321)	$394 ($191 to $597)	$394 ($191 to $597)	$501 ($246 to $756)	$172 ($71 to $274)	$282 ($185 to $379)	$285 ($187 to $382)	$292 ($164 to $420)
2007	$707 (-$1 083 to $2 497)	$1 709 (-$540 to $3 958)	$1 709 (-$540 to $3 958)	$1 696 (-$668 to $4 059)	$315 (-$1 267 to $1 897)	$1 403 (-$616 to $3 422)	$1 321 (-$705 to $3 346)	$1 328 (-$725 to $3 381)
2008	$2 158 (-$140 to $4 456)	$2 466 ($41 to $4 891)	$2 466 ($41 to $4 891)	$2 393 (-$177 to $4 962)	$987 (-$577 to $2 552)	$1 558 (-$213 to $3 329)	$1 458 (-$319 to $3 235)	$1 453 (-$362 to $3 267)

Model	Fixed effects				Random effects			
	Model 1	Model 5	Model 7	Model 12	Model 1	Model 5	Model 7	Model 12
2009	$3 665 ($802 to $6 527)	$3 322 ($379 to $6 265)	$3 322 ($379 to $6 265)	$3 291 ($215 to $6 367)	$1 800 ($144 to $3 457)	$1 802 (-$2 to $3 606)	$1 666 (-$137 to $3 470)	$1 678 (-$173 to $3 529)
2010	$3 602 ($434 to $6 770)	$3 937 ($658 to $7 216)	$3 937 ($658 to $7 216)	$3 908 ($512 to $7 304)	$1 537 (-$193 to $3 267)	$2 163 ($312 to $4 013)	$1 853 (-$19 to $3 726)	$1 851 (-$61 to $3 763)
2011	$3 773 ($149 to $7 396)	$4 346 ($587 to $8 106)	$4 346 ($587 to $8 106)	$4 268 ($402 to $8 134)	$1 256 (-$648 to $3 160)	$2 246 ($255 to $4 237)	$1 770 (-$268 to $3 807)	$1 730 (-$337 to $3 797)
2012	$3 593 (-$746 to $7 933)	$2 747 (-$1 719 to $7 213)	$2 747 (-$1 719 to $7 213)	$2 864 (-$1 667 to $7 395)	$465 (-$1 799 to $2 729)	$69 (-$2 145 to $2 282)	-$456 (-$2 732 to $1 821)	-$401 (-$2 717 to $1 915)
2013	$6 492 ($1 417 to $11 567)	$4 167 (-$911 to $9 245)	$4 167 (-$911 to $9 245)	$4 454 (-$670 to $9 577)	$2 570 (-$224 to $5 364)	$772 (-$1 791 to $3 336)	$169 (-$2 476 to $2 814)	$223 (-$2 462 to $2 909)
2014	$8 886 ($3 018 to $14 753)	$5 640 ($90 to $11 190)	$5 640 ($90 to $11 190)	$5 913 ($319 to $11 507)	$4 536 ($709 to $8 362)	$1 736 (-$1 434 to $4 906)	$1 024 (-$2 191 to $4 239)	$885 (-$2 324 to $4 094)
Age 45 to 64	-	-	-	-	-$510 (-$1 624 to $603)	-$556 (-$1 623 to $510)	-$518 (-$1 556 to $520)	-$527 (-$1 564 to $510)
Age 65+	-	-	-	-	-$1 200 (-$2 491 to $90)	-$1 432 (-$2 671 to -$194)	-$1 417 (-$2 629 to -$205)	-$1 436 (-$2 649 to -$222)
Centre A	-	-	-	-	-$147 (-$1 744 to $1 450)	-$122 (-$1 723 to $1 479)	-$295 (-$1 866 to $1 277)	-$295 (-$1 866 to $1 275)
Centre B	-	-	-	-	$3 189 ($1 191 to $5 186)	$3 187 ($1 229 to $5 145)	$3 132 ($1 193 to $5 071)	$3 133 ($1 197 to $5 069)
Centre C	-	-	-	-	$2 826 ($1 503 to $4 150)	$2 786 ($1 554 to $4 018)	$2 559 ($1 337 to $3 781)	$2 556 ($1 335 to $3 778)
Centre D	-	-	-	-	$732 (-$512 to $1 976)	$521 (-$635 to $1 677)	$331 (-$829 to $1 490)	$335 (-$824 to $1 494)
Centre E	-	-	-	-	$1 345 (-$275 to $2 964)	$959 (-$600 to $2 518)	$550 (-$1 057 to $2 157)	$546 (-$1 057 to $2 150)
Centre F	-	-	-	-	$2 717 ($1 390 to $4 044)	$2 620 ($1 368 to $3 873)	$2 321 ($1 061 to $3 581)	$2 319 ($1 058 to $3 580)

Model	Fixed effects				Random effects			
	Model 1	Model 5	Model 7	Model 12	Model 1	Model 5	Model 7	Model 12
Centre G	-	-	-	-	$1 797 ($372 to $3 222)	$1 523 ($144 to $2 902)	$1 316 (-$103 to $2 735)	$1 320 (-$77 to $2 717)
Centre H	-	-	-	-	$677 (-$570 to $1 924)	$622 (-$539 to $1 783)	$439 (-$710 to $1 588)	$438 (-$711 to $1 587)
Centre I	-	-	-	-	$1 024 (-$614 to $2 661)	$892 (-$642 to $2 426)	$812 (-$685 to $2 310)	$815 (-$681 to $2 311)
Centre J	-	-	-	-	$1 237 (-$35 to $2 510)	$1 112 (-$51 to $2 275)	$1 081 (-$52 to $2 215)	$1 092 (-$37 to $2 220)
Centre K	-	-	-	-	$1 338 (-$178 to $2 855)	$1 300 (-$107 to $2 707)	$1 139 (-$270 to $2 547)	$1 137 (-$264 to $2 537)
CRC	-	-	-	-	$1 557 ($855 to $2 259)	$1 597 ($940 to $2 255)	$1 527 ($895 to $2 159)	$1 530 ($895 to $2 165)
NSCLC	-	-	-	-	$828 (-$146 to $1 801)	$568 (-$346 to $1 482)	$530 (-$384 to $1 444)	$534 (-$389 to $1 457)
Month and comorbidity interaction	-	-	-	-$4 (-$12 to $3)	-	-	-	$0 (-$6 to $6)
2010 cohort	-	-	-	-	-	-	$567 (-$138 to $1 271)	$576 (-$129 to $1 280)
Constant	-	-	-	-	$1 243 (-$853 to $3 339)	$3 401 ($1 106 to $5 696)	$3 534 ($1 242 to $5 826)	$3 709 ($1 377 to $6 041)
Observations	4 373	4 373	4 373	4 373	4 373	4 373	4 373	4 373
Clusters	228	228	228	228	228	228	228	228

Note: The identities of the centres have been deliberated obscured

Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Table 128: Coefficients for fixed and random effects with logged costs as the dependent variable

Model	Fixed effects				Random effects			
	Model 1	Model 5	Model 7	Model 12	Model 1	Model 5	Model 7	Model 12
Second line of therapy	.947 (.693 to 1.201)	.947 (.720 to 1.174)	.947 (.720 to 1.174)	.940 (.716 to 1.164)	.788 (.566 to 1.010)	.863 (.665 to 1.061)	.869 (.673 to 1.065)	.870 (.674 to 1.067)
Third line of therapy	1.360 (.931 to 1.789)	1.180 (.812 to 1.547)	1.180 (.812 to 1.547)	1.167 (.815 to 1.519)	1.113 (.736 to 1.490)	1.052 (.730 to 1.374)	1.057 (.737 to 1.376)	1.052 (.736 to 1.367)
Fourth line of therapy	2.091 (1.296 to 2.887)	1.453 (.842 to 2.063)	1.453 (.842 to 2.063)	1.448 (.811 to 2.085)	1.646 (.80 to 2.491)	1.104 (.482 to 1.726)	1.106 (.491 to 1.721)	1.116 (.473 to 1.759)
Fifth line of therapy	2.355 (.625 to 4.085)	1.280 (.625 to 1.936)	1.280 (.625 to 1.936)	1.404 (.701 to 2.107)	1.837 (.054 to 3.619)	.880 (.252 to 1.508)	.863 (.228 to 1.498)	.934 (.261 to 1.606)
Months	-.069 (-.088 to -.049)	-.315 (-.369 to -.262)	-.315 (-.369 to -.262)	-.396 (-.488 to -.305)	-.050 (-.061 to -.038)	-.291 (-.341 to -.241)	-.289 (-.340 to -.238)	-.359 (-.444 to -.274)
Months squared	-	.011 (.007 to .015)	.011 (.007 to .015)	.022 (.010 to .034)	-	.012 (.008 to .016)	.012 (.008 to .016)	.021 (.009 to .033)
Months cubed	-	.0 (.0 to .0)	.0 (.0 to .0)	-.001 (-.001 to .0)	-	.0 (.0 to .0)	.0 (.0 to .0)	-.001 (-.001 to .0)
Months to the power of 4	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
Months to the power of 5	-	-	-	.0 (.0 to .0)	-	-	-	.0 (.0 to .0)
Death	.141 (-.114 to .396)	.215 (-.026 to .455)	.215 (-.026 to .455)	.212 (-.029 to .453)	.239 (.010 to .468)	.316 (.099 to .534)	.328 (.109 to .548)	.329 (.108 to .550)
Death month	.361 (-.069 to .791)	.195 (-.223 to .614)	.195 (-.223 to .614)	.216 (-.203 to .635)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
Comorbidity	-.004 (-.055 to .047)	.114 (.066 to .163)	.114 (.066 to .163)	.158 (.102 to .215)	-.068 (-.721 to .585)	.355 (-.262 to .971)	.338 (-.283 to .959)	.339 (-.286 to .964)

2007	.203 (-.547 to .952)	.593 (-.067 to 1.253)	.593 (-.067 to 1.253)	.585 (-.089 to 1.258)	.559 (-.026 to 1.144)	.511 (.006 to 1.017)	.485 (-.019 to .989)	.493 (-.028 to 1.014)
2008	.604 (-.304 to 1.513)	.659 (-.043 to 1.362)	.659 (-.043 to 1.362)	.635 (-.112 to 1.382)	.475 (-.093 to 1.042)	.677 (.181 to 1.173)	.622 (.109 to 1.135)	.621 (.093 to 1.149)
2009	1.420 (.464 to 2.376)	1.181 (.394 to 1.968)	1.181 (.394 to 1.968)	1.179 (.344 to 2.013)	.186 (-.417 to .790)	.598 (.065 to 1.132)	.516 (-.049 to 1.080)	.488 (-.090 to 1.067)
2010	1.466 (.502 to 2.430)	1.498 (.673 to 2.323)	1.498 (.673 to 2.323)	1.495 (.627 to 2.362)	-.059 (-.809 to .690)	-.246 (-.926 to .433)	-.339 (-1.049 to .371)	-.295 (-1.006 to .416)
2011	1.386 (.342 to 2.429)	1.574 (.656 to 2.493)	1.574 (.656 to 2.493)	1.546 (.589 to 2.504)	.743 (-.098 to 1.585)	-.166 (-.902 to .570)	-.272 (-1.039 to .495)	-.217 (-.982 to .548)
2012	1.435 (.179 to 2.691)	.980 (-.167 to 2.127)	.980 (-.167 to 2.127)	1.052 (-.134 to 2.238)	1.514 (.505 to 2.523)	.143 (-.692 to .978)	.019 (-.841 to .878)	-.048 (-.912 to .815)
2013	2.554 (1.084 to 4.024)	1.296 (-.031 to 2.624)	1.296 (-.031 to 2.624)	1.440 (.072 to 2.809)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
2014	3.557 (2.011 to 5.102)	1.814 (.395 to 3.234)	1.814 (.395 to 3.234)	1.921 (.488 to 3.353)	-.167 (-.413 to .080)	-.196 (-.426 to .034)	-.189 (-.414 to .036)	-.196 (-.417 to .026)
Age 45 to 64	-	-	-	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
Age 65+	-	-	-	-	-.272 (-.823 to .278)	-.251 (-.721 to .218)	-.280 (-.736 to .176)	-.278 (-.737 to .181)
Centre A	-	-	-	-	.857 (.474 to 1.241)	.846 (.599 to 1.094)	.809 (.547 to 1.071)	.809 (.549 to 1.069)
Centre B	-	-	-	-	.153 (-.261 to .567)	.060 (-.244 to .363)	.027 (-.283 to .337)	.034 (-.271 to .338)
Centre C	-	-	-	-	.209 (-.372 to .791)	.030 (-.460 to .519)	-.041 (-.542 to .461)	-.040 (-.543 to .463)
Centre D	-	-	-	-	.827 (.421 to 1.234)	.788 (.496 to 1.080)	.738 (.437 to 1.040)	.738 (.437 to 1.040)
Centre E	-	-	-	-	.487 (.008 to .966)	.361 (.0 to .723)	.327 (-.047 to .702)	.334 (-.038 to .706)
Centre F	-	-	-	-	.125 (-.282 to .532)	.108 (-.176 to .392)	.078 (-.212 to .367)	.078 (-.211 to .367)

Centre G	-	-	-	-	.154 (-.286 to .595)	.102 (-.218 to .421)	.088 (-.228 to .404)	.095 (-.218 to .407)
Centre H	-	-	-	-	.168 (-.267 to .604)	.119 (-.183 to .422)	.115 (-.187 to .417)	.125 (-.176 to .426)
Centre I	-	-	-	-	.142 (-.339 to .622)	.127 (-.235 to .489)	.101 (-.260 to .462)	.103 (-.258 to .463)
Centre J	-	-	-	-	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)	.0 (.0 to .0)
Centre K	-	-	-	-	.318 (.133 to .502)	.336 (.171 to .501)	.324 (.159 to .489)	.328 (.162 to .494)
CRC	-	-	-	-	7.020 (6.341 to 7.699)	7.870 (7.294 to 8.446)	.0 (.0 to .0)	.0 (-.002 to .001)
NSCLC	-	-	-	-	-	-	.095 (-.111 to .301)	.0 (.0 to .0)
Month and comorbidity interaction	-	-	-	-.002 (-.004 to .0)	-	-	-	.102 (-.107 to .310)
2010 cohort	-	-	-	-	-	-	-	-
Constant	-	-	-	-	-	-	-	-
Observations	4 201	4 201	4 201	4 201	4 201	4 201	4 201	4 201
Clusters	228	228	228	228	228	228	228	228

Note: The identities of the centres have been deliberated obscured
Abbreviations: CRC: colorectal cancer; NSCLC: non-small cell lung cancer

Appendix E: Literature search for studies with two or more lines of therapy

Table 129 summarises the inclusion and exclusion of articles after the full-text review for each of the searches and the resultant pearl searches. The detailed for each search is described below. The last search was on the 27/06/2017.

Table 129: Summary of full-text review of literature search for studies with two or more lines of therapy

Search	Medline search	Medline pearl search	EconLit	EconLit pearl search	PubMed search	PubMed pearl search
Number of full-text reviews	76	25	35	3	54	2
Included	19	25	11	3	22	1
Excluded	57	0	24	0	32	1
			Reason for exclusion			
Unable to gain a copy in English					2	
Excluded because not an article	3		2			
Not involving human subjects	15				2	
Excluded because not a cancer			3			
Not involving chemotherapy					3	
Not involving multiple lines of therapy			16		9	1
Not involving a choice in multiple lines of therapy	39		3		16	
			Inclusion category			
RCT	5	5			3	

Search	Medline search	Medline pearl search	EconLit	EconLit pearl search	PubMed search	PubMed pearl search
Non-RCT	7	14			3	
Discussion	6	4	11	3	14	1
Inclusion as economic evaluation (discussion)	1	2			2	

Abbreviation: RCT: randomised controlled trial

Medline search

The literature considering the use of sequences of chemotherapy was not well developed. There were many economic evaluations comparing alternative treatments within a line of therapy. The economic evaluation of therapies across different lines of therapy was, however, sparse.

Therefore, this literature search adopted a wide approach to keywords. The results were hand searched and allocated. Medline, PubMed and EconLit were searched. Medline was searched on the 7/03/14 and replaced by PubMed searches which concluded on 27/06/2017

After initial consideration, included articles were allocated to one or more of four different literature categories-

1. Randomised Controlled Trial category. This required an RCT of two protocols and movement from one protocol to another required either progression of disease or unacceptable toxicity;
2. non-RCT data collection- either retrospective or prospective information about patients who received two protocols of treatment with progression of disease or unacceptable toxicity separated the protocols;
3. Economic Evaluation- if two lines of therapy were considered or discussed, separated by progression of disease or unacceptable toxicity, these were also included in the economic evaluation discussions in Chapter 3; and
4. Discussion, meaning there was a discussion of the implications of multiple lines of therapy but no collection of data within the paper.

Table 130: Flow of Medline search

Action	Criteria	Return
Search Medline	"sequenc*".m_titl	128 940
Search Medline	"algorith*".m_titl	19 863
Search Medline	chemotherapy.mp. or Drug Therapy/	321 289
Search Medline	Combined	617
Removal of duplicates	Using endnote duplicate function	608
Abstract review	Reviewed abstract to consider for full review	76
Full review	Kept from full review	19
	Discussion	6
	Economic Evaluation	1
	Non-randomised controlled trials	7
	Randomised controlled trials	5
	Excluded	57
	Excluded as not an article	3
	Excluded as not in human subjects	15
	Excluded as not a comparison of multiple lines of therapy	39

Table 131: Full-text review of Medline search

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Management of castrate resistant prostate cancer-recent advances and optimal sequence of treatments	[23]	Prostate cancer	Inclusion	Propose a treatment sequence based on evidence, no discussion of economics. Suggests that the future sequencing will be dependent on the biomarkers that are present	No	Included as discussion

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
A three-arm randomized phase II study of oral vinorelbine plus capecitabine versus oral vinorelbine and capecitabine in sequence versus docetaxel plus capecitabine in patients with metastatic breast cancer previously treated with anthracyclines	[573]	Breast cancer	Exclusion	Several different regimes for treatment of metastatic breast cancer after the use of anthracyclines. Notable that there was a discussion over the use of drugs in sequence	No	Not a comparison of multiple lines of therapy
A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study)	[99]	NSCLC	Inclusion	Treatment sequence within elderly NSCLC	No	Inclusion as RCT
Second-line epidermal growth factor receptor inhibitors followed by third-line pemetrexed or the reverse sequence: a retrospective analysis of 83 Chinese patients with advanced lung adenocarcinoma	[574]	NSCLC	Inclusion	Two sequences in a select population, interesting that there is a difference between the two arms, notable for being a retrospective study	No	Inclusion as non-RCT
Targeted and cytotoxic therapy in coordinated sequence (TACTICS): erlotinib, bevacizumab, and standard chemotherapy for non-small-cell lung cancer, a phase II trial	[259]	NSCLC	Exclusion	Small phase II trial of multiple lines of therapy within a single progression	No	Not a comparison of multiple lines of therapy
The sequence of drug administration influences the antitumor effects of bevacizumab and cyclophosphamide in a neuroblastoma model	[575]	Glioblastoma	Exclusion	Based on a model, no regime post-progression	No	Not in human subjects
[Sequence-dependent effect of docetaxel with gefitinib on the proliferation and signal protein expression of human lung adenocarcinoma cell SPC-A1]	[576]	NSCLC	Exclusion	Discussion of the biochemistry associated with NSCLC	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Sequential taxane and anthracycline-containing neo-adjuvant regimens; any rationale behind the sequence?	[577]	Breast cancer	Exclusion	Letter- based on treatment sequence within a regime	No	Not an article
Synergistic interaction between sunitinib and docetaxel is sequence dependent in human non-small lung cancer with EGFR TKIs-resistant mutation	[578]	NSCLC	Exclusion	Concurrent or sequential treatment within a line of therapy	No	Not a comparison of multiple lines of therapy
Cetuximab after bevacizumab in metastatic colorectal cancer: is it the best sequence?	[579]	CRC	Inclusion	Suggestion that prior treatments may impact on current treatments	No	Inclusion as discussion
A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study)	[100]	NSCLC	Inclusion	NSCLC and elderly patients might be similar to another paper by same authors- check	No	Inclusion as RCT
Docetaxel/cisplatin followed by FOLFIRI versus the reverse sequence in metastatic gastric cancer	[257]	Gastric cancer	Inclusion	Problems with patient accrual, found no difference	No	Inclusion as RCT
In vitro sequence-dependent synergism between paclitaxel and gefitinib in human lung cancer cell lines	[580]	NSCLC	Exclusion	Lab-based testing of cell lines	No	Not in human subjects
Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors	[581]	Renal cell cancer	Inclusion	Strictly speaking only in second line, but might useful confirmatory data	No	Inclusion as non-RCT
Optimal sequence of implied modalities in the adjuvant setting of breast cancer treatment: an update on issues to consider	[582]	Breast cancer	Exclusion	About the use of the three different modalities in the treatment of breast cancer	No	Not a comparison of multiple

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
						lines of therapy
BMS-690514, a VEGFR and EGFR tyrosine kinase inhibitor, shows anti-tumoural activity on non-small-cell lung cancer xenografts and induces sequence-dependent synergistic effect with radiation	[583]	NSCLC	Exclusion	Discussion of the issues associated with the combination of radiotherapy and chemotherapy	No	Not a comparison of multiple lines of therapy
Sequence-dependent hematologic side effects of topotecan and cisplatin in persistent or recurrent cervical cancer	[584]	Cervical cancer	Exclusion	Multiple pharmaceutical agents within a single line of therapy	No	Not a comparison of multiple lines of therapy
Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301)	[255]	Pancreatic cancer	Inclusion	Two lines of therapy reversed around the first progression	No	Inclusion as RCT
Does the sequence of taxane administration affect the outcome of patients with breast cancer in the adjuvant and neoadjuvant settings?	[585]	Breast cancer	Exclusion	Letter to the editor	No	Not an article
Non-platinum-based first-line followed by platinum-based second-line chemotherapy or the reverse sequence in patients with advanced non-small cell lung cancer: a retrospective analysis by the lung cancer group of the Hellenic Oncology Research Group	[266]	NSCLC	Inclusion	Retrospective, again this did not show a difference	No	Inclusion as non-RCT
Delivery of adjuvant sequential dose-dense FEC-Doc to patients with breast cancer is feasible, but dose reductions and toxicity are dependent on treatment sequence	[586]	Breast cancer	Exclusion	Multiple agents in a line of therapy	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Gemcitabine and pemetrexed administered in rapid sequence as front-line chemotherapy for advanced non-small-cell lung cancer: a phase II clinical trial	[587]	NSCLC	Exclusion	Multiple agents in a line of therapy	No	Not a comparison of multiple lines of therapy
Review of the contemporary cytotoxic and biologic combinations available for the treatment of metastatic breast cancer	[263]	Breast cancer	Inclusion	Discussion but not a trial	No	Included as discussion
Cost-minimization analysis of sequence changes between FOLFIRI and FOLFOX6 therapy for advanced colorectal cancer in Japan	[93]	CRC	Inclusion	Cost-minimisation of sequences	Yes	Economic evaluation
Letrozole therapy alone or in sequence with tamoxifen in women with breast cancer	[588]	Breast cancer	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Dual epidermal growth factor receptor and vascular endothelial growth factor receptor inhibition with vandetanib sensitizes bladder cancer cells to cisplatin in a dose- and sequence-dependent manner	[589]	Bladder cancer	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Gemcitabine and pemetrexed combination: the key role of the sequence of drugs administration	[590]	NSCLC	Exclusion	Letter to the editor	No	Not an article
Combining endocrine agents with chemotherapy: which patients and what sequence?	[591]	Breast cancer	Inclusion	Discussion piece	No	Included as discussion
Sequence-dependent synergism and antagonism between paclitaxel and gemcitabine in breast cancer cells: The importance of scheduling	[592]	Breast cancer	Exclusion	In Vitro	No	Not in human subjects

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Allogeneic granulocyte macrophage colony-stimulating factor-secreting tumor immunotherapy alone or in sequence with cyclophosphamide for metastatic pancreatic cancer: a pilot study of safety, feasibility, and immune activation	[593]	Pancreatic cancer	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Severe sequence-specific toxicity when capecitabine is given after fluorouracil and leucovorin	[594]	CRC	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Does an optimal therapeutic sequence exist in advanced non-small cell lung cancer?	[14]	NSCLC	Inclusion	Discussion piece, some discussion around third versus second line but mainly about second line	No	Included as discussion
Synergistic interaction between trifluorothymidine and docetaxel is sequence dependent	[595]	CRC	Exclusion	Discussion of in vitro issues	No	Not in human subjects
XELOX followed by XELIRI or the reverse sequence in advanced colorectal cancer	[596]	CRC	Inclusion	First and second line treatment, prospective but not randomised	No	Inclusion as non-RCT
Dose-dense adjuvant chemotherapy in node-positive breast cancer: docetaxel followed by epirubicin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomized phase II study	[597]	Breast cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Sequence dependent antitumour efficacy of the vascular disrupting agent ZD6126 in combination with paclitaxel	[598]	Nil	Exclusion	In vitro study	No	Not in human subjects

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Gemcitabine and vinorelbine in recurrent advanced non-small cell lung cancer: sequence does matter	[599]	NSCLC	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Sequence-dependent administration of 5-fluorouracil maintains methotrexate antineoplastic activity in human estrogen-negative breast cancer and protects against methotrexate cytotoxicity in human bone marrow	[600]	Breast cancer	Exclusion	In vitro experimentation	No	Not in human subjects
Sequence-dependent administration of raloxifene and 5-fluorouracil/pemetrexed protects against pemetrexed cytotoxicity in human bone marrow	[601]	Multiple	Exclusion	In vitro experimentation	No	Not in human subjects
What is the best sequence of chemotherapy in advanced colorectal cancer? Final results of a five-arm study	[265]	CRC	Inclusion	First and second line therapy for CRC	No	Inclusion as non-RCT
Optimized sequence of drug administration and schedule leads to improved dose delivery for gemcitabine and paclitaxel in combination: a phase I trial in patients with recurrent ovarian cancer	[602]	Ovarian cancer	Exclusion	Multiple agents within a single line of therapy	No	Not a comparison of multiple lines of therapy
First- and second-line chemotherapy with docetaxel or mitoxantrone in patients with hormone-refractory prostate cancer: does sequence matter?	[264]	Prostate cancer	Inclusion	The reversal of two lines of therapy	No	Inclusion as non-RCT
Planned sequence of gemcitabine followed by vinorelbine in the treatment of elderly patients with advanced non-small cell lung cancer	[603]	NSCLC	Exclusion	Consideration of two agents within a line of therapy	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Influence of altering administration sequence of docetaxel, gemcitabine and cisplatin in patients with advanced non-small cell lung cancer	[604]	NSCLC	Exclusion	Consideration of three agents in a line of therapy	No	Not a comparison of multiple lines of therapy
Raloxifene attenuation of 5-FU/methotrexate cytotoxicity in human breast cancer cells: the importance of sequence in combination chemotherapy	[605]	Breast cancer	Exclusion	In vitro experimentation	No	Not in human subjects
Topotecan and liposomal doxorubicin in recurrent ovarian cancer: is sequence important?	[245]	Ovarian cancer	Inclusion	Retrospective, small numbers	No	Inclusion as non-RCT
Sequence dependence of hematologic toxicity using carboplatin and topotecan for primary therapy of advanced epithelial ovarian cancer: a phase I study of the Gynecologic Oncology Group	[606]	Ovarian cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin, vinorelbine, and fluorouracil chemotherapy, surgery, and radiotherapy: long-term results	[607]	Breast cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
FOLFIRI regimen in advanced colorectal cancer: the experience of the Gruppo Oncologico dell'Italia Meridionale (GOIM)	[608]	CRC	Exclusion	First line therapy only	No	Not a comparison of multiple lines of therapy
Innovative sequence of docetaxel-gemcitabine based on preclinical data in the treatment of advanced non-small cell lung cancer: a phase I study	[609]	NSCLC	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
A phase IB study of the pharmacokinetics of gemcitabine and pemetrexed, when administered in rapid sequence to patients with advanced solid tumors	[610]	Multiple	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Sequential chemotherapy of cisplatin and vinorelbine followed by paclitaxel and gemcitabine in advanced non-small-cell lung cancer. A single institution phase II study	[611]	NSCLC	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Sequence effect of docetaxel and carboplatin on toxicity, tumor response and pharmacokinetics in non-small-cell lung cancer patients: a phase I study of two sequences	[612]	NSCLC	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study	[68]	CRC	Inclusion	Two lines of therapy given in sequence on progression	No	Inclusion as RCT
Does the Sequence of Gemcitabine and Vinorelbine Affect their Efficacy in Non-small Cell Lung Cancer In Vitro?	[613]	NSCLC	Exclusion	In vitro scientific experiment	No	Not in human subjects
Carboplatin plus paclitaxel combination chemotherapy: impact of sequence of drug administration on treatment-induced neutropenia	[614]	Ovarian cancer	Exclusion	Sequence within the first line of therapy	No	Not a comparison of multiple lines of therapy
Oxaliplatin-5-fluorouracil and ionizing radiation. Importance of the sequence and influence of p53 status	[615]	CRC	Exclusion	Multiple drugs within a line of therapy	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Is there a benefit by the sequence anastrozole–formestane for postmenopausal metastatic breast cancer women?	[616]	Breast cancer	Inclusion	Multiple treatments with breast cancer in different lines of therapy for endocrine therapy	No	Included as discussion
Phase I pharmacodynamic study of time and sequence dependency of hydroxyurea in combination with gemcitabine: a California Cancer Consortium Trial	[617]	Multiple	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Sequence-dependent synergistic cytotoxicity of ecteinascidin-743 and paclitaxel in human breast cancer cell lines in vitro and in vivo	[618]	Breast cancer	Exclusion	In vitro experimentation	No	Not in human subjects
Sequence-dependent synergism between the new generation platinum agent ZD0473 and paclitaxel in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines	[619]	Ovarian cancer	Exclusion	In vitro experimentation	No	Not in human subjects
Phase I pharmacokinetic and sequence finding study of the combination of docetaxel and methotrexate in patients with solid tumours	[620]	Multiple	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Randomized trial of postoperative adjuvant therapy in stage II and III rectal cancer to define the optimal sequence of chemotherapy and radiotherapy: a preliminary report	[621]	Rectal cancer	Exclusion	Sequences of different modalities within a line of therapy	No	Not a comparison of multiple lines of therapy
Sequence effect of irinotecan and fluorouracil treatment on pharmacokinetics and toxicity in chemotherapy-naive metastatic colorectal cancer patients	[622]	CRC	Exclusion	Pharmacodynamics of a single line of therapy	No	Not a comparison of multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Sequence-dependent toxicity profile in modified FAMTX (fluorouracil-adriamycin-methotrexate) chemotherapy with lenograstim support for advanced gastric cancer: a feasibility study	[623]	Gastric cancer	Exclusion	Within a single line of therapy	No	Not a comparison of multiple lines of therapy
Sequence effect of epirubicin and paclitaxel treatment on pharmacokinetics and toxicity	[624]	Breast cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Study of dose escalation and sequence switching of administration of the combination of docetaxel and doxorubicin in advanced breast cancer	[625]	Breast cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Double high-dose chemotherapy with stem cell rescue (HD-SCR) in patients with breast cancer - effects of sequence	[626]	Breast cancer	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Phase I pharmacologic study of oral topotecan and intravenous cisplatin: sequence-dependent hematologic side effects	[627]	Multiple	Exclusion	Within a line of therapy	No	Not a comparison of multiple lines of therapy
Synergistic antitumor activity of irinotecan in combination with 5-fluorouracil in rats bearing advanced colorectal cancer: role of drug sequence and dose	[628]	CRC	Exclusion	In vitro scientific experimentation	No	Not in human subjects
Sequence-dependent Antitumor Efficacy of Combination Chemotherapy of Nedaplatin, a	[629]	NSCLC	Exclusion	In vitro scientific experiment	No	Not in human subjects

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Novel Platinium Complex, with 5-Flurouracil in an *in vivo* Murine Tumour Model						
Sequence effect of irinotecan (CPT-11) and topoisomerase II inhibitors in vivo	[630]	Nil	Exclusion	In vivo scientific experiment	No	Not in human subjects
Sequence-dependent antitumor activity of paclitaxel (taxol) and cisplatin in vivo	[631]	Nil	Exclusion	In vivo scientific experiment conducted in non-human	No	Not in human subjects
Intraperitoneal cytosine arabinoside administered in sequence with systemic cisplatin, doxorubicin, and cyclophosphamide in advanced ovarian cancer	[632]	Ovarian cancer	Exclusion	Multiple agents in a single line of therapy	No	Not a comparison of multiple lines of therapy
Sequence and schedule-dependent synergy of trimetrexate in combination with 5-fluorouracil in vitro and in mice	[633]	Nil	Exclusion	In vitro and in vivo scientific study	No	Not a comparison of multiple lines of therapy
Modulation of Chemotherapeutic Efficacy by Vascular Disrupting Agents: Optimizing the Sequence and Schedule	[431,634]	Nil	Exclusion	Although interesting, was a discussion about a single line of therapy	No	Not a comparison of multiple lines of therapy

Twenty-five articles were identified via pearl searching, these are listed in Table 132 and the inclusion or exclusion criteria are shown below.

Table 132: Recovered literature from pearl search of recovered Medline articles

Title	Reference	Type of Cancer	Inclusion/Exclusion	Comment	Type
Regorafenib in combination with FOLFOX or FOLFIRI as first- or second-line treatment of colorectal cancer: results of a multicenter, phase Ib study	[635]	CRC	Inclusion	The use of biological agents in either first or second line	Included as discussion
Sequential treatment of advanced-stage lung adenocarcinoma harboring wild-type EGFR gene: second-line pemetrexed followed by third-line erlotinib versus the reverse sequence	[636]	NSCLC	Inclusion		Inclusion as non-RCT
Retrospective comparison of triple-sequence therapies in metastatic renal cell carcinoma	[637]	Renal cell carcinoma	Inclusion		Inclusion as non-RCT
[Comparison of the efficacy of second line EGFR TKIs followed by third line pemetrexed or the reverse sequence in the treatment of advanced lung adenocarcinoma]	[638]	Lung cancer	Inclusion	Not able to get an English translation of the main text, was able to get English translation of abstract	Inclusion as non-RCT
A pooled analysis of sequential therapies with sorafenib and sunitinib in metastatic renal cell carcinoma	[261]	Renal cell carcinoma	Inclusion,		Inclusion as non-RCT
Optimizing further treatment choices in short- and long-term responders to first-line therapy for patients with advanced renal cell carcinoma	[639]	Renal cell carcinoma	Inclusion		Included as discussion
Sequential treatment with sorafenib and sunitinib in metastatic renal cell carcinoma: clinical outcomes from a retrospective clinical study	[640]	Renal cell carcinoma	Inclusion		Included as discussion
First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial	[258]	NSCLC	Inclusion		Inclusion as RCT
Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma--data from the Czech registry	[641]	Renal Cell Carcinoma	Inclusion		Inclusion as non-RCT

Title	Reference	Type of Cancer	Inclusion/Exclusion	Comment	Type
Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases	[262]	Renal Cell Carcinoma	Inclusion		Inclusion as non-RCT
Prognostic factors of second and third line chemotherapy using 5-fu with platinum, irinotecan, and taxane for advanced gastric cancer	[642]	Gastric cancer	Inclusion		Inclusion as non-RCT
Sequential therapies with sorafenib and sunitinib in advanced or metastatic renal cell carcinoma	[643]	Renal Cell Carcinoma	Inclusion		Inclusion as non-RCT
Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial	[256]	Colorectal Carcinoma	Inclusion		Inclusion as RCT
A retrospective analysis of non-platinum-based first- and second-line chemotherapy in patients with advanced non-small cell lung cancer	[644]	NSCLC	Inclusion	Appears to be a duplicate of Agelaki et al. (2010)[266]- Only one was included in the data extraction	Inclusion as non-RCT
Sequential sorafenib and sunitinib for renal cell carcinoma	[645]	Renal Cell Carcinoma	Inclusion		Inclusion as non-RCT
Advanced breast cancer: diagnosis and treatment: Full Guideline	[90]	Breast Cancer	Inclusion	Included in Chapter 3	Inclusion as economic evaluation
Sequential therapy with sorafenib and sunitinib in renal cell carcinoma	[646]	Renal Cell Carcinoma	Inclusion		Inclusion as non-RCT
Docetaxel chemotherapy of Korean patients with hormone- refractory prostate cancer: comparative analysis between 1st-line and 2nd-line docetaxel	[647]	Prostate cancer	Inclusion		Inclusion as non-RCT
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation	[94]	Colorectal cancer	Inclusion	Included in Chapter 3	Inclusion as economic evaluation
Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa	[648]	Prostate cancer	Inclusion		Inclusion as non-RCT

Title	Reference	Type of Cancer	Inclusion/Exclusion	Comment	Type
Response to second-line chemotherapy in patients with hormone refractory prostate cancer receiving two sequences of mitoxantrone and taxanes	[260]	Prostate cancer	Inclusion		Inclusion as non-RCT
Randomized Multicenter Phase II Study of Gemcitabine Versus Docetaxel as First-Line Therapy with Second-Line Crossover in Advanced-Stage Non–Small-Cell Lung Cancer	[254]	NSCLC	Inclusion		Inclusion as RCT
Metastatic colorectal cancer: integrating irinotecan into combination and sequential chemotherapy	[649]	Colorectal cancer	Inclusion		Included as discussion
Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer (MRC FOCUS): a randomised controlled trial	[72]	Colorectal cancer	Inclusion		Inclusion as RCT
Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial	[71]	Colorectal cancer	Inclusion		Inclusion as RCT

EconLit search

This was undertaken in the database EconLit on the 15/06/2015 and after several unsuccessful attempts the very broad terms “chemotherapy” or “cancer” were used. 1330 results were returned. Four were removed as duplicates and the remainder had the titles and abstracts were reviewed, 32 were extracted for more comprehensive review.

Table 133: Results of EconLit search

Action	Criteria	Return
Search of EconLit	“"cancer" or "chemotherapy”” on 7/03/2014	1330
Removal of duplicates	Via endnote matching function	1326
Reviewed abstracts for full-text review	Included in full-text review	35

Full-text review	**Excluded**	**24**
	Excluded because not an article	2
	Excluded because not cancer	3
	Excluded because not multiple lines of therapy	16
	Excluded because not a choice in multiple lines of therapy	3
	Inclusion	**11**
	Included in Chapter 2	6
	Included in other papers in Chapter 3	5

Table 134: Results of full-text review of EconLit recovered articles

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Estimating Treatment Cost Functions for Progressive Diseases: A Multiproduct Approach with an Application to Breast Cancer	[301]	Breast cancer	Exclusion	Interesting discussion about costs in Australia	Costing	Not involving multiple lines of therapy
Sequencing surgery, radiotherapy and chemotherapy: insights from a mathematical analysis	[327]	Carcinoma	Exclusion		Nil	Not involving multiple lines of therapy
Analysis and comparison of multimodal cancer treatments	[326]	Carcinoma	Exclusion		Nil	Not involving multiple lines of therapy
A Bayesian Approach to Markov Modelling in Cost-Effectiveness Analyses: Application to Taxane Use in Advanced Breast Cancer	[329]	Breast cancer	Exclusion	Use of Markov modelling	Economic evaluation	Not involving multiple lines of therapy
Survival Analysis of Breast and Small-Cell Lung Cancer Patients Using Conditional Logistic Regression Models	[369]	Breast cancer, Small cell lung cancer	Exclusion	Modelling time to failure using conditional logistic models	Nil	Not involving multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Bayesian Model Averaging Continual Reassessment Method in Phase I Clinical Trials	[370]	Nil	Exclusion	Modelling toxicity	Nil	Not involving cancer
Reimbursement and value-based pricing: stratified cost-effectiveness analysis may not be the last word	[84]	All	Inclusion	Centred on the UK	Includes an example of first line and second line treatment	Included in the other articles discussed in Section 3.1.6
Modelling Population-Based Cancer Survival Trends by Using Join Point Models for Grouped Survival Data	[295]	All cancer	Exclusion	Modelling population-level survival	Nil	Not involving multiple lines of therapy
Cost study of the clinical management of prostate cancer in France: results on the basis of population-based data	[650]	Prostate cancer	Exclusion	Lowest costs with watchful waiting	Costing study	Not involving multiple lines of therapy
Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer: Comment	[113]	Prostate cancer	Inclusion	Modelling adaptive decision rules	Nil	Included in the other articles discussed in Section 3.1.8
Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer: Comment	[406]	Prostate cancer	Inclusion	Modelling adaptive decision rules	Nil	Included in the other articles discussed in Section 3.1.8
Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer: Comment: Erratum	[651]	Prostate cancer	Exclusion	Modelling adaptive decision rules	Nil	Not an article
Physician response to financial incentives when choosing drugs to treat breast cancer	[652]	Breast Cancer	Inclusion	Mainly centred on the US	Interesting discussion about choice of therapy	Included in the other articles discussed in Section 3.1.6

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Multilevel Bayesian Models for Survival Times and Longitudinal Patient-Reported Outcomes with Many Zeros	[414]	Mesothelioma	Exclusion	Combination of patient-reported outcome and survival data	Patient-reported outcomes	Not involving multiple lines of therapy
Landmark Prediction of Long-Term Survival Incorporating Short-Term Event Time Information	[421]	No cancer	Exclusion	Combination of short-term and long-term information		Not involving cancer
Valuing end-of-life care in the United States: the case of new cancer drugs	[6]	All	Inclusion	Mainly centred on the US	Good discussion about cost	Discussion included in Chapter 2
Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer	[112]	Prostate cancer	Inclusion	Modelling adaptive decision rules	Nil	Included in the other articles discussed in Section 3.1.8
Evaluation of Viable Dynamic Treatment Regimes in a Sequentially Randomized Trial of Advanced Prostate Cancer, Rejoinder	[432]	Prostate cancer	Exclusion	Modelling adaptive decision rules	Nil	Not an article
Improving the Efficiency of Cost-Effectiveness Analysis to Inform Policy Decisions in the Real-World: Lessons from the Pharmacoeconomics Research Unit at Cancer Care Ontario	[26]	All cancers	Inclusion	Importance of assumptions	Discussion about real-world cost-effectiveness	Discussion included in Chapter 2
A systematic review of economic evaluations in second and later lines of therapy for the treatment of non-small cell lung cancer	[83]	Non-small cell lung cancer	Exclusion	3 state Markov models most common	Cost-effectiveness	Not involving a choice in multiple lines of therapy
The Impact of Recent Chemotherapy Innovation on the Longevity of Myeloma Patients: U.S. and International Evidence	[444,445]	Multiple myeloma	Inclusion	Increases in the number of regimes associated with larger declines in mortality rate	Relationship between survival and number of therapies	Discussion included in Chapter 2

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Cancer Survival Extension from Drug Treatments	[449]	Lung, colon and breast cancer	Exclusion	Survival benefit attributable to new therapies	Nil	Not involving a choice in multiple lines of therapy
Cancer Care: Assuring Quality to Improve Survival	[450]	All cancer	Exclusion	Wide variation in the inputs to cancer care	Nil	Not involving multiple lines of therapy
The Log-Beta Weibull Regression Model with Application to Predict Recurrence of Prostate Cancer	[451]	Prostate cancer	Exclusion	Probability of being recurrence free	Nil	Not involving multiple lines of therapy
Joint Confidence Region Estimation of L-Moment Ratios with an Extension to Right Censored Data	[460]	Breast cancer	Exclusion	Censoring information	Nil	Not involving multiple lines of therapy
Estimating Person-Centered Treatment (PeT) Effects Using Instrumental Variables: An Application to Evaluating Prostate Cancer Treatments	[468]	Prostate cancer	Exclusion	Person centred treatment effects	Nil	Not involving multiple lines of therapy
Generalized Inverse Multiobjective Optimization with Application to Cancer Therapy	[470]	Prostate cancer	Exclusion	Inverse optimisation problem	Nil	Not involving multiple lines of therapy
Steady-State Gibbs Sampler Estimation for Lung Cancer Data	[477]	Lung cancer	Exclusion	Use of Weibull survival model as stopping rule	Nil	Not involving multiple lines of therapy
Paying on the Margin for Medical Care: Evidence from Breast Cancer Treatments	[478]	Breast cancer	Exclusion	Welfare gains from health insurance policies	Benefit from alternative treatments	Not involving multiple lines of therapy
Semiparametric Selection Models with Binary Outcomes	[485]	Nil	Exclusion	Econometrics	Nil	Not involving cancer
Has Medical Innovation Reduced Cancer Mortality?	[487]	All cancers	Inclusion	Increasing numbers of cancer molecules becoming available	Increasing technology leads	Discussion included in Chapter 2

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
					to increasing benefit	
Economic Evaluations of Trastuzumab in HER2-Positive Metastatic Breast Cancer: A Systematic Review and Critique	[492]	Breast cancer	Exclusion	Wide variety of techniques and drivers of cost-effectiveness ratios	Review of economic evaluations	Not involving a choice in multiple lines of therapy
Regularized Regression Incorporating Network Information: Simultaneous Estimation of Covariate Coefficients and Connection Signs	[503]	Ovarian cancer, B-cell lymphoma	Exclusion	Review of higher dimension data	Nil	Not involving multiple lines of therapy
Pricing in the Market for Anticancer Drugs	[27]	All cancers	Inclusion	Rapidly increasing numbers of drugs	Increasing prices	Discussion included in Chapter 2
The Impact of Pharmaceutical Innovation on Premature Mortality, Cancer Mortality, and Hospitalization in Slovenia, 1997-2010	[535]	All cancers	Inclusion	Increasing numbers of new chemical entities	Low cost per life year saved	Discussion included in Chapter 2

The references from the selected articles were also searched and several other articles were added to the literature review

Table 135: Additional articles recovered from 'pearl' searching for recovered EconLit articles

Title	Reference	Type of Cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
The price tag on progress--chemotherapy for colorectal cancer	[25]	Colorectal	Inclusion	Mainly centred on the US	Increasing colorectal cancer costs in multiple lines of therapy	Discussion included in Chapter 2

Title	Reference	Type of Cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Lessons from a time capsule: evolution, not revolution, in therapy for advanced non-small-cell lung cancer	[653]	NSCLC	Inclusion	Discussion including importance of multiple lines of therapy		Discussion included in Chapter 2
Projections of the cost of cancer care in the United States: 2010-2020	[60]	All	Inclusion	Mainly centred on the US	Discussion about increasing costs of cancer based on recent treatment trends	Discussion included in Chapter 2

PubMed search

Searched PubMed with search string ((("cancer") AND "first-line") AND "second") AND (("sequence" or "algorithm")) on the 27/06/2017

Table 136: PubMed search

Action	Criteria	Return
Search of PubMed	((("cancer") AND "first-line") AND "second") AND (("sequence" or "algorithm")) on 27/06/2016	217
Remove duplicates	Removed 1 using endnote function	216
Removal of duplicates from previous searches	Removed 122 from prior searches	96
Full-text review	Removed 40 on title and abstract screen	54
Outcome of full-text review	**Inclusion**	**22**
	Inclusion for discussion	14
	Inclusion as non-randomised controlled trials	3
	Inclusion as randomised controlled trial	3
	Inclusion as economic evaluation	2
	Exclusion	**32**
	Unable to gain a copy in English	2

Action	Criteria	Return
	Not involving human subjects	2
	Not involving chemotherapy	3
	Not involving multiple lines of therapy	9
	Not involving a choice in multiple lines of therapy	16

Table 137: Inclusion and exclusions of PubMed search

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Systemic Therapy for Metastatic Colorectal Cancer: Patterns of Chemotherapy and Biologic Therapy Use in US Medical Oncology Practice	[176]	CRC	Inclusion	Discussion of lines of therapy	Nil	Included for discussion
Treatment paradigms for patients with metastatic non-small cell lung cancer, squamous lung cancer: first, second, and third-line	[654]	Lung cancer	Inclusion	Discussion of lines of therapy	Nil	Included for discussion
A population-based overview of sequences of targeted therapy in metastatic renal cell carcinoma	[655]	Renal cell carcinoma	Inclusion	Real-world consideration of numbers of patients receiving therapy	Nil	Included as non-RCT
Maintaining clarity: Review of maintenance therapy in non-small cell lung cancer	[656]	NSCLC	Exclusion	Overview of the potential treatment options	Nil	Not a choice in multiple lines of therapy
Axitinib versus sorafenib in advanced renal cell carcinoma: subanalyses by prior therapy from a randomised phase III trial	[657]	Renal cell carcinoma	Exclusion	Re-analysis of a second line clinical trial	Nil	Not involving multiple lines of therapy
No clear evidence of a clinical benefit of a sequential therapy regimen with abiraterone acetate and enzalutamide	[658]	Prostate cancer	Exclusion	Discussion of anti-androgen therapy	Nil	Not involving chemotherapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Treatment patterns in metastatic renal cell carcinoma: a retrospective review of medical records from US community oncology practices	[659]	Renal cell carcinoma	Inclusion	Real-world consideration of numbers of patients receiving therapy	Nil	Included as non-RCT
Docetaxel and intermittent erlotinib in patients with metastatic Non-Small Cell Lung Cancer; a phase II study from the Hellenic Cooperative Oncology Group	[660]	NSCLC	Exclusion	Trial involving sequencing of agents within a line of therapy	Nil	Not involving multiple lines of therapy
Targeted therapies in metastatic colorectal cancer: a systematic review and assessment of currently available data	[661]	CRC	Exclusion	Overview of the use of targeted therapies in CRC	Nil	Not a choice in multiple lines of therapy
Colorectal Cancer: Personalized Therapy	[662]	CRC	Exclusion	Review of selection of first line therapy	Nil	Not involving multiple lines of therapy
[Treatment of advanced NSCLC with unknown EGFR gene status--TKI or chemotherapy?]	[663]	NSCLC	Exclusion	-	-	Unable to gain a copy in English
Treatment algorithm in 2014 for advanced non-small cell lung cancer: therapy selection by tumour histology and molecular biology	[664]	NSCLC	Exclusion	Discussion about increasing customisation of treatment	Nil	Not a choice in multiple lines of therapy
Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma	[252]	Renal cell carcinoma	Inclusion	Two alternative treatment sequences	Nil	Included as an RCT
Predictors of CD34+ cell mobilization and collection in adult men with germ cell tumors: implications for the salvage treatment strategy	[665]	Germ cell tumour	Exclusion	Discussion about salvage for stem cell therapy	Nil	Not a choice in multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Improving outcomes in metastatic clear cell renal cell carcinoma by sequencing therapy	[666]	Renal cell carcinoma	Inclusion	Discussion about appropriate sequencing	Nil	Included for discussion
Optimal first-line and second-line treatments for metastatic renal cell carcinoma: current evidence	[667]	Renal cell carcinoma	Inclusion	Discussion about appropriate sequencing	Nil	Included for discussion
Sequential treatment of icotinib after first-line pemetrexed in advanced lung adenocarcinoma with unknown EGFR gene status	[668]	NSCLC	Exclusion	Retrospective review of second line treatment	Nil	Not involving multiple lines of therapy
New treatment options for ALK-Rearranged Non-Small Cell Lung cancer	[669]	NSCLC	Exclusion	Treatment options for first line therapy	Nil	Not involving multiple lines of therapy
Generations of epidermal growth factor receptor tyrosine Kinase inhibitors: Perils and progress	[670]	NSCLC	Exclusion	Treatments involving EGFR mutations	Nil	Not a choice in multiple lines of therapy
STRATEGIC-1: A multiple-lines, randomized, open-label GERCOR phase III study in patients with unresectable wild-type RAS metastatic colorectal cancer	[671]	CRC	Inclusion	Sequencing involving two lines of therapy- protocol only	Nil	Included as discussion
Effects of preset sequential administrations of sunitinib and everolimus on tumour differentiation in Caki-1 renal cell carcinoma	[672]	Renal cell carcinoma	Exclusion	In vitro experimentation	Nil	Not involving human subjects
SWITCH: A randomised, sequential, open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell cancer	[118]	Renal cell carcinoma	Inclusion	Sequencing involving two lines of therapy	Nil	Included as an RCT

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Outcomes from second-line therapy in long-term responders to first-line tyrosine kinase inhibitor in clear-cell metastatic renal cell carcinoma	[673]	Renal cell carcinoma	Exclusion	Retrospective outcomes of treatment sequences but all patients received TKI in first line	Nil	Not a choice in multiple lines of therapy
Treatment algorithms in Stage IV melanoma	[674]	Melanoma	Inclusion	Discussion of sequencing	Nil	Included for discussion
Everolimus and temsirolimus are not the same second-line in metastatic renal cell carcinoma. A systematic review and meta-analysis of literature data	[675]	Renal cell carcinoma	Exclusion	Comparison of second line treatment	Nil	Not involving multiple lines of therapy
Molecular analysis of sunitinib resistant renal cell carcinoma cells after sequential treatment with RAD001 (everolimus) or sorafenib	[676]	Renal cell carcinoma	Exclusion	In vitro experimentation	Nil	Not involving human subjects
Identifying activating mutations in the EGFR gene: prognostic and therapeutic implications in non-small cell lung cancer	[677]	NSCLC	Exclusion	Review of the activating mutations in the EGFR gene	Nil	Not a choice in multiple lines of therapy
Optimizing the sequence of anti-EGFR-targeted therapy in EGFR-mutant lung cancer	[678]	NSCLC	Inclusion	Considering the treatment sequence for NSCLC	Nil	Included for discussion
Efficacy of chemotherapy after first-line gefitinib therapy in EGFR mutation-positive advanced non-small cell lung cancer-data from a randomized phase III study comparing gefitinib with carboplatin plus paclitaxel (NEJ002)	[679]	NSCLC	Exclusion	Impact of chemotherapy after first line EGFR therapy	Nil	Not involving multiple lines of therapy
Impact of Subsequent Therapies on Outcome of the FIRE-3/AIO KRK0306 trial: First-Line Therapy With FOLFIRI Plus Cetuximab or Bevacizumab in Patients With KRAS Wild-Type Tumors in Metastatic Colorectal cancer	[271]	CRC	Inclusion	Impact of later line chemotherapy	Nil	Included for discussion

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Sequencing systemic therapies for metastatic kidney cancer	[680]	Renal cell carcinoma	Inclusion	Review of evidence for sequencing treatments in renal cell carcinoma	Nil	Included for discussion
Appropriateness of systemic treatments in unresectable metastatic well-differentiated pancreatic neuroendocrine tumors	[681]	Neuroendocrine tumour	Exclusion	Delphi review of possible options	Nil	Not a choice in multiple lines of therapy
Efficacy and Safety of Sequential Use of Everolimus in Patients With Metastatic Renal Cell Carcinoma Previously Treated With Bevacizumab With or Without Interferon Therapy: Results From the European AVATOR Study	[682]	Renal cell carcinoma	Exclusion	Review of second line therapy after known first line treatment	Nil	Not involving multiple lines of therapy
Efficacy of targeted treatment beyond third-line therapy in metastatic kidney cancer: retrospective analysis from a large-volume cancer center	[683]	Renal cell carcinoma	Inclusion	Discussion of fourth line treatment of renal cell carcinoma	Nil	Included for discussion
Simulation and comparison of progression-free survival among patients with non-squamous non-small-cell lung cancer receiving sequential therapy	[553]	NSCLC	Inclusion	Simulation of up to five lines of therapy	Nil	Included for discussion
Comparison of Gefitinib Versus Chemotherapy in Patients with Non-small Cell Lung Cancer with Exon 19 Deletion	[684]	NSCLC	Exclusion	Comparison of Gefitinib versus chemotherapy within a line of therapy	Nil	Not involving multiple lines of therapy
[Sequential Treatment of Advanced Squamous Lung Cancer: First-line Gemcitabine +/- platinum Followed by Second-line Taxanes +/- platinum Versus Reverse Sequence]	[685]	NSCLC	Exclusion	Retrospective comparison of sequences of lines of therapy	Nil	Unable to gain a copy in English
Axitinib after Sunitinib in Metastatic Renal Cancer: Preliminary Results from Italian "Real-World" SAX Study	[686]	Renal cell carcinoma	Exclusion	Retrospective review of axitinib in combination with sunitinib	Nil	Not a choice in multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Cost-effectiveness analysis of 1st through 3rd line sequential targeted therapy in HER2-positive metastatic breast cancer in the United States	[687]	Breast cancer	Inclusion	Economic evaluation of multiple lines of therapy	Yes	Inclusion in economic evaluation of multiple lines of therapy
Sequencing Treatment for Castration-Resistant Prostate Cancer	[688]	Prostate cancer	Inclusion	Discussion of sequencing therapy	Nil	Included for discussion
Comparative Assessment of Efficacies Between 2 Alternative Therapeutic Sequences With Novel Androgen Receptor-Axis-Targeted Agents in Patients With Chemotherapy-Naive Metastatic Castration-Resistant Prostate Cancer	[689]	Prostate cancer	Exclusion	Discussion of sequencing therapy of androgen deprivation	Nil	Not involving chemotherapy
Patterns of Treatment Sequences in Chemotherapy and Targeted Biologics for Metastatic Colorectal Cancer: Findings from a Large Community-Based Cohort of Elderly Patients	[690]	CRC	Inclusion	Empirical distribution of treatments in colorectal cancer	Nil	Included for discussion
Efficacy of a sequential treatment strategy with GEMOX-based followed by FOLFIRI-based chemotherapy in advanced biliary tract cancers	[691]	Biliary tract cancer	Exclusion	Retrospective review of treatment sequences for biliary cancer	Nil	Not a choice in multiple lines of therapy
CpG island methylator phenotype is associated with the efficacy of sequential oxaliplatin- and irinotecan-based chemotherapy and EGFR-related gene mutation in Japanese patients with metastatic colorectal cancer	[692]	CRC	Exclusion	Review of genetic impacts on survival	Nil	Not a choice in multiple lines of therapy
Advances in management of hepatocellular carcinoma	[693]	Hepatocellular carcinoma	Exclusion	Review of recent treatment advances	Nil	Not a choice in multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
Chemotherapy for ovarian cancer in the Netherlands: a population-based study on treatment patterns and outcomes	[694]	Ovarian cancer	Inclusion	Empirical distribution of treatments in ovarian cancer	Nil	Included for discussion
Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC	[253]	Renal cell carcinoma	Inclusion	Crossover trial involving treatment sequence in first and second line of therapy	Nil	Included as an RCT
Relation of early tumor shrinkage (ETS) observed in first-line treatment to efficacy parameters of subsequent treatment in FIRE-3 (AIOKRK0306)	[695]	CRC	Exclusion	Correlation of shrinkage and overall survival	Nil	Not a choice in multiple lines of therapy
Cost-Effectiveness of Treatment Sequences of Chemotherapies and Targeted Biologics for Elderly Metastatic Colorectal Cancer Patients	[696]	CRC	Inclusion	Economic evaluation of multiple lines of therapy	Yes	Inclusion in economic evaluation of multiple lines of therapy
Survival of melanoma patients treated with novel drugs: retrospective analysis of real-world data	[697]	Melanoma	Inclusion	Real-world data on treatment sequences in melanoma	Nil	Included as non-RCT
Sequential treatment of tyrosine kinase inhibitor and platinum-based doublet chemotherapy on EGFR mutant non-small cell lung cancer: a meta-analysis of randomized controlled clinical trials	[698]	NSCLC	Exclusion	Meta-analysis of survival	Nil	Not a choice in multiple lines of therapy
Immune Checkpoint Inhibitor Therapy: What Line of Therapy and How to Choose?	[699]	NSCLC	Exclusion	Discussion of new treatments in NSCLC	Nil	Not a choice in multiple lines of therapy
Can we define the optimal sequence of epidermal growth factor receptor tyrosine kinase inhibitors for the treatment of	[700]	NSCLC	Exclusion	Discussion of recent studies for EGFR TKIs	Nil	Not a choice in multiple lines of therapy

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
epidermal growth factor receptor-mutant nonsmall cell lung cancer?						
Exploring the optimal sequence of abiraterone and enzalutamide in patients with chemotherapy-naive castration-resistant prostate cancer: The Kyoto-Baltimore collaboration	[701]	Prostate cancer	Exclusion	Retrospective review	Nil	Not involving chemotherapy

From the included articles above, some more articles were reviewed.

Table 138: Pearl searched articles from PubMed search

Title	Reference	Type of cancer	Inclusion/Exclusion	Comment	Economic	Reason for exclusion
First-line erlotinib versus gemcitabine/cisplatin in patients with advanced EGFR mutation-positive non-small-cell lung cancer: analyses from the phase III, randomized, open-label, ENSURE study	[702]	NSCLC	Exclusion		Nil	Not involving multiple lines of therapy
Sequential Therapies and the Cost-Effectiveness of Treating Metastatic Colon Cancer Patients	[703]	CRC	Exclusion		Yes	Included in Section 2.1 as discussion

Appendix F: Data extraction of studies for two or more lines of therapy

Randomised controlled trials identified in the literature

Only a small number (12) randomised controlled trials (RCT), reported in 13 papers, were identified from the literature search. The details of the original search and the pearl search are in Appendix E. An element of caution must be noted regarding the completeness because five papers were identified through the pearl searching rather than through keywords.

The data extracted included the criteria of quality as determined by the CONSORT checklist.[247] Details of the study design, population of interest, protocol and criteria to move from one line of therapy to the next were extracted. Information about the outcomes of overall survival (OS) (median and one-year), progression free survival (PFS) (median), overall response (OR) and disease control (DC) were extracted. Information about adverse events was also extracted. In the absence of documental outcomes for median OS, median PFS or one-year survival the survival curves were used in by visual inspection and ruler measurement.

To provide some degree of comparability between studies, the different types of progression are discussed. Unfortunately, there is no standard set of nomenclature for progression over two lines of therapy. The approach taken is the form PFS_{nm}, where n and m represent the time from the beginning to either progression or death. For example, PFS_{01} represents from recruitment to progression or death in the first line of therapy, PFS_{02} represents from recruitment to progression or death in the second line of therapy, PFS_{12} represents the beginning of the protocol in the second line of therapy to progression or death.

Toxicity is also an important area where comparisons can be made. Only a proportion of patients move onto a second line therapy and often the length of time on a second line therapy is less than that on a first line therapy. Therefore, adverse event per unit time would have been the most useful indicator but this was often not available, and a number of proxies have been used. These proxies included the calculated incidence of grade 3 or grade 4 adverse events per median time and per median number of cycles of chemotherapy.

None of these trials were designed for the pseudo-crossover. Therefore, a second set of quality indicators for the purpose of assessing the information produced for comparing protocols in two different lines of therapy using a meta-analysis. If all of the points were

scored as present, then all of the analysis expected to be undertaken in Section 6.2 could be completed.

One point was scored for each of the following:

- median PFS_{01} and median PFS_{12} were described separately with a confidence interval;
- the number of events or the number of patients at risk was enumerated for each PFS;
- OS and one-year survival was described separately with a confidence interval;
- response rate and disease control rate were described separately for each line of therapy;
- adverse events were described for each line of therapy with at least three been described in each line of therapy and a total for grade 3 and 4 also required; and
- the number of cycles of the protocols and intensity were described for each line of therapy.

This produced a score of up to six for each article.

Tournigand et al. (2004)[68]

Tournigand et al. (2004)[68] was a phase III trial of patients who had metastatic colorectal cancer (CRC). It considered the introduction of two new pharmaceuticals (oxaliplatin and irinotecan) against the background of an older pharmaceutical (5-FU). Combinations of pharmaceuticals (oxaliplatin and 5-FU [FOLFOX] and irinotecan and 5-FU[FOLFIRI]) had been shown to have activity in both first and second line therapy. The trial was to give one agent initially and then the other post-progression or after unacceptable toxicity. Treatment continued until progression, unacceptable toxicity or patient choice. The eligibility criteria of the trial were broad for patient performance status (WHO 0-2) but restrictive for the level of liver disease allowed. There was both external and investigator review of progression.

226 patients were recruited, six patients were not treated, and the remaining 220 were analysed. 109 were in the arm that received FOLFIRI followed by FOLFOX and 111 were in the arm that received FOLFOX followed by FOLFIRI.

Table 139: Trial arms for Tournigand et al. (2004)[68]

Description	First line protocol	Second line protocols	Change with progression	Change with toxicity
FOLFIRI/FOLFOX	FOLFIRI	FOLFOX	Yes	Yes
FOLFOX/FOLFIRI	FOLFOX	FOLFIRI	Yes	Yes

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Table 140: CONSORT quality checklist for Tournigand et al. (2004)[68]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	229	
1b	Structured summary	Yes	229	
2a	Scientific background	Yes	229-230	
2b	Specific Objectives	Yes	230	To evaluate the best sequence of treatment of the two new pharmaceuticals
3a	Description of trial design	Yes	230-231	
3b	Important changes after commencement	N/A		
4a	Eligibility criteria	Yes	230	Adenocarcinoma of the colon and rectum with at least one unresectable metastasis WHO 0-2 Age 18-75
4b	Setting and location	No		The study authors were all French
5	Interventions described	Yes	230-231	Included a diagram of the chemotherapy
6a	Completely defined prespecified outcome measures	Yes	231	PFS_{02} was the primary outcome measure
6b	Changes to trial outcomes after commencement	No		The trial design was not altered
7a	Sample size determined	Yes	231	80% power to detect a 20% difference
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	Yes		Stratified by centre and presence or absence of measurable disease
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	No	230	The blinding was not discussed. The scans were subject to external review, but it was not discussed whether the reviewers were not blinded
11b	Similarity of interventions	Yes	230	
12a	Statistical methods used	Yes	231	Discussion of the statistical analysis undertaken
12b	Methods for additional analysis	No		

Number	Checklist item	Yes/No	Page reported	Comments
13a	Numbers in each group	Yes	231	Discussed in patient characteristics
13b	For each group, losses and exclusions after randomisation	Yes	231	Discussed in patient characteristics
14a	Dates defining recruitment and follow up	Yes	231-232	
14b	Why the trial ended or was stopped	Yes	231-232	
15	A table showing baseline demographics	Yes	Table 1, 231	
16	For each group, the number of participants and whether by original assignment	Yes	231	Discussed in patient characteristics
17a	Effect size and confidence interval included	Yes	232	Confidence interval for each OS
17b	For binary results- absolute and relative included	No	233	Only the absolute difference for differences in toxicity and response rates presented
18	Results of other analyses included	Yes	232-235	Tumour response, toxicity, PFS, chemotherapy dosage and performance status
19	Harms included	Yes	233-234	Toxicity was a section within the results
20	Trial limitations discussed	Yes	235-236	
21	Generalisability discussed	Yes	235-236	
22	Interpretation consistent with results discussed	Yes	235-236	
23	Registration number	No		
24	Where the full trial protocol can be accessed	No		Not discussed
25	Sources of funding	Yes	229	Sponsored by Aventis, Paris, France

Abbreviations: PFS: progression free survival; RCT: randomised controlled trial; WHO: World Health Organization

Table 141: Quality of comparison information in Tournigand et al. (2004)[68]

Number	Checklist item	Score	Page reported	Notes
1	PFS_{01} and PFS_{12}	1	232	All reported
2	Number at risk or number of events	0	N/A	Not reported
3	OS and 1 year survival	0.5	N/A	Overall survival was reported but not 1-year survival
4	OR and DC rate	1	Table 2, page 232	
5	Adverse events	1	Table 3, page 234	
6	Usage	1	233-234	Medians only were reported

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Overall there was no statistical difference between the two groups on median survival. It was 21.5 months for FOLFIRI/FOLFOX and 20.6 months for FOLFOX/FOLFIRI. The factors associated with increased survival included good performance status and markers of limited disease. The second line therapy in FOLFIRI/FOLFOX arm had a longer PFS, than the FOLFOX/FOLFIRI arm. The delay to treatment in the second line setting was a median of 15 (in the FOLFOX/FOLFIRI arm) and 21 days (in the FOLFIRI/FOLFOX arm) after the identification of progression in the first line setting.

Table 142: Outcome results for Tournigand et al. (2004)[68]

Descriptor	FOLFIRI/FOLFOX	FOLFOX/FOLFIRI
Overall survival median	21.5 (16.9-25.2) months	20.6 (17.7-24.6) months
Source of information	Text on page 232	Text on page 232
One-year survival rate	Not reported	Not reported
Source of information	Estimated from Figure 4, page 233	Estimated from Figure 4, page 233
Progression free survival for first line therapy (PFS_{01}) median	8.5 (7.0-9.5) months	8 (6.2-9.4) months
Source of information	Text on page 232	Text on page 232
Progression free survival for second line therapy (PFS_{12})	4.2 months	2.5 months
Source of information	Text on page 232	Text on page 232
Progression free survival for both therapies (PFS_{02}) median	14.2 (12-16.9) months	10.9 (9.0-14.6) months
Source of information	Text on page 232	Text on page 232
Portion of group receiving second line therapy	74%	62%
Source of information	Text on page 232	Text on page 232
Overall response rate in first line	56%	54%
Source of information	Table 2 on page 233	Table 2 on page 233
Overall response rate in second line	15%	4%
Source of information	Table 2 on page 233	Table 2 on page 233
Disease control rate in first line	76%	81%
Source of information	Table 2 on page 233, combined overall response rate and stable disease rate	Table 2 on page 233, combined overall response rate and stable disease rate
Disease control rate in second line	63%	34%
Source of information	Table 2 on page 233, combined overall response rate and stable disease rate	Table 2 on page 233, combined overall response rate and stable disease rate

Abbreviations: Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Patients who received FOLFIRI in the first line received a median of 13 cycles. While those that received FOLFIRI in the second line received a median of six cycles. Six patients had to stop FOLFIRI for toxicity in the first line, and one patient had to stop for toxicity while receiving second line therapy.

Table 143: Toxicity of FOLFIRI in Tournigand et al. (2004)[68]

Indicator of FOLFIRI	In First Line	In Second Line
Progression free survival	8.5 months	2.5 months
Number of patients	110	68
Median cycles	13	6
Intensity	Irinotecan 85.9% 5-FU 22%	Irinotecan 87.3% 5-FU 11%
Grade 3 or 4 neutropenia (%)	24%	21%
% per cycle (median)	1.84%	3.5%
% per PFS (median) per year	33.89%	100.8%
Grade 3 or 4 febrile neutropenia (%)	7%	1%
% per cycle (median)	0.5%	0.2%
% per PFS (median in years)	9.9%	4.8%
Grade 3 or 3 diarrhoea (%)	14%	8%
% per cycle (median)	1.1%	1.3%
% per PFS (median) per year	19.8%	38.4%

Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; PFS: progression free survival

Patients who received FOLFOX in the first line received a median of 12 cycles. While those that received it in the second line received a median of eight cycles. 12 patients had to stop treatment with FOLFOX in the first line compared to ten patients in the second line.

Table 144: Toxicity of FOLFOX in Tournigand et al. (2004)[68]

Indicator of FOLFOX	In First Line	In Second Line
Progression free survival	8 months	4.2 months
Number of patients	110 patients	82 patients
Median cycles	12 cycles	8 cycles
Intensity	Oxaliplatin 84.7% 5-FU 33%	Oxaliplatin 90.1% 5-FU 10%
Grade 3 or 4 neutropenia (%)	44%	17%
% per cycle (median)	3.7%	2.1%
% per PFS (median) per year	66.0%	48.6%
Grade 3 or 4 febrile neutropenia (%)	0%	1%
% per cycle (median)	0%	0.1%
% per PFS (median) per year	0%	2.9%

Indicator of FOLFOX	In First Line	In Second Line
Grade 3 or 3 neurological (%)	34%	20%
% per cycle (median)	2.8%	2.5%
% per PFS (median) per year	51%	57.1%

Abbreviations: 5-FU: 5-fluorouracil; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; PFS: progression free survival

Manegold et al. (2005)[254]

Manegold et al. (2005)[254] was a phase II trial published in 2005. It was a trial of patients with NSCLC with sequential treatment of gemcitabine and docetaxel. The trial was ceased because of poor recruitment resulting from the lack of docetaxel being given for two cycles. It should be noted that the use of single agent treatment in patients with good performance status is now considered an inferior treatment with one of the influential trials being published at the same time as Manegold et al. (2005). The resultant change in the standard of therapy may have had an impact on recruitment.

Inclusion criteria were reasonable with performance status 0-2 being included. Patients were randomised to one of two arms. For those patients randomised to the gemcitabine first arm a maximum of six cycles of treatment was given. The same number of cycles was given for the docetaxel first arm. Two cycles were to be given before progression of disease was considered and in order to be considered for the trial 2 months of the first pharmaceutical had to be given. This is an impediment of the trial as an "intent to treat" analysis cannot be undertaken. Toxicity was not a criterion for failure and movement onto the next line of treatment.

150 patients were recruited, 101 patients into the gemcitabine first arm and 49 into the docetaxel first arm. Three patients in the gemcitabine first arm did not receive the study pharmaceuticals. The lower rate of docetaxel patients was not due to a 2:1 randomisation strategy but rather because of the lack of feasibility of treatment.

Table 145: CONSORT quality checklist for Manegold et al. (2005)[254]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	208	Randomized Multicenter Phase II Study of Gemcitabine Versus Docetaxel as First-Line Therapy with Second-Line Crossover in Advanced-Stage Non–Small-Cell Lung Cancer
1b	Structured summary	Yes	208	
2a	Scientific background	Yes	208-209	
2b	Specific Objectives	Yes	209	

Number	Checklist item	Yes/No	Page reported	Comments
3a	Description of trial design	Yes	209-210	
3b	Important changes after commencement	Yes	210	As a result of the planned interim analysis the feasibility of the arm containing docetaxel was low and that arm ceased recruitment
4a	Eligibility criteria	Yes	209	
4b	Setting and location	Yes	210	11 centres in Germany
5	Interventions described	Yes	209-210	
6a	Completely defined prespecified outcome measures	Yes	209-210	Main outcome measure was to be feasibility. Feasibility was defined as two or more complete cycles of first line treatment, two or more treatments in second line treatment and a survival of greater than 7 months from the start of treatment
6b	Changes to trial outcomes after commencement	Yes	210	Feasibility was not achieved
7a	Sample size determined	Yes	210	Interim analysis to be performed after 34 patients in each arm. Maximum number of patients to be enrolled was 190
7b	Explanation of interim analysis and stopping design	Yes	210	Interim analysis to be performed after 34 patients in each arm. Maximum number of patients to be enrolled was 190
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	No		
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	No		
11b	Similarity of interventions	Yes		In that both interventions were intravenous treatments
12a	Statistical methods used	No	210	There was a discussion about how the point estimate for the primary endpoint was to be calculated
12b	Methods for additional analysis	Yes	210	Some discussion of statistical tests for secondary endpoints
13a	Numbers in each group	Yes	210	101 on the gemcitabine/docetaxel arm and 49 on the docetaxel/gemcitabine

Number	Checklist item	Yes/No	Page reported	Comments
13b	For each group, losses and exclusions after randomisation	Yes	210	3 patients in the gemcitabine/docetaxel arm did not receive treatment
14a	Dates defining recruitment and follow up	Yes	210	From February 1998 to January 1999
14b	Why the trial ended or was stopped	Yes	210	
15	A table showing baseline demographics	Yes	210, Table 2	
16	For each group, the number of participants and whether by original assignment	Yes	210	101 on the gemcitabine/docetaxel arm and 49 on the docetaxel/gemcitabine
17a	Effect size and confidence interval included	No	210	The primary endpoint was feasibility, only the point estimates were given for this
17b	For binary results- absolute and relative included	No	Table 4	Only absolute numbers for tumour response were included
18	Results of other analyses included	Yes	211	
19	Harms included	Yes	211	
20	Trial limitations discussed	Yes	212	
21	Generalisability discussed	Yes	212	
22	Interpretation consistent with results discussed	Yes	212	
23	Registration number	No		
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	Yes	213	The study was supported by grants from Lilly Deutschland GmbH, Bad Homburg, Germany; and Aventis Pharma Deutschland GmbH, a company of the Sanofi-Aventis Group, Berlin, Germany

Abbreviation: RCT: randomised controlled trial

Table 146: Quality checklist for data extraction for Manegold et al. (2005)[254]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0	N/A	The PFS for first line treatment was discussed but not the PFS_{12}

Number	Checklist item	Score	Page reports	Notes
2	Number at risk or number of events	0	N/A	Not reported
3	OS and 1 year survival	0	211	Confidence intervals were not included
4	OR and DC rate	1	Table 4	Additionally, the length of response was reported
5	Adverse events	0	Table 5	Aggregates for each arm of the trial were reported but not by individual line of therapy
6	Usage	1	210-211	Medians were presented

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

There was a higher first line mortality for patients in the docetaxel arm. Nine patients died within two cycles of treatment. The subgroup of patients who received two pharmaceuticals had improved outcomes compared to the larger population.

Table 147: Outcome results for Mangold et al. (2005)[254]

Descriptor	Gemcitabine/Docetaxel	Docetaxel/Gemcitabine
Overall survival median	9 months	5 months
Source of information	Page 211	Page 211
One-year survival rate	32%	21%
Source of information	Page 211	Page 211
Progression free survival for first line therapy (PFS_{01}) median	4.3 months	2.2 months
Source of information	Page 211- note these results were for time to progression rather than progression free survival	Page 211- note these results were for time to progression rather than progression free survival
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	Not reported	Not reported
Source of information	N/A	N/A
Portion of group receiving second line therapy	39%	39%
Source of information	Table 4	Table 4
Overall response rate in first line	10%	8%
Source of information	Table 4	Table 4
Overall response rate in second line	5%	11%
Source of information	Table 4	Table 4

Descriptor	Gemcitabine/Docetaxel	Docetaxel/Gemcitabine
Disease control rate in first line	55%	45%
Source of information	Table 4	Table 4
Disease control rate in second line	36%	43%
Source of information	Table 4	Table 4

Toxicities were reported in aggregate in Table 5 of the publication, individual toxicities within each line of therapy were not reported.

Koopman et al. (2007)[71]

Koopman et al. (2007)[71] was a phase III trial. It was a trial of patients with untreated metastatic CRC. It had two arms and patients were treated with three pharmaceuticals for CRC (irinotecan, oxaliplatin and the oral equivalent of 5-FU [capecitabine]). Eight hundred and twenty patients were recruited for the trial. The only protocol that was repeated between the arms of the trial was capecitabine and oxaliplatin. This protocol was in the third line of the sequential arm and the second line of the combination arm. Disease progression and unacceptable toxicity were reasons for movement onto a later line of therapy.

Table 148: Trial arms for Koopman et al. (2007)[71]

Description	First line treatment	Second line treatment	Third line treatment
Sequential	Capecitabine	irinotecan	capecitabine and oxaliplatin
Combination	capecitabine plus irinotecan	capecitabine and oxaliplatin	

Table 149: CONSORT quality checklist for Koopman et al. (2007)[71]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	135	Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial
1b	Structured summary	Yes	135	
2a	Scientific background	Yes	135	
2b	Specific Objectives	Yes	135	The specific objective was to investigate if combination treatment was better than sequential treatment
3a	Description of trial design	Yes	135-136	

Number	Checklist item	Yes/No	Page reported	Comments
3b	Important changes after commencement	No		Not discussed
4a	Eligibility criteria	Yes	136	
4b	Setting and location	Yes	135	74 centres in the Netherlands
5	Interventions described	Yes	136	
6a	Completely defined prespecified outcome measures	Yes	138	Primary endpoint was overall survival
6b	Changes to trial outcomes after commencement	No		Not discussed
7a	Sample size determined	Yes	137-138	A sample size of 800 was estimated to be required to have an 80% power to detect a 20% reduction in the hazard of death
7b	Explanation of interim analysis and stopping design	Yes	139	An interim safety analysis was undertaken and had been published
8a	Method used to generate random allocation	Yes	137	Randomisation was done centrally by a minimisation technique with stratification according WHO performance status, LDH, previous adjuvant treatment, predominant metastases and treatment centre
8b	Type of randomisation and restriction	Yes	137	Randomisation was done centrally by a minimisation technique with stratification according WHO performance status, LDH, previous adjuvant treatment, predominant metastases and treatment centre
9	Allocation concealment	Yes	137	Randomisation was done centrally by a minimisation technique with stratification according WHO performance status, LDH, previous adjuvant treatment, predominant metastases and treatment centre
10	Who generated allocation, enrolment and assignment	Yes	137	It was generated centrally
11a	Blinding	Yes	135	This was an open-label study; CT scans were assessed by the investigators
11b	Similarity of interventions	Yes	136-137	All participants could receive treatment sequentially or in combination
12a	Statistical methods used	Yes	137-138	The primary endpoint was overall survival, and this was estimated with the Kaplan-Meier method
12b	Methods for additional analysis	Yes	138	

Number	Checklist item	Yes/No	Page reported	Comments
13a	Numbers in each group	Yes	Figure 1	Diagram showing the numbers and flow
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	138	All data prior to May 2007 was included in the report
14b	Why the trial ended or was stopped	Yes	138	All data prior to May 2007 was included in the report
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	Diagram showing the numbers and flow
17a	Effect size and confidence interval included	Yes	Table 2	Overall median survival, confidence intervals and the difference between groups was included
17b	For binary results- absolute and relative included	Yes	Table 2	Relative differences were not included but a confidence interval was
18	Results of other analyses included	Yes	Table 2, Table 3	
19	Harms included	Yes	Table 3	The adverse events were organised for the total length of the trial
20	Trial limitations discussed	Yes	140-141	Comparison between this trial and other trials was discussed. The importance of new treatments was noted
21	Generalisability discussed	Yes	140	Comparison to other trial data
22	Interpretation consistent with results discussed	Yes	141	
23	Registration number	Yes	135	NCT00312000
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	Yes	142	There was also a discussion on page 138 about the fact that the funding source had no role in the design, conduct, data collection, data analysis or study interpretation

Abbreviation: CT: computerised tomography; LDH: Lactate dehydrogenase; RCT: randomised controlled trial; WHO: World Health Organization

Table 150: Quality checklist for data extraction for Koopman et al. (2007)[71]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		

Number	Checklist item	Score	Page reports	Notes
2	Number at risk or number of events	0	Figure 1 and Figure 2	Present for overall survival but not for line of therapy
3	OS and 1-year survival	1	Table 2	
4	OR and DC rate	1	Table 2	
5	Adverse events	0	Table 3	Several adverse events were documented but not by line of therapy
6	Usage	1	In the prose at the top of page 139	

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Overall the median survival was not statistically different for the two arms of the trial, it was 16.3 months in the sequential group and 17.4 months in the combination group.

Table 151: Outcome results for Koopman et al. (2007)[71]

Descriptor	Sequential	Combination
Overall survival median	16.3 months (14.3 to 18.1)	17.4 months (15.2 to 19.2)
Source of information	Table 2	Table 2
One-year survival rate	64% (59 to 69)	67% (62 to 72)
Source of information	Table 2	Table 2
Progression free survival for first line therapy (PFS_{01}) median	5.8 months (5.1 to 6.2)	7.8 months (7.0 to 8.3)
Source of information	Table 2	Table 2
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	8.7 months (8.2 to 9.6)	10.3 months (9.3 to 10.8)
Source of information	Table 2	Table 2
Progression free survival for third line therapy (PFS_{23})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for three therapies (PFS_{03}) median	10.3 months (9.0 to 11.1)	N/A
Source of information	Table 2	N/A
Portion of group receiving second line therapy	62%	53%
Source of information	Figure 1	Figure 1
Portion of group receiving third line therapy	36%	N/A
Source of information	Figure 1	Figure 1
Overall response rate in first line	20% (17 to 26)	41% (36 to 46)

Descriptor	Sequential	Combination
Source of information	Table 2	Table 2
Overall response rate in second line	10% (6 to 15)	12% (7 to 17)
Source of information	Table 2	Table 2
Overall response rate in third line	4% (1 to 9)	N/A
Source of information	Table 2	N/A
Disease control rate in first line	74% (69 to 79)	87% (82 to 90)
Source of information	Table 2	Table 2
Disease control rate in second line	71% (65 to 77)	63% (56 to 70)
Source of information	Table 2	Table 2
Disease control rate in third line	57% (48 to 66)	N/A
Source of information	Table 2	N/A

Toxicities were reported in aggregate and could not be separated by lines of therapy.

Seymour et al. (2007)[72]

Seymour et al. (2007)[72] was a phase III trial. It was a trial of patients with untreated metastatic CRC. It was a complicated trial with multiple arms covering two lines of therapy. Two of the arms received either irinotecan or oxaliplatin with 5-FU in the first line. Two arms had the same protocols in the second line. Those that received irinotecan and oxaliplatin in the second line received 5-FU in the first line. There were 356 patients allocated to each of the four arms. The next line of therapy was started after failure of the previous line, it was not specifically mentioned, but failure appeared to be progression.

Table 152: Trial arms for Seymour et al. (2007)[72]

Description	First Line Treatment	Second Line Treatment
B-ir	5-FU	FOLFIRI
B-ox	5-FU	FOLFOX
C-ir	FOLFIRI	
C-ox	FOLFOX	

Abbreviations: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Table 153: CONSORT quality checklist for Seymour et al. (2007)[72]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	143	Different strategies of sequential and combination chemotherapy for patients with poor prognosis advanced colorectal cancer

Number	Checklist item	Yes/No	Page reported	Comments
				(MRC FOCUS): a randomised controlled trial
1b	Structured summary	Yes	143	
2a	Scientific background	Yes	143-144	
2b	Specific Objectives	Yes		
3a	Description of trial design	Yes	144-145	
3b	Important changes after commencement	Yes	146	Changes in salvage chemotherapy occurred after December 2002, changes in practice internationally introduced a supplementary analysis
4a	Eligibility criteria	Yes	144	
4b	Setting and location	Yes	147	59 centres in the United Kingdom and one centre in Cyprus
5	Interventions described	Yes	144-146	
6a	Completely defined prespecified outcome measures	No	146	Changes in practice internationally introduced a supplementary analysis
6b	Changes to trial outcomes after commencement	Yes	146	Changes in practice internationally introduced a supplementary analysis
7a	Sample size determined	Yes	146	The planned sample size was 2100, to detect an absolute improvement in the 2-year survival from 15% to 22.5% with 80% power
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	Yes		Patients were randomly assigned with a minimisation procedure to stratify for clinician, performance status, primary tumour resected or in situ, and distant metastases present or absent.
8b	Type of randomisation and restriction	Yes		Patients were randomly assigned with a minimisation procedure to stratify for clinician, performance status, primary tumour resected or in situ, and distant metastases present or absent.
9	Allocation concealment	No		Not discussed, assumed to be open-label

Number	Checklist item	Yes/No	Page reported	Comments
10	Who generated allocation, enrolment and assignment	No		Not discussed
11a	Blinding	No		Not discussed, assumed to be open-label
11b	Similarity of interventions	Yes	144-145	
12a	Statistical methods used	Yes	146	
12b	Methods for additional analysis	Yes	146-147	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	147	From May 1 to December 31 recruitment and randomisation occurred
14b	Why the trial ended or was stopped	No		
15	A table showing baseline demographics	Yes	Table 2	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Table 4	Presented as hazard rates and differences in median survival. Both results were presented with confidence intervals
17b	For binary results- absolute and relative included	No	Table 6	
18	Results of other analyses included	Yes	Table 3, Table 6	
19	Harms included	Yes	Table 6	
20	Trial limitations discussed	Yes	151	The arrival of newer targeted agents is a significant limitation
21	Generalisability discussed	Yes	151	
22	Interpretation consistent with results discussed	Yes	151	
23	Registration number	Yes	143	ISRCTN 79877428
24	Where the full trial protocol can be accessed	Ni		
25	Sources of funding	Yes	144, 147	UK Medical Research Council. There was a discussion on page 147 of the role undertaken by the funder

Abbreviation: RCT: randomised controlled trial; UK: United Kingdom

Table 154: Quality checklist for data extraction for Seymour et al. (2007)[72]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	1	Table 6	
2	Number at risk or number of events	1	Figure 1 and Figure 2	
3	OS and 1 year survival	1	148 and Table 4	year rather than one-year survival was reported
4	OR and DC rate	1	Table 6	
5	Adverse events	1	Table 3	
6	Usage	1	147	

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

There was no statistical difference in overall survival for the four arms described above. It ranged from 15.0 months as the median survival for B-ir to 16.7 months as the median survival for C-ir.

Table 155: Outcome results for Seymour et al. (2007)[72]

Descriptor	B-ir	B-ox	C-ir	C-ox
Overall survival median	15 months	15.2 months	16.7 months	15.4 months
Source of information	Table 5	Table 5	Table 5	Table 5
One-year survival rate	Not reported	Not reported	Not reported	Not reported
Source of information	N/A	N/A	N/A	N/A
Progression free survival for first line therapy (PFS_{01}) median	6.3 months	6.3 months	8.5 months	8.7 months
Source of information	Table 6	Table 6	Table 6	Table 6
Progression free survival for second line therapy (PFS_{12})	4.4 months	4.8 months	Unknown	Unknown
Source of information	Table 6	Table 6	N/A	N/A
Portion of group receiving second line therapy	52%	56%	50%	50%
Source of information	Table 1	Table 1	Table 1	Table 1
Portion of group receiving third line therapy	43%	42%	Not stated	Not stated
Source of information	Table 1	Table 1	N/A	N/A
Overall response rate in first line	Not stated for study arm	Not stated for study arm	49%	57%
Source of information	N/A	N/A	Table 6	Table 6

Descriptor	B-ir	B-ox	C-ir	C-ox
Overall response rate in second line	16%	23%	N/A	N/A
Source of information	Table 6	Table 6	Table 6	Table 6
Disease control rate in first line	Not stated for study arm	Not stated for study arm	75%	78%
Source of information	Table 6	Table 6	Table 6	Table 6
Disease control rate in second line	53%	60%	N/A	N/A
Source of information	Table 6	Table 6	Table 6	Table 6

Patients who received FOLFIRI in the first line received a median of 12 cycles. While those that received FOLFIRI in the second line received a median of six cycles.

Table 156: Toxicity of FOLFIRI in Seymour et al. (2007)[72]

Indicator of FOLFIRI	In First Line	In Second Line
Progression free survival	8.5 months	4.4 months
Number of patients	342	185
Median cycles	12	6
Grade 3 or 4 neutropenia (%)	19%	18%
% per cycle (median)	1.58%	3.0%
% per PFS (median) per year	26.8%	49.1%

Abbreviation: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; PFS: progression free survival

Patients who received FOLFOX in the first line received a median of 12 cycles. While those that received it in the second line received a median of six cycles. 12 patients had to stop treatment with FOLFOX in the first line compared to ten patients in the second line.

Table 157: Toxicity of FOLFOX in Seymour et al. (2007)[72]

Indicator of FOLFOX	In First Line	In Second Line
Progression free survival	8.7 months	4.8 months
Number of patients	344 patients	201 patients
Median cycles	12 cycles	6 cycles
Grade 3 or 4 neutropenia (%)	28%	25%
% per cycle (median)	2.3%	4.2%
% per PFS (median) per year	38.6%	62.5%

Abbreviation: FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin; PFS: progression free survival

Dahan et al. (2010)[255]

Dahan et al. (2010)[255] was a phase III trial into patients with metastatic pancreatic adenocarcinoma. It considered the sequencing of two older pharmaceuticals for the treatment of this very aggressive cancer. One treatment was the regarded standard, gemcitabine. The other was the combination of cisplatin and 5-FU which was not as well regarded as an option for pancreatic carcinoma, although it had shown activity in numerous other adenocarcinomas.

The trial was to give one protocol and then the other on either progression or unacceptable toxicity. Inclusion criteria were very reasonable: a performance status of two or less, bilirubin was allowed to be less than 50, and there were no restrictions on the liver enzymes (ALT or AST). Two hundred and two patients were recruited, 100 received first line gemcitabine and 102 received first line cisplatin and 5-FU. Six patients did not receive any chemotherapy but were included in the intent to treat analysis. Progression was required for the initiation of the second line of therapy.

Table 158: Trial arms for Dahan et al. (2010)[255]

Description	First Line Treatment	Second Line Treatment
Gemcitabine/cisplatin	Gemcitabine	5-FU and cisplatin
Cisplatin/gemcitabine	5-FU and cisplatin	Gemcitabine

Abbreviation: 5-FU: 5-fluorouracil

Table 159: CONSORT quality checklist for Dahan et al. (2010)[255]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	1527	Combination 5-fluorouracil, folinic acid and cisplatin (LV5FU2-CDDP) followed by gemcitabine or the reverse sequence in metastatic pancreatic cancer: final results of a randomised strategic phase III trial (FFCD 0301)
1b	Structured summary	Yes	1527	
2a	Scientific background	Yes	1527-1528	
2b	Specific Objectives	Yes	1528	The primary endpoint was overall survival
3a	Description of trial design	Yes	1528	
3b	Important changes after commencement	No		
4a	Eligibility criteria	Yes	1528	
4b	Setting and location	Yes	1529	33 French centres
5	Interventions described	Yes	1528	

Number	Checklist item	Yes/No	Page reported	Comments
6a	Completely defined prespecified outcome measures	Yes	1528	
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	1528	202 patients were required to be recruited, to detect an increase in overall survival was 6.5 months to 10 months with 80% power
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	Yes		All eligible patients were randomised 1:1 through a minimisation program at the FFCD centre (Dijon)
8b	Type of randomisation and restriction	Yes		All eligible patients were randomised 1:1 through a minimisation program at the FFCD centre (Dijon)
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	No		Not discussed
11b	Similarity of interventions	Yes	1528	
12a	Statistical methods used	Yes	1528	
12b	Methods for additional analysis	Yes	1528	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	1529	Recruitment occurred between August 2003 and May 2006
14b	Why the trial ended or was stopped	No		
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Table 4	Confidence intervals around the median overall survival were presented
17b	For binary results- absolute and relative included	No	Table 4	
18	Results of other analyses included	Yes	Table 4	

Number	Checklist item	Yes/No	Page reported	Comments
19	Harms included	Yes	Table 3	
20	Trial limitations discussed	Yes	1532	
21	Generalisability discussed	Yes	1532	
22	Interpretation consistent with results discussed	Yes	1532	
23	Registration number	No		
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	No		

Abbreviation: RCT: randomised controlled trial

Table 160: Quality checklist for data extraction for Dahan et al. (2010)[255]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		
2	Number at risk or number of events	0		
3	OS and 1-year survival	1	Table 4	Both one-year and two-year survival rates given
4	OR and DC rate	1	Table 4	
5	Adverse events	1	Table 3	
6	Usage	1	Table 2	Median duration of treatment in weeks given

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Overall the difference in median survival between the trial arms was not significantly significant. Median overall survival was 8.03 months in the gemcitabine/cisplatin arm and 6.7 months in the cisplatin/gemcitabine arm.

Table 161: Outcome results for Dahan et al. (2010)[255]

Descriptor	Gemcitabine/cisplatin	Cisplatin/gemcitabine
Overall survival median	8.03 months	6.7 months
Source of information	Table 4	Table 4
One-year survival rate	32.7%	28.8%
Source of information	Table 4	Table 4
Progression free survival for first line therapy (PFS_{01}) median	3.5 months	3.4 months
Source of information	Table 4	Table 4
Progression free survival for second line therapy (PFS_{12})	Not stated	Not stated
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	5.8 months	5.0 months
Source of information	Table 4	Table 4

Descriptor	Gemcitabine/cisplatin	Cisplatin/gemcitabine
Portion of group receiving second line therapy	55%	69%
Source of information	Figure 1	Figure 1
Overall response rate in first line	19%	15%
Source of information	Table 4	Table 4
Overall response rate in second line	7%	10%
Source of information	Table 4	Table 4
Disease control rate in first line	44%	47%
Source of information	Table 4	Table 4
Disease control rate in second line	45%	38%
Source of information	Table 4	Table 4

Patients who received gemcitabine in the first line received it for a median of 10 weeks, while those received in the second line received for a median of eight weeks. The result for the second line has been calculated by subtracting the median for PFS_{01} away from the median of PFS_{02}. The number of cycles was assumed to equal the number of weeks. For gemcitabine, it appeared that there is a significant increase in toxicity associated with using it in the second line rather than the first line, both in aggregate or associated with elapsing time.

Table 162: Toxicity of gemcitabine in Dahan et al. (2010)[255]

Indicator of Gemcitabine	In First Line	In Second Line
Progression free survival	3.5 months	1.63 months
Number of patients	96	69
Median cycles	10	8
Grade 3 or 4 haematological toxicity (%)	35%	58%
% per cycle (median)	3.5%	7.25%
% per PFS (median) per year	120%	427%
All Grade 3 or 4 toxicities (%)	64%	74%
% per cycle (median)	6.4%	9.25%
% per PFS (median) per year	219%	545%
Grade 3 or 4 non-haematological (%)	46%	51%
% per cycle (median)	4.6%	6.38%
% per PFS (median) per year	158%	375%

Abbreviation: PFS: progression free survival

For cisplatin in the first line treatment, a median of five weeks was given in the first line and a median of four weeks was given in the second line. The result for second line was calculated by subtracting the medians from each other. Because there is a two-week cycle for cisplatin, it has been assumed that 2.5 and 2 cycles were used respectively.

Table 163: Toxicity of cisplatin in Dahan et al. (2010)[255]

Indicator of Cisplatin	In First Line	In Second Line
Progression free survival	3.4 months	2.3 months
Number of patients	101 patients	55 patients
Median cycles	2.5	2
Grade 3 or 4 haematological toxicity (%)	50%	33%
% per cycle (median)	20%	16.5%
% per PFS (median) per year	176%	172%
All Grade 3 or 4 toxicities (%)	79%	69%
% per cycle (median)	31.6%	34.5%
% per PFS (median) per year	279%	360%
Grade 3 or 4 non-haematological (%)	53%	51%
% per cycle (median)	21.2%	25.5%
% per PFS (median) per year	187%	266%

Abbreviation: PFS: progression free survival

Ducreux et al. (2011)[256]

Ducreux et al. (2011)[256] was an open-label phase III trial into patients who had advanced CRC. It was not a trial were the lines of therapy were equivalent. Instead patients received all three active agents (5-FU, irinotecan and oxaliplatin) for CRC over two or three lines of therapy. Patients were required to have metastatic colorectal disease, but not to have received chemotherapy and to be of performance status 0-2. The trial was open-label and non-blinded. Treatment failure was either progression or toxicity.

410 patients were enrolled, 205 to each arm and 203 patients received first line treatment in each arm. The trial was ceased early when the approval for bevacizumab in the treatment of metastatic CRC was given. Subsequently, the recruitment drastically reduced.

Table 164: Trial arms for Ducreux et al. (2011)[256]

Description	First Line Treatment	Second Line Treatment	Third Line Treatment
Sequential	5-FU	FOLFOX	FOLFIRI
Combination	FOLFOX	FOLFIRI	

Abbreviation: 5-FU: 5-fluorouracil; FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; FOLFOX: a protocol consisting of 5-fluorouracil, leucovorin and oxaliplatin

Table 165: CONSORT quality checklist for Ducreux et al. (2011)[256]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	1032	Sequential versus combination chemotherapy for the treatment of advanced colorectal cancer (FFCD 2000–05): an open-label, randomised, phase 3 trial
1b	Structured summary	Yes	1032	
2a	Scientific background	Yes	1032-1033	
2b	Specific Objectives	Yes	1035	The primary endpoint was the time from randomisation to the second PFS or death
3a	Description of trial design	Yes	1033-1034	
3b	Important changes after commencement	Yes	1036	The recruitment was stopped prior to the planned interim analysis because new approvals changed the treatment of CRC
4a	Eligibility criteria	Yes	1033	
4b	Setting and location	Yes	1033	53 centres in France
5	Interventions described	Yes	1034-1035	
6a	Completely defined prespecified outcome measures	Yes	1035	The primary endpoint was the time from randomisation to the second PFS or death
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	1035	570 patients for a detection of the second PFS with 90% power
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	Yes	1034	A detailed discussion of randomisation including the method
8b	Type of randomisation and restriction	Yes	1034	
9	Allocation concealment	Yes	1034	
10	Who generated allocation, enrolment and assignment	Yes	1034	
11a	Blinding	Yes	1034	It was identified as an open-label study in the title
11b	Similarity of interventions	Yes	1034	
12a	Statistical methods used	Yes	1035	Time to event was estimated using reverse Kaplan-Meier method
12b	Methods for additional analysis	Yes		

Number	Checklist item	Yes/No	Page reported	Comments
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	1033	Patients were recruited between February 1 2002 to February 1 2006
14b	Why the trial ended or was stopped	Yes	1036	
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Table 3	
17b	For binary results- absolute and relative included	Yes	Table 3	
18	Results of other analyses included	Yes	Table 3, Table 4, Table 5	
19	Harms included	Yes	Table 4, Table 5	
20	Trial limitations discussed	Yes	1040	
21	Generalisability discussed	Yes	1040	
22	Interpretation consistent with results discussed	Yes	1040	
23	Registration number	Yes	1032	NCT00126256
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	Yes	1032	Sanofi-Aventis France, a discussion was held about the role of the funder on page 1035

Abbreviation: PFS: progression free survival; RCT: randomised controlled trial

Table 166: Quality checklist for data extraction Ducreux et al. (2011)[256]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		Not included
2	Number at risk or number of events	0	Figure 2	Number at risk for first line and overall survival recorded in the figure but not for the second line of therapy
3	OS and 1 year survival	1	Table 3	
4	OR and DC rate	1	Table 3	
5	Adverse events	1	Table 4 and supplementary appendix	

Number	Checklist item	Score	Page reports	Notes
6	Usage	1	1036-1037	

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

The difference in median survival between the groups was not statistically significant. It was 16.4 months in the sequential group and 16.2 months in the combination group. The PFS_{01} was different between the two groups being 5.3 months in the sequential group. The PFS_{02} and PFS_{03} were not statistically significantly different between the two groups.

Table 167: Outcome results for Ducreux et al. (2011)[256]

Descriptor	Sequential	Combination
Overall survival median	16.4 months	16.2 months
Source of information	Table 3	Table 3
One-year survival rate	65%	64%
Source of information	Table 3	Table 3
Progression free survival for first line therapy (PFS_{01}) median	5.3 months- assumed typographical error written as 53 (4.4-6.0)	7.6 months
Source of information	Table 3	Table 3
Progression free survival for both therapies (PFS_{02}) median	10.5 months	10.3 months
Source of information	Table 3	Table 3
Progression free survival for both therapies (PFS_{03}) median	13.2 months	12.9 months
Source of information	Table 3	Table 3
Portion of group receiving second line therapy	76%	73%
Source of information	Figure 1	Figure 1
Portion of group receiving third line therapy	55%	44%
Source of information	Figure 1	Figure 1
Overall response rate in first line	34%	58%
Source of information	Table 3	Table 3
Overall response rate in second line	21%	11%
Source of information	Table 3	Table 3
Overall response rate in third line	8%	8%
Source of information	Table 3	Table 3
Disease control rate in first line	68%	83%
Source of information	Table 3	Table 3
Disease control rate in second line	77%	50%
Source of information	Table 3	Table 3

Descriptor	Sequential	Combination
Disease control rate in second line	47%	24%
Source of information	Table 3	Table 3

FOLFOX was given in the sequential group in the second line. It was given for a median of eight cycles. For the combination group it was given in the first line and was given for a median 12 cycles. An interesting point was raised in the discussion of the results, namely that the rate of neuropathy was lower in the second line group potentially because of the diminished amount of time in which treatment was received.

Table 168: Toxicity of FOLFOX in Ducreux et al. (2011)[256]

Indicator of FOLFOX	In First Line	In Second Line
Progression free survival	7.6 months	5.2 months
Number of patients	203 patients	156 patients
Median cycles	12	8
Grade 3 or 4 anaemia toxicity (%)	5%	4%
% per cycle (median)	0.42%	0.5%
% per PFS (median) per year	8%	9%
Grade 3 or 4 neutropenia (%)	31%	24%
% per cycle (median)	2.6%	3%
% per PFS (median) per year	49%	55%
Grade 3 or 4 diarrhoea (%)	5%	3%
% per cycle (median)	0.4%	0.4%
% per PFS (median) per year	8%	7%

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; PFS: progression free survival

FOLFIRI was given in the second line and the third line for the combination and the sequential group respectively. Six cycles were the median amount given in second line and third line.

Table 169: Toxicity of FOLFIRI in Ducreux et al. (2011)[256]

Indicator of FOLFIRI	In Second Line	In Third Line
Progression free survival	2.7 months	2.7 months
Number of patients	150 patients	112 patients
Median cycles	6 cycles	6 cycles
Grade 3 or 4 anaemia toxicity (%)	2%	5%
% per cycle (median)	0.3%	0.8%
% per PFS (median) per year	9%	22%
Grade 3 or 4 neutropenia (%)	23%	23%

Indicator of FOLFIRI	In Second Line	In Third Line
% per cycle (median)	3.8%	3.8%
% per PFS (median) per year	102%	102%
Grade 3 or 4 diarrhoea (%)	7%	4%
% per cycle (median)	1.2%	0.7%
% per PFS (median) per year	31%	18%

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; PFS: progression free survival

Kim et al. (2011)[257]

Kim et al. (2011)[257] was a phase II trial into patients who had metastatic gastric cancer. It considered the use of two lines of therapy which had shown activity in gastric cancer, namely docetaxel and irinotecan. At the time there was no standard accepted chemotherapy regime. At the time of publication there were limited head to head trials between agents for gastric cancer. Patients were required to have had recurrent or metastatic gastric cancer. No previous chemotherapy for metastatic disease was permitted. Patients were randomised to one of two arms. Disease progression or unacceptable toxicity was required in order to progress to the next line of therapy. The trial was terminated early because of poor patient recruitment.

Fifty-eight patients were enrolled, 28 received docetaxel as first line treatment and 30 patients received irinotecan-based therapy in the first line.

Table 170: Trial arms for Kim et al. (2011)[257]

Description	First Line Treatment	Second Line Treatment
Irinotecan	FOLFIRI	Docetaxel and cisplatin
Docetaxel	Docetaxel and cisplatin	FOLFIRI

Abbreviation: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan

Table 171: CONSORT quality checklist for Kim et al. (2011)[257]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	No		Docetaxel/cisplatin followed by FOLFIRI versus the reverse sequence in metastatic gastric cancer
1b	Structured summary	Yes	177	
2a	Scientific background	Yes	178	
2b	Specific Objectives	Yes	178	The specific objective was to evaluate the protocols in terms of efficacy and tolerability
3a	Description of trial design	Yes	178	
3b	Important changes after commencement	No		
4a	Eligibility criteria	Yes	178	

Number	Checklist item	Yes/No	Page reported	Comments
4b	Setting and location	No		
5	Interventions described	Yes	178	
6a	Completely defined prespecified outcome measures	Yes	179	A primary endpoint was not defined, the statistical considerations suggest that disease-free survival was the primary outcome
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	179	Sample size of 190 and a total of 77 events were required
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	No		
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	Yes	179	Scans were assessed by a radiologist and oncologist who were blinded to the tumour assessments
11b	Similarity of interventions	Yes	178	
12a	Statistical methods used	Yes	179	Kaplan-Meier estimates were used
12b	Methods for additional analysis	Yes	179	
13a	Numbers in each group	Yes	Table 2	
13b	For each group, losses and exclusions after randomisation	No		The text states that 54 of 58 patients were assessable but not why the four excluded patients were excluded
14a	Dates defining recruitment and follow up	Yes	179	The patients were enrolled from April 2005 to August 2008
14b	Why the trial ended or was stopped	Yes	181	The trial was terminated early because of poor patient recruitment
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	No		
17a	Effect size and confidence interval included	Yes	179-180	
17b	For binary results- absolute and relative included	No		

Number	Checklist item	Yes/No	Page reported	Comments
18	Results of other analyses included	Yes	Table 2, Table 3, Table 4	
19	Harms included	Yes	Table 3, Table 4	
20	Trial limitations discussed	Yes	182-183	
21	Generalisability discussed	Yes	182-183	
22	Interpretation consistent with results discussed	Yes	182-183	
23	Registration number	No		
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	No		

Abbreviation: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; RCT: randomised controlled trial

Table 172: Quality checklist for data extraction for Kim et al. (2011)[257]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		
2	Number at risk or number of events	0		
3	OS and 1 year survival	0.5	179	The median overall survival was reported but not the one-year survival rate
4	OR and DC rate	1		
5	Adverse events	1	181, Table 3, Table 4	
6	Usage	1	179	

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Overall there was no statistical difference between the two groups on median survival. It was 13.4 months in the docetaxel arm and 12.5 months in the irinotecan arm. The trial also gave the number of cycles for each of the arms of treatment, there were 139 cycles of docetaxel in the first line and 83 in the second line. For irinotecan there were 212 cycles in the first line and 75 in the second. Consistent with the other publications this means the average number of chemotherapies given in the first line for docetaxel was 4.6 and in the second line was 3.8. For irinotecan the average number of cycles given in the first line was 7.1 and in the second line was 5.3.

Table 173: Outcome results for Kim et al. (2011)[257]

Descriptor	Docetaxel/irinotecan	Irinotecan/docetaxel
Overall survival median	12.5 (8.2 to 16.8) months	13.4 (10 to 16.8) months
Source of information	Page 180, Figure 3	Page 180, Figure 3

Descriptor	Docetaxel/irinotecan	Irinotecan/docetaxel
One-year survival rate	Approx. 50%	Approx. 50%
Source of information	Not reported directly, read off the overall survival Kaplan-Meier (Figure 3)	Not reported directly, read off the overall survival Kaplan-Meier (Figure 3)
Progression free survival for first line therapy (PFS_{01}) median	4.3 (0.8 to 7.8) months	3.4 (0 to 6.9) months
Source of information	Page 180, Figure 1	Page 180, Figure 1
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	8.1 months	6.7 months
Source of information	Page 180, Figure 2	Page 180, Figure 2
Portion of group receiving second line therapy	53.6%	73.3%
Source of information	Page 179	Page 179
Overall response rate in first line	25.9%	13.8%
Source of information	Table 2	Table 2
Overall response rate in second line	20%	30%
Source of information	Table 2	Table 2
Disease control rate in first line	85.2%	79%
Source of information	Table 2	Table 2
Disease control rate in second line	46.7%	55%
Source of information	Table 2	Table 2

Because of the small number of patients, the numbers of toxicities were relatively small and only the haematological adverse events were included in the paper. These were displayed as the rate per cycle.

Le Caer et al. (2011)[100]

Le Caer et al. (2011)[100] was a phase II trial into elderly patients who had advanced NSCLC. It considered the use of two protocol, an older protocol of gemcitabine and docetaxel and a newer protocol of erlotinib. Erlotinib is a cancer pharmaceutical that is more effective in patients with a specific mutation. This mutation is more prevalent in non-smokers who develop NSCLC. Another characteristic of erlotinib is that it is an oral treatment taken daily. Both regimes have been shown to have action in patients with NSCLC. Patients were eligible if over 65 years of age and were ineligible on the basis of significant comorbidities.

Ninety-nine patients were analysed, 48 received the combination of gemcitabine and docetaxel as first line and 51 received the erlotinib as first line therapy. The gemcitabine treatment did not continue until progression, a maximum of 24 weeks of treatment was given. Toxicity was not listed as a reason for changing to a new line of therapy in the publication.

Table 174: Trial arms of Le Caer et al. (2011)[100]

Description	First Line Treatment	Second Line Treatment
Gemcitabine	Gemcitabine/Docetaxel	Erlotinib
Erlotinib	Erlotinib	Gemcitabine/Docetaxel

Table 175: CONSORT quality checklist for Le Caer et al. (2011)

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	1123	A multicentre phase II randomised trial of weekly docetaxel/gemcitabine followed by erlotinib on progression, vs the reverse sequence, in elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0504 study)
1b	Structured summary	Yes	1123	
2a	Scientific background	Yes	1123-1124	
2b	Specific Objectives	Yes	1124	The feasibility and activity of weekly chemotherapy followed by erlotinib or the reverse sequence
3a	Description of trial design	Yes		
3b	Important changes after commencement	No		
4a	Eligibility criteria	Yes	1124	
4b	Setting and location	No		Twenty-two centres were involved but where these centres were was not explicitly given. Presumably they were in France.
5	Interventions described	Yes	1124	
6a	Completely defined prespecified outcome measures	Yes	1124	
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	1125	

Number	Checklist item	Yes/No	Page reported	Comments
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	No		
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	Yes	1124	Described as open-label phase II study
11b	Similarity of interventions	Yes	1124	
12a	Statistical methods used	Yes	1125	
12b	Methods for additional analysis	Yes	1125	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	1125	Recruitment occurred between July 2006 and November 2008
14b	Why the trial ended or was stopped	No		
15	A table showing baseline demographics	Yes	Table 2	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Table 4	
17b	For binary results- absolute and relative included	No	Table 4	
18	Results of other analyses included	Yes	Table 4, Table 5	
19	Harms included	Yes	Table 5	
20	Trial limitations discussed	Yes	1127-1128	
21	Generalisability discussed	Yes	127-1128	
22	Interpretation consistent with results discussed	Yes	127-1128	
23	Registration number	Yes	1124	NCT 00418704
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	Yes	1128	There was a description of the role of the sponsors on page 1125: the sponsors had no role in the study design,

Number	Checklist item	Yes/No	Page reported	Comments
				study realisation, data analysis or manuscript preparation. GFPC have the result property. The data were analysed by the GFPC statistician and interpreted by the authors.

Abbreviation: RCT: randomised controlled trial

Table 176: Quality checklist for data extraction for Le Caer et al. (2011)

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		
2	Number at risk or number of events	0	Figure 3	Only for overall survival and time to second progression
3	OS and 1 year survival	1	Figure 3	
4	OR and DC rate	1	Table 4	
5	Adverse events	1	Table 5	
6	Usage	1	1125	Mean numbers of cycles were reported

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

The difference in median overall survival between the arms was not statistically significant. It was 9.4 months in the gemcitabine arm and 7.1 months in the erlotinib arm. The mean treatment lengths were similar in first and second line treatment.

Table 177: Outcome results for Le Caer et al. (2011)[100]

Descriptor	Gemcitabine followed by erlotinib	Erlotinib followed by gemcitabine
Overall survival median	9.4 months	7.1 months
Source of information	Page 1126	Page 1126
One-year survival rate	36.2%	31.4%
Source of information	Page 1126	Page 1126
Progression free survival for first line therapy (PFS_{01}) median	4.7 months	2.7 months
Source of information	Page 1126. It was reported as time to progression	Page 1126. It was reported as time to progression
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	7.5 months	5.8 months
Source of information	Page 1126. Reported as time to progression	Page 1126. Reported as time to progression

Descriptor	Gemcitabine followed by erlotinib	Erlotinib followed by gemcitabine
Portion of group receiving second line therapy	60% (29/48)	47% (24/51)
Source of information	Figure 1	Figure 1
Overall response rate in first line	20.8%	17.6%
Source of information	Table 4	Table 4
Overall response rate in second line	6.3%	11.8%
Source of information	Table 4	Table 4
Disease control rate in first line	54.1%	49%
Source of information	Table 4	Table 4
Disease control rate in second line	25.1%	26.5%
Source of information	Table 4	Table 4

For gemcitabine there was a similar length of treatment in first and second line, the mean treatment length was 1.83 cycles.

Table 178: Toxicity of gemcitabine in Le Caer et al. (2011)[100]

Indicator of gemcitabine	In First Line	In Second Line
Progression Free Survival	4.7 months	3.1 months
Number of patients	48	24
Median cycles	1.83	1.83
Grade 3 or 4 haematological toxicity (%)	44%	100%
% per cycle (median)	23.9%	55%
% per PFS (median) per year	112%	387%
Grade 3 or 4 non-haematological (%)	17%	100%
% per cycle (median)	9%	55%
% per PFS (median) per year	43%	387%

Abbreviation: PFS: progression free survival

For erlotinib, there was a difference in that more erlotinib was used in the second line rather than the first line. 3.1 months were used in first line and 4.7 months were used in second line. It should be noted the numbers suggest that some erlotinib may have been used post-progression.

Table 179: Toxicity of erlotinib in Le Caer et al. (2011)[100]

Indicator of erlotinib	In First Line	In Second Line
Progression Free Survival	2.7 months	2.8 months

Indicator of erlotinib	In First Line	In Second Line
Number of patients	51	29
Median cycles	3.1	4.7
Grade 3 or 4 haematological toxicity (%)	0%	0%
% per cycle (median)	0%	0%
% per PFS (median) per year	0%	0%
Grade 3 or 4 non-haematological (%)	26%	10%
% per cycle (median)	8.4%	2.1%
% per PFS (median) per year	116%	43%

Abbreviation: PFS: progression free survival

Gridelli et al. (2012)[258]

Gridelli et al. (2012)[258] was a phase III trial into patients with advanced NSCLC. It considered the use of the combination of cisplatin and gemcitabine in one line of therapy and the use of the oral agent erlotinib in the other. The trial was ceased early because the use of erlotinib in the first line was found to cross the predetermined non-inferiority threshold. That is, the use of erlotinib in the first line was found to be inferior to the use of cisplatin and gemcitabine in the first line. The trial was randomised, and the eligibility criteria were broad. Seven hundred and eighty patients were entered into the trial, 380 in each arm. A new line of therapy could only be initiated for disease progression.

Table 180: Trial arms for Gridelli et al. (2012)[258]

Description	First Line Treatment	Second Line Treatment
Cisplatin	Cisplatin/gemcitabine	Erlotinib
Erlotinib	Erlotinib	Cisplatin/gemcitabine

Table 181: CONSORT quality checklist for Gridelli et al. (2012)[258]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	3002	First-Line Erlotinib Followed by Second-Line Cisplatin-Gemcitabine Chemotherapy in Advanced Non–Small-Cell Lung Cancer: The TORCH Randomized Trial
1b	Structured summary	Yes	3002	
2a	Scientific background	Yes	3002-3003	
2b	Specific Objectives	Yes	3002	To see whether first line erlotinib followed by cisplatin-gemcitabine was non-inferior to the reverse sequence
3a	Description of trial design	Yes	3003-3004	

Number	Checklist item	Yes/No	Page reported	Comments
3b	Important changes after commencement	Yes	3008	
4a	Eligibility criteria	Yes	3003	
4b	Setting and location	Yes	3003	Italy and Canada
5	Interventions described	Yes		
6a	Completely defined prespecified outcome measures	Yes	3005-3006	
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	3005	900 patients and 669 events were estimated to have occurred. Based on a hazard ratio of 1.25 being the upper limit
7b	Explanation of interim analysis and stopping design	Yes	3005	
8a	Method used to generate random allocation	Yes	3004	Centrally automated
8b	Type of randomisation and restriction	Yes	3004	Used histology, smoking status, sex, age, centre and performance status as strata
9	Allocation concealment	Yes	3003	The study was open-label
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	Yes	3003	Defined as open-label
11b	Similarity of interventions	Yes	3004	
12a	Statistical methods used	Yes	3005	Application of a multivariate Cox model was planned to estimate HR adjusted by histology, smoking status, sex, age, ethnicity, performance status, country and size of centre as covariates
12b	Methods for additional analysis	Yes	3005-3006	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	3008	The follow up referred to the 760 patients that were enrolled at 1 June 2011
14b	Why the trial ended or was stopped	Yes	3008	Trial was ceased because the experimental arm (erlotinib first) was not shown to be non-inferior at November 2009

Number	Checklist item	Yes/No	Page reported	Comments
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	3008	
17b	For binary results- absolute and relative included	No	Table 2	
18	Results of other analyses included	Yes	Table 2, 3009, Figure 4, Figure 5	
19	Harms included	Yes	Table 2	
20	Trial limitations discussed	Yes	3009-3010	
21	Generalisability discussed	Yes	3009-3010	
22	Interpretation consistent with results discussed	Yes	3009-3010	
23	Registration number	No		Although it is noted that it was registered with ClinicalTrials.gov
24	Where the full trial protocol can be accessed	Yes	3007	The full protocol was available from the author
25	Sources of funding	Yes	3002	There was also a comment that the sponsor had no role in trial design, conduction, analysis, interpretation or presentation of the results

Abbreviation: RCT: randomised controlled trial

Table 182: Quality checklist for data extraction for Gridelli et al. (2012)[258]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		
2	Number at risk or number of events	0	Figure 2	Figure 2 reported the total events and the number of participants that were still at risk for overall survival
3	OS and 1 year survival	0.5	Figure 2	One-year survival rate was not reported
4	OR and DC rate	1	3009	
5	Adverse events	0	Table 2	Included both lines of treatment, that is the adverse events were not separate
6	Usage	0		

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

There was a statistically significant difference between the two lines of therapy, the cisplatin arm had a median survival of 11.6 months, while the erlotinib arm had a median survival of 8.7 months. PFS02 was 8.9 months in the cisplatin arm and 6.4 months in the erlotinib arm. This

difference was statistically significant. There was also a statistically significant difference in the PFS01 with it being 5.4 months in the cisplatin arm and 2.2 months in the erlotinib arm.

Table 183: Outcome results for Gridelli et al. (2012)[258]

Descriptor	Cisplatin	Erlotinib
Overall survival median	11.6 (10.2 to 13.3) months	8.7 (7.4 to 10.5) months
Source of information	Figure 2	Figure 2
One-year survival rate	55%	45%
Source of information	Estimated from Kaplan Meier curve (Figure 2)	Estimated from Kaplan Meier curve (Figure 2)
Progression free survival for first line therapy (PFS_{01}) median	5.4 (4.8 to 6.3) months	2.2 (2.1 to 2.4) months
Source of information	Figure 5	Figure 5
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	8.9 (8.1 to 9.7) months	6.4 months
Source of information	Figure 4	Figure 4
Portion of group receiving second line therapy	59% (226/380)	51% (194/380)
Source of information	Figure 1	Figure 1
Overall response rate in first line	28%	21.4%
Source of information	Page 3 009	Page 3 009
Overall response rate in second line	12%	22.7%
Source of information	Page 3 009	Page 3 009
Disease control rate in first line	Not reported	Not reported
Source of information	N/A	N/A
Disease control rate in second line	Not reported	Not reported
Source of information	N/A	N/A

Toxicity was not separated by line of therapy, composite results for both arms were presented.

Le Caer et al. (2012)[99]

Le Caer et al. (2012)[99] was a phase II trial in NSCLC in elderly patients. It considered the use of gemcitabine in one arm and erlotinib in the other. As discussed above both are active in lung cancer but are not considered the treatment of choice in the general population.

One hundred patients were enrolled but only 94 received a dose: 44 patients received gemcitabine and 50 patients received erlotinib. Disease progression was required to move onto the next line of therapy.

Table 184: Trial arms for Le Caer et al. (2012)[99]

Description	First Line Treatment	Second Line Treatment
Gemcitabine	Gemcitabine	Erlotinib
Erlotinib	Erlotinib	Gemcitabine

Table 185: CONSORT quality checklist for Le Caer et al. (2012)[99]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	97	A multicenter phase II randomized trial of gemcitabine followed by erlotinib at progression, versus the reverse sequence, in vulnerable elderly patients with advanced non-small-cell lung cancer selected with a comprehensive geriatric assessment (the GFPC 0505 study)
1b	Structured summary	Yes	91	
2a	Scientific background	Yes	97-98	
2b	Specific Objectives	Yes	98	Study the feasibility and activity of weekly gemcitabine follow by erlotinib versus the reserve sequence
3a	Description of trial design	Yes	98	
3b	Important changes after commencement	No		
4a	Eligibility criteria	Yes	98	
4b	Setting and location	No	98,99	Multicenter study, with 22 centres involved. Country not identified in text, presumably France
5	Interventions described	Yes	98	
6a	Completely defined prespecified outcome measures	Yes	98-99	
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	99	50 participants in each arm. Assumed that there was a two-month difference in time to second progression
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	No		

Number	Checklist item	Yes/No	Page reported	Comments
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	Yes	98	Open-label trial, central review for response, did not identify if the assessment was blinded to treatment or clinical assessment
11b	Similarity of interventions	Yes	98	
12a	Statistical methods used	Yes	99	Kaplan-Meier analysis
12b	Methods for additional analysis	Yes	99	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	99	Enrolment occurred between May 2006 and January 2010
14b	Why the trial ended or was stopped	No		
15	A table showing baseline demographics	Yes	Table 2	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Table 4	
17b	For binary results-absolute and relative included	No	Table 4	
18	Results of other analyses included	Yes	Table 4, Table 5	
19	Harms included	Yes	Table 5	
20	Trial limitations discussed	Yes	101-102	
21	Generalisability discussed	Yes	101-102	
22	Interpretation consistent with results discussed	Yes	101-102	
23	Registration number	No		

Number	Checklist item	Yes/No	Page reported	Comments
24	Where the full trial protocol can be accessed	No		
25	Sources of funding	Yes	102	

Abbreviation: RCT: randomised controlled trial

Table 186: Quality checklist for data extraction for Le Caer et al. (2012)[99]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0		
2	Number at risk or number of events	0		
3	OS and 1 year survival	1	Table 4	
4	OR and DC rate	1	Table 4	
5	Adverse events	1	Table 5	
6	Usage	1	99	Mean number of cycles were given

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

The difference in the median overall survival was not statistically significant. It was 4.4 months in the gemcitabine arm and 3.9 months for erlotinib.

Table 187: Outcome results for Le Caer et al. (2012)

Descriptor	Gemcitabine	Erlotinib
Overall survival median	4.4 (3.1 to 7.2) months	3.9 (3 to 6) months
Source of information	Page 99, Table 4	Page 99, Table 4
One-year survival rate	27.3%	20%
Source of information	Page 99	Page 99
Progression free survival for first line therapy (PFS_{01}) median	2.5 (2 to 5) months	2.2 (1.8 to 3.8) months
Source of information	Page 99, Table 4	Page 99, Table 4
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	4.3 (3 to 6.2) months	3.5 (2.9 to 5.6) months
Source of information	Page 99, Table 4	Page 99, Table 4
Portion of group receiving second line therapy	48% (21/44)	46% (23/50)
Source of information	Figure 1	Figure 1
Overall response rate in first line	11.4%	12%
Source of information	Table 4	Table 4
Overall response rate in second line	4.5%	8%

Descriptor	Gemcitabine	Erlotinib
Source of information	Table 4	Table 4
Disease control rate in first line	34.1%	32%
Source of information	Table 4	Table 4
Disease control rate in second line	18.1%	14%
Source of information	Table 4	Table 4

Table 188: Toxicity of gemcitabine in Le Caer et al. (2012)[99]

Indicator of gemcitabine	In First Line	In Second Line
Progression Free Survival	2.5 months	1.3 months
Number of patients	44 patients	23 patients
Median Cycles	3 and one-third cycle	2 and one-third cycles
Grade 3 or 4 anaemia toxicity (%)	9.1%	0%
% per cycle (median)	2.7%	0%
% per PFS (median) per year	44%	0%
Grade 3 or 4 neurological (%)	11.4%	21%
% per cycle (median)	3.4%	10.3%
% per PFS (median) per year	55%	222%

Abbreviation: PFS: progression free survival

Table 189: Toxicity of erlotinib in Le Caer et al. (2012)[99]

Indicator of erlotinib	In First Line	In Second Line
Progression Free Survival	2.2 months	1.8 months
Number of patients	50 patients	21 patients
Median cycles	2.2	1.8
Grade 3 or 4 anaemia toxicity (%)	4%	4.4%
% per cycle (median)	1.8%	2.2%
% per PFS (median) per year	22%	29%
Grade 3 or 4 neurological (%)	6%	4.7%
% per cycle (median)	33%	31%
% per PFS (median) per year	2.7%	2.6%

Abbreviation: PFS: progression free survival

Eichelberg et al. (2015)[118]

Eichelberg et al. (2015)[118] was a phase III trial in renal cell carcinoma. It considered the use of gemcitabine in one arm and erlotinib in the other. As discussed above, both are active treatments but are not considered the treatment of choice in the general population.

Three hundred and sixty-five patients were enrolled but 12 did not receive study treatment. Second line treatment occurred after progression or toxicity.

Table 190: Trial arms of Eichelberg et al. (2015)[118]

Description	First Line Treatment	Second Line Treatment
Sorafenib	Sorafenib	Sunitinib
Sunitinib	Sunitinib	Sorafenib

Table 191: CONSORT quality checklist for Eichelberg et al. (2015)[118]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	Yes	837	SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer
1b	Structured summary	Yes	837-838	
2a	Scientific background	Yes	838	Sequential therapies are standard practice, choosing the agents is a key clinical problem
2b	Specific Objectives	Yes	838	Testing hypothesis that one sequence is superior to the other
3a	Description of trial design	Yes	838	
3b	Important changes after commencement	Yes	839	Design changed to the superiority design after the start of recruitment.
4a	Eligibility criteria	Yes	838	
4b	Setting and location	Yes	839	72 centres in Germany, Austria and the Netherlands
5	Interventions described	Yes	838	
6a	Completely defined prespecified outcome measures	Yes	839	Although there were some post hoc analyses conducted
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes	839	Altered three times
7b	Explanation of interim analysis and stopping design	No		
8a	Method used to generate random allocation	Yes	838	
8b	Type of randomisation and restriction	Yes	838	
9	Allocation concealment	No		
10	Who generated allocation, enrolment and assignment	Yes	838	
11a	Blinding	No	838	Open-label
11b	Similarity of interventions	Yes	838	
12a	Statistical methods used	Yes	838-839	
12b	Methods for additional analysis	Yes	838-839	
13a	Numbers in each group	Yes	Figure 1	

Number	Checklist item	Yes/No	Page reported	Comments
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	839	Recruitment occurred between February 2009 and December 2011, 15 August 2013 was the end of follow up
14b	Why the trial ended or was stopped	Yes	839	
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	Figure 2	
17b	For binary results- absolute and relative included	No		Absolute differences only discussed
18	Results of other analyses included	Yes		
19	Harms included	Yes	Table 3	
20	Trial limitations discussed	Yes	844-845	
21	Generalisability discussed	Yes	844-845	
22	Interpretation consistent with results discussed	Yes	844-845	
23	Registration number	Yes	838	NCT00732914
24	Where the full trial protocol can be accessed	Yes	838	www.clinicaltrials.gov
25	Sources of funding	Yes	846	

Abbreviation: RCT: randomised controlled trial

Table 192: Quality checklist for data extraction for Eichelberg et al. (2015)[118]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	1	Figure 3	
2	Number at risk or number of events	1	Figure 1	
3	OS and 1 year survival	0.5	Figure 2	
4	OR and DC rate	1	Table 3	
5	Adverse events	1	In the supplementary materials	

Number	Checklist item	Score	Page reports	Notes
6	Usage	1	In the supplementary material	Mean number of weeks of treatment were given

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Table 193: Outcome results for Eichelberg et al. (2015)[118]

Descriptor	Sorafenib	Sunitinib
Overall survival median	31.5 (23.3-36.9) months	30.2 (23.6-50.1) months
Source of information	Figure 2	Figure 2
One-year survival rate	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for first line therapy (PFS_{01}) median	5.9 (5.5-7.9) months	8.5 (7.1-11.2) months
Source of information	Figure 3	Figure 3
Progression free survival for second line therapy (PFS_{12})	2.8 (2.7-2.9) months	5.4 (3.0-5.5) months
Source of information	Figure 3	Figure 3
Progression free survival for both therapies (PFS_{02}) median	12.5 (10.5-17.2) months	14.9 (10.5-17.2) months
Source of information	Figure 2	Figure 2
Portion of group receiving second line therapy	57%	42%
Source of information	Figure 1	Figure 1
Overall response rate in first line	30.8%	29.4%
Source of information	Table 2	Table 2
Overall response rate in second line	18%	6.6%
Source of information	Table 2	Table 2
Disease control rate in first line	69%	64%
Source of information	Table 2	Table 2
Disease control rate in second line	49%	32%
Source of information	Table 2	Table 2

Table 194: Toxicity of sorafenib in Eichelberg et al. (2015)[118]

Indicator of Sorafenib	In First Line	In Second Line
Progression free survival	5.9 (5.5-7.9) months	5.4 (3.0-5.5) months
Number of patients	177	76
Median cycles	Not reported	Not reported
Mean Cycles	37.5 weeks of treatment	16 weeks of treatment
Grade 3 or 4 toxicity (%)	66%	36%
% per cycle (median)	N/A	N/A

Abbreviation: PFS: progression free survival

Table 195: Toxicity of sunitinib in Eichelberg et al. (2015)[118]

Indicator of Sunitinib	In First Line	In Second Line
Progression free survival	8.5 (7.1-11.2) months	2.8 (2.7-2.9) months
Number of patients	176	91
Median cycles	Not reported	Not reported
Mean Cycles	43.9 weeks of treatment	28.2 weeks of treatment
Grade 3 or 4 anaemia toxicity (%)	67%	51%

Abbreviation: PFS: progression free survival

Knox et al. (2017)[253]

Motzer et al. (2014)[252] was a phase II trial in patients with metastatic renal cell carcinoma. It considered the use of sunitinib in one arm and everolimus in the other. There were 471 participants in the trial, 238 in the everolimus trial arm and 233 in the sunitinib trial arm. The final report of this trial was published in Knox et al. (2017)[253] and only the second publication has been included.

Table 196: Trial arms of Knox et al. (2017)[253]

Description	First Line Treatment	Second Line Treatment
Everolimus	Everolimus	Sunitinib
Sunitinib	Sunitinib	Everolimus

Table 197: CONSORT quality checklist for Knox et al. (2017)[253]

Number	Checklist item	Yes/No	Page reported	Comments
1a	Identification as an RCT in title	No		Final overall survival analysis for the phase II RECORD-3 study of first-line everolimus followed by sunitinib versus first-line sunitinib followed by everolimus in metastatic RCC
1b	Structured summary	Yes	1339	
2a	Scientific background	Yes	1340	
2b	Specific Objectives	Yes	1340	Compare safety and efficacy of treatment sequences
3a	Description of trial design	Yes	1340	
3b	Important changes after commencement	No		No obvious changes
4a	Eligibility criteria	Yes	1340	
4b	Setting and location	Partially		International
5	Interventions described	Yes		
6a	Completely defined prespecified outcome measures	Yes	1340	PFS, combined PFS and OS

Number	Checklist item	Yes/No	Page reported	Comments
6b	Changes to trial outcomes after commencement	No		
7a	Sample size determined	Yes		Primary endpoint was first line PFS, 1 month difference was considered important, HR of 1.1 implied, 318 patients required
7b	Explanation of interim analysis and stopping design	Yes	1340	Interim analysis did not demonstrate non-inferiority in first line
8a	Method used to generate random allocation	No		
8b	Type of randomisation and restriction	No		
9	Allocation concealment	No	1340	Open-label
10	Who generated allocation, enrolment and assignment	No		
11a	Blinding	Yes		Open-label treatment
11b	Similarity of interventions	Yes		
12a	Statistical methods used	Yes	1340	
12b	Methods for additional analysis	Yes	1340	
13a	Numbers in each group	Yes	Figure 1	
13b	For each group, losses and exclusions after randomisation	Yes	Figure 1	
14a	Dates defining recruitment and follow up	Yes	1340	October 2009 and June 2011, median duration of follow up was 3.7 years
14b	Why the trial ended or was stopped	No		
15	A table showing baseline demographics	Yes	Table 1	
16	For each group, the number of participants and whether by original assignment	Yes	Figure 1	
17a	Effect size and confidence interval included	Yes	1341	
17b	For binary results- absolute and relative included	N/A		
18	Results of other analyses included	Yes	1341-1342	
19	Harms included	Yes		

Number	Checklist item	Yes/No	Page reported	Comments
20	Trial limitations discussed	No		
21	Generalisability discussed	Yes	1343-1344	
22	Interpretation consistent with results discussed	Yes	1343-1344	
23	Registration number	Yes	1339	ClinicalTrials.gov identifier, NCT00903175
24	Where the full trial protocol can be accessed	Yes		
25	Sources of funding	Yes	1344	Supported by Novartis

Abbreviation: OS: overall survival; PFS: progression free survival; RCC: renal cell carcinoma; RCT: randomised controlled trial

Table 198: Quality checklist for data extraction for Knox et al. (2017)[253]

Number	Checklist item	Score	Page reports	Notes
1	PFS_{01} and PFS_{12}	0	Table 1	PFS_{01} was reported
2	Number at risk or number of events	0	Not included	The number at risk for overall survival was included
3	OS and 1 year survival	0.5	1341	The overall survival was included
4	OR and DC rate	0	Not included	
5	Adverse events	1	1341	Only overall grade 3 and grade 4 included, other adverse events were for all adverse events
6	Usage	1	1341	Exposure was given in months

Abbreviations: DC: disease control; OR: overall response; OS: overall survival; PFS: progression free survival

Table 199: Outcome results for Knox et al. (2017)[253]

Descriptor	Everolimus	Sunitinib
Overall survival median	22.4 (18.6-33.3) months	29.5 (22.8-33.1) months
Source of information	Page 1341, Figure 2	Page 1341, Figure 2
One-year survival rate	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for first line therapy (PFS_{01}) median	7.9 (5.6-8.2) months	10.7 (8.2-11.5) months
Source of information	Page 1341	Page 1341
Progression free survival for second line therapy (PFS_{12})	Not reported	Not reported
Source of information	N/A	N/A
Progression free survival for both therapies (PFS_{02}) median	21.7 (15.1-26.7) months	22.2 (16-29.8) months
Source of information	Page 1341, Figure 2	Page 1341, Figure 2
Portion of group receiving second line therapy	55%	51%

Source of information	Figure 1	Figure 1
Overall response rate in first line	Not reported	Not reported
Source of information	N/A	N/A
Overall response rate in second line	Not reported	Not reported
Source of information	N/A	N/A
Disease control rate in first line	Not reported	Not reported
Source of information	N/A	N/A
Disease control rate in second line	Not reported	Not reported
Source of information	N/A	N/A

Table 200: Toxicity of everolimus in Knox et al. (2017)[253]

Indicator of everolimus	In first line	In second line
Progression Free Survival	7.9 (5.6-8.2) months	Not reported
Number of patients	238	116
Median Cycles	5.6 months exposure	3.4 months exposure
Intensity	94% (from Motzer et al. 2014)[252]	98% (from Motzer et al., 2014)[252]
Grade 3 or 4 all suspected to be related to treatment (%)	47%	47%
% per cycle (median)	8%	14%
% of adverse events as rate per cycle (as exponential)	10.7%	17.0%
% per PFS (median) per year	71%	Not calculated

Abbreviation: PFS: progression free survival

Table 201: Toxicity of sunitinib in Knox et al. (2017)[253]

Indicator of Sunitinib	In First Line	In Second Line
Progression Free Survival	10.7 (8.2-11.5) months	Not reported
Number of patients	233	128
Median Cycles	8.3 months	5.7 months
Grade 3 or 4 all suspected to be related to treatment (%)	63%	57%
% per cycle (median)	8%	10%
% of adverse events as rate per cycle (as exponential)	11.3%	13.8%
% per PFS (median) per year	71%	Not calculated

Abbreviation: PFS: progression free survival

Non-randomised trials identified in the literature

Twenty-four non-randomised and observational trials identified in the literature in comparison to the RCT literature. One was removed because the full-text was unable to be recovered in English.[638] Two had similar authors and the same patient group, including exactly the same number of participants, only one was included.[266,644] Two publications did not have any information that could be extracted by line of therapy.[659,697] This resulted in 20 publications, a summary of the details is shown in Table 202. The available information for each study is shown in Table 203.

Unlike the RCTs the non-RCTs were more likely to report information about the progression free survival in each line of therapy and less likely to have information about the intensity of treatment.

Table 202: Non-RCT included in literature review

Study	Title	Cancer	Alternatives	Conclusions on effectiveness	Conclusions on safety	Prospective/ retrospective
Dupont (2006)[245]	Topotecan and liposomal doxorubicin in recurrent ovarian cancer: is sequence important?	Ovarian cancer	Topotecan Liposomal doxorubicin	Decrease	Unclear	Retrospective
Michels et al. (2006)[264]	First- and second-line chemotherapy with docetaxel or mitoxantrone in patients with hormone-refractory prostate cancer: does sequence matter?	Prostate cancer	Docetaxel Mitoxantrone	Decrease	Worsening	Retrospective
Oh et al. (2006)[260]	Response to second-line chemotherapy in patients with hormone refractory prostate cancer receiving two sequences of mitoxantrone and taxanes	Prostate cancer	Taxanes Mitoxantrone	Decrease	N/A	Retrospective
Popov et al. (2006)[265]	What is the best sequence of chemotherapy in advanced colorectal cancer? Final results of a five-arm study	Colorectal cancer	FOLFIRI	Decrease	Nil	Prospective
Sakar et al. (2007)[596]	XELOX followed by XELIRI or the reverse sequence in advanced colorectal cancer	Colorectal cancer	XELOX XELIRI	Decrease	Decrease	Prospective
Berthold et al. (2008)[648]	Survival and PSA response of patients in the TAX 327 study who crossed over to receive docetaxel after mitoxantrone or vice versa	Prostate cancer	Docetaxel Mitoxantrone	N/A	N/A	Retrospective
Joung et al. (2008)[647]	Docetaxel chemotherapy of Korean patients with hormone- refractory prostate cancer: comparative analysis between 1st-line and 2nd-line docetaxel	Prostate cancer	Docetaxel	Decrease	Worsening	Retrospective
Dudek et al. (2009)[646]	Sequential therapy with sorafenib and sunitinib in renal cell carcinoma	Renal cell carcinoma	Sunitinib Sorafenib	Decrease	No difference	Retrospective
Sablin et al. (2009)[645]	Sequential sorafenib and sunitinib for renal cell carcinoma	Renal cell carcinoma	Sunitinib Sorafenib	Similar	N/A	Retrospective
Agelaki et al. (2010)[266]	Non-platinum-based first-line followed by platinum-based second-line chemotherapy or the reverse sequence in patients with advanced non-small cell lung cancer: a retrospective analysis by the lung	NSCLC	Platinum Non-platinum	Decrease	N/A	Retrospective

Study	Title	Cancer	Alternatives	Conclusions on effectiveness	Conclusions on safety	Prospective/ retrospective
	cancer group of the Hellenic Oncology Research Group					
Busch et al. (2011)[581]	Sequence therapy in patients with metastatic renal cell carcinoma: comparison of common targeted treatment options following failure of receptor tyrosine kinase inhibitors	Renal cell carcinoma	Sunitinib Sorafenib	Decrease	N/A	Retrospective
Herrmann et al. (2011)[643]	Sequential therapies with sorafenib and sunitinib in advanced or metastatic renal cell carcinoma	Renal cell carcinoma	Sunitinib Sorafenib	Decrease	N/A	Retrospective
Park et al. (2011)[642]	Prognostic factors of second and third line chemotherapy using 5-fu with platinum, irinotecan, and taxane for advanced gastric cancer	Gastric cancer	Taxanes FOLFIRI	Similar	N/A	Retrospective
Porta et al. (2011)[262]	Sequential use of sorafenib and sunitinib in advanced renal-cell carcinoma (RCC): an Italian multicentre retrospective analysis of 189 patient cases	Renal cell carcinoma	Sunitinib Sorafenib	Similar/Decreased	N/A	Retrospective
Buchler et al. (2012)[641]	Sunitinib followed by sorafenib or vice versa for metastatic renal cell carcinoma--data from the Czech registry	Renal cell carcinoma	Sunitinib Sorafenib	Decreased	Decreased	Retrospective
Hong et al. (2012)[574]	Second-line epidermal growth factor receptor inhibitors followed by third-line pemetrexed or the reverse sequence: a retrospective analysis of 83 Chinese patients with advanced lung adenocarcinoma	NSCLC	TKI Pemetrexed	Similar or improved	N/A	Retrospective
Stenner et al. (2012)[261]	A pooled analysis of sequential therapies with sorafenib and sunitinib in metastatic renal cell carcinoma	Renal cell carcinoma	Sunitinib Sorafenib	Decreased	N/A	Retrospective
Busch et al. (2013)[637]	Retrospective comparison of triple-sequence therapies in metastatic renal cell carcinoma	Renal cell carcinoma	mTORi rTKI	Decreased	Decreased	Retrospective
Fiala et al. (2013)[636]	Sequential treatment of advanced-stage lung adenocarcinoma harboring wild-type EGFR gene: second-line pemetrexed followed by third-line erlotinib versus the reverse sequence	NSCLC	Pemetrexed Erlotinib	Similar	N/A	Retrospective

Study	Title	Cancer	Alternatives	Conclusions on effectiveness	Conclusions on safety	Prospective/ retrospective
Alimohamed et al. (2014)[655]	A population-based overview of sequences of targeted therapy in metastatic renal cell carcinoma	Renal cell carcinoma	Sunitinib Sorafenib	Decreased	N/A	Prospective

Abbreviations: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan; N/A: not applicable; mTORi: mammalian target of rapamycin inhibitor; NSCLC: non-small cell lung cancer; rTKI: receptor tyrosine kinase inhibitor; TKI: tyrosine kinase inhibitor

Table 203: Information extracted from non-RCTs

Study	CR by line	OR by line	DC by line	PFS_{01}	PFS_{12}	Toxicity by line	Cycles by line	Intensity by line
Agelaki et al. (2010)[266]	Yes	Yes	Yes	Yes	Yes	No	No	No
Alimohamed et al. (2014)[655]	No	No	No	Yes	Yes	No	No	No
Berthold et al. (2008)[648]	No	No	No	No	No	No	No	No
Buchler et al. (2012)[641]	No	No	No	No	No	Yes	Yes	No
Busch et al. (2011)[581]	No	No	No	Yes	Yes	No	No	No
Busch et al. (2013)[637]	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Dudek et al. (2009)[646]	Yes	Yes	Yes	No	No	Yes	No	No
Dupont (2006)[245]	No	No	No	No	No	Yes	Yes	No
Fiala et al. (2013)[636]	No	No	No	Yes	Yes	No	No	No
Herrmann et al. (2011)[643]	No	Yes	No	Yes	Yes	No	No	No
Hong et al. (2012)[574]	No	Yes	Yes	Yes	Yes	No	No	No
Joung et al. (2008)[647]	Yes	Yes	Yes	Yes	Yes	Yes	No	No
Michels et al. (2006)[264]	No	No	No	Yes	Yes	Yes	Yes	No
Oh et al. (2006)[260]	No	No	No	Yes	Yes	No	No	No
Park et al. (2011)[642]	Yes	Yes	Yes	No	No	No	No	No
Popov et al. (2006)[265]	Yes	Yes	Yes	Yes	Yes	No	No	No
Porta et al. (2011)[262]	No	No	No	Yes	Yes	No	No	No
Sablin et al. (2009)[645]	No	Yes	Yes	Yes	Yes	No	Yes	No
Sakar et al. (2007)[596]	No	Yes	No	Yes	Yes	Yes	No	No

Study	CR by line	OR by line	DC by line	PFS_{01}	PFS_{12}	Toxicity by line	Cycles by line	Intensity by line
Stenner et al. (2012)[261]	No	No	No	Yes	Yes	No	No	No
Totals	**30%**	**50%**	**40%**	**75%**	**75%**	**35%**	**20%**	**0%**

There are several problems with the retrospective trials of two lines of therapy that make it less useful when considering the impact of displacement. The first problem is inclusion requires a participant to receive two lines of therapy. As seen in the RCT literature analysis it will exclude a significant minority of patients to for whom two lines of therapy could have been considered prior to the start of therapy. This results in a significant degree of bias and the internal validity of these trials is limited.

The second problem flow from the non-randomised nature of therapy. It is possible that the selection of patients to one or other therapy might be done with knowledge that is not available to the observer and as such it is possible that the relative benefit of the therapy is not comparable directly to the relative efficacy of the two therapies. However, it may give a more realistic picture of the relative impact of the toxicity and PFS in practice, that is the external validity of a pharmaceuticals use may be greater. Unfortunately, the toxicity data for retrospective studies is not as detailed as was documented in the RCT studies and therefore, it is difficult to develop a meta-analysis of the relative toxicity of first line versus second line therapy.

Dupont (2006)[245]

Dupont (2006)[245] was a retrospective analysis of patients treated with two lines of therapy who had ovarian cancer. Patients were included if they were treated with both topotecan and doxorubicin. Patients were included if they had other treatments as well. 89 patients had received both treatments, 64 received doxorubicin first and 25 received topotecan first.

There was a difference in the amount of time that each pharmaceuticals was given depending on whether it was given first or second within the sequence. The difference in the median survival of patients was not statistically significant, 18.3 months in patients who received doxorubicin first and 17.8 months in patients who received topotecan first. An increased portion of patients were removed due to toxicity if a pharmaceutical was used in second line rather than first.

Table 204: Information from Dupont (2006)[245]

Protocol	**Topotecan**		**Liposomal doxorubicin**	
Line of therapy	**Initial**	**Subsequent**	**Initial**	**Subsequent**
Numbers	25	64	64	25
Complete response	8%	6%	2%	0%
Median cycles	5	4	3	2

Protocol	Topotecan		Liposomal doxorubicin	
Line of therapy	Initial	Subsequent	Initial	Subsequent
Adverse events	16%	6%	12%	28%

Michels et al. (2006)[264]

Michels et al. (2006)[264] was a retrospective analysis of patients who received docetaxel or mitoxantrone for metastatic prostate cancer. Sixty-eight patients were identified, 35 received docetaxel first and 33 received mitoxantrone first. There was a trend to improved median survival when docetaxel was given in first line (median OS 22 months versus 15 months). Chemotherapy was given for longer in first line than second line for both pharmaceuticals. Second line treatment was associated with a higher adverse event rate than first line treatment.

Table 205: Information from Michels et al. (2006)[264]

Protocol	Docetaxel		Mitoxantrone	
Line of therapy	Initial	Subsequent	Initial	Subsequent
Numbers	35	33	33	35
PFS	6 months	2-3 months	5 months	2-3 months
Median cycles	6 cycles	3 cycles	5 cycles	3 cycles
Adverse events	31%	64%	54%	46%

Abbreviation: PFS: progression free survival

Oh et al. (2006)[260]

Oh et al. (2006)[260] was a retrospective analysis of patients who received two lines of therapy for prostate cancer. The two lines of therapy were mitoxantrone based and taxane based. Sixty-eight patients were identified, 33 patients received mitoxantrone based therapy first, 35 received taxane based therapy first. Overall survival was not statistically significant between the two groups.

Table 206: Information from Oh et al. (2006)[260]

Protocol	Taxanes		Mitoxantrone	
Line of therapy	Initial	Subsequent	Initial	Subsequent
Numbers	35	33	33	35
Median PFS	17 weeks	16.3 weeks	10.1 weeks	6.1 weeks

Abbreviation: PFS: progression free survival

Popov et al. (2006)[265]

Popov et al. (2006)[265] was a prospective study in which 193 patients chose from a number of options for CRC for first and second line therapy. They found that treatment with all three

active agents (5-FU, Oxaliplatin and irinotecan) was superior to treatment with two or fewer agents. Only one protocol was given in two different lines of therapy, FOLFIRI was given as the initial line of therapy cohort E and the subsequent line of therapy in cohort C.

Table 207: Information from Popov et al. (2006)[265]

Protocol		**FOLFIRI**
Line of therapy	**Initial (E)**	**Subsequent (C)**
Numbers	46	43
Complete response	9%	0%
Partial response	30%	19%
Overall response rate	39%	19%
Stable disease	41%	44%
Disease control	80%	63%
Median PFS	9	6

Abbreviation: PFS: progression free survival

Sakar et al. (2007)[596]

Sakar et al. (2007)[596] was a prospective observation conducted in CRC. Patients were treated with either XELOX (capecitabine and oxaliplatin) or XELIRI (capecitabine and irinotecan) in consecutive lines of therapy. 121 patients were enrolled, 57 received XELIRI in the first line of therapy and 64 received XELOX.

The difference in median overall survival was not statistically significant. The median survival was 19 months in the XELIRI first arm and 20 months in the XELOX first arm. The median PFS_{01} in each arm was seven months.

Table 208: Information from Sakar et al. (2007)[596]

Protocol		**XELOX**		**XELIRI**
Line of therapy	**Initial**	**Subsequent**	**Initial**	**Subsequent**
Numbers	64	57	57	64
Overall response rate	48%	10%	45%	8%
Median PFS	7	3	7	2
Adverse events	Available	Available	Available	Available

Abbreviation: PFS: progression free survival; XELIRI: a protocol consisting of irinotecan and capecitabine; XELOX: a protocol consisting of oxaliplatin and capecitabine

Table 209: Toxicity of XELIRI in Sakar et al. (2007)[596]

XELIRI	**In First Line**	**In Second Line**
Progression Free Survival	7 months	2 months
Number of patients	54 patients	67 patients
Grade 3 or 4 neutropenia (%)	23%	19%

XELIRI	In First Line	In Second Line
% per PFS (median) per year	39%	114%
Grade 3 or 4 febrile neutropenia (%)	4%	0%
% per PFS (median in years)	7%	0%
Grade 3 or 3 diarrhoea (%)	11%	3%
% per PFS (median) per year	19%	18%

Abbreviations: PFS: progression free survival; XELIRI: a protocol consisting of irinotecan and capecitabine

Table 210: Toxicity of XELOX in Sakar et al. (2007)[596]

Indicator of XELOX	In First Line	In Second Line
Progression Free Survival	7 months	3 months
Number of patients	67 patients	54 patients
Grade 3 or 4 neutropenia (%)	40%	21%
% per PFS (median) per year	69%	84%
Grade 3 or 4 febrile neutropenia (%)	4%	0%
% per PFS (median) per year	7%	0%
Grade 3 or 3 neurological (%)	30%	30%
% per PFS (median) per year	51%	120%

Abbreviations: PFS: progression free survival; XELOX: a protocol consisting of oxaliplatin and capecitabine

Berthold et al. (2008)[648]

Berthold et al. (2008)[648] was a retrospective analysis of a trial for prostate cancer. A first line trial comparing mitoxantrone and docetaxel had a degree of crossover captured in the trial database. This was analysed in the Berthold et al. (2008)[648] paper. Crossover was identified for 232 men. 89 received docetaxel every three weeks and crossed over to mitoxantrone, 76 received docetaxel every week and crossed over to mitoxantrone and 67 crossed over from mitoxantrone to docetaxel. There was no discussion about the progression from first line therapy but the PFS_{12} was similar for both arms. There was no toxicity data, but the authors commented that toxicity would be expected to be higher in second line therapy.

Joung et al. (2008)[647]

Joung et al. (2008)[647] was a retrospective analysis of Korean patients who had received first or second line treatment with docetaxel for prostate cancer. 47 patients were identified, 19 patients in first line and 28 patients in second line. It suggested that there was a longer time to progression from receiving docetaxel in second line rather than first line (4 months versus 2 months). It also concluded that there was no difference observable in the toxicities experienced as an aggregate number.

Table 211: Information from Joung et al. (2008)[647]

Protocol		Docetaxel
Line of therapy	**1**	**2**
Numbers	47	19
Complete response	15%	6%
Partial response	23%	6%
Overall response rate	54%	44%
Stable disease	77%	50%
Disease control	8%	0%
Median PFS	4	2
Adverse events	Yes	Yes

Abbreviation: PFS: progression free survival

Dudek et al. (2009)[646]

Dudeck et al. (2009)[646] was a retrospective study assessing metastatic renal cell carcinoma treated with two lines of tyrosine kinas inhibitors. Twenty-nine patients received sorafenib followed by sunitinib and 20 patients the reverse order.

Table 212: Information from Dudek et al. (2009)[646]

Protocol	Sunitinib		Sorafenib	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	20	29	29	20
Complete response	5%	21%	7%	5%
Partial response	5%	21%	7%	5%
Overall response rate	65%	38%	62%	30%
Stable disease	70%	59%	69%	35%
Disease control	0%	0%	0%	0%
PFS	22 weeks	20 weeks	25 weeks	10 weeks
Adverse events	10%	7%	10%	15%

Abbreviation: PFS: progression free survival

There was no difference between the two groups for PFS_{01}. This was 25 weeks for sorafenib and 22 weeks for sunitinib. There was a trend to improved PFS_{12} for those who took sunitinib second line (20 weeks) versus those who took sorafenib in second line (10 weeks). Median overall survival time was different between the groups (102 weeks versus 45 weeks) but this had not reached statistical difference.

Sablin et al. (2009)[645]

Sablin et al. (2009)[645] was a retrospective study conducted in patients with renal cell carcinoma. It examined the sequential use of sunitinib and sorafenib. Median overall survival was 135 weeks in the group who received sorafenib first and 82 weeks in the group that

received sunitinib first. This difference was statistically significant. There was no discussion about results of toxicity within the paper, except to point out that the rate was similar between the two groups and less noted in second line.

Table 213: Information from Sablin et al. (2009)[645]

Protocol	Sunitinib		Sorafenib	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	22	68	68	22
Complete response	0%	0%	0%	0%
Partial response	23%	15%	16%	9%
Overall response rate	23%	15%	16%	9%
Stable disease	55%	51%	66%	55%
Disease control	77%	66%	82%	64%
Median PFS	22 weeks	28 weeks	26 weeks	17 weeks
Mean cycles	27 weeks	28 weeks	33 weeks	22 weeks

Abbreviation: PFS: progression free survival

Agelaki et al. (2010)[266]

Agelaki et al. (2010)[266] was a retrospective study undertaken in patients with NSCLC. It was an opportunistic study undertaken in patients who had been enrolled in RCTs for first line therapy. The distinction was made between patients who were randomised to first line therapy with platinum containing agents or non-platinum containing agents. The groups considered were those that crossed over to the other protocol.

Two hundred and sixty-seven patients were identified as receiving non-platinum agents in the first line and 123 patients were identified as receiving platinum agents in the first line. There was no statistical difference between the two groups in overall survival.

Table 214: Information from Agelaki et al. (2010)[266]

Protocol	Platinum		Non-platinum	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	123	267	267	123
Complete response	2%	1%	1%	0%
Partial response	44%	12%	21%	7%
Overall response rate	46%	13%	21%	7%
Stable disease	29%	28%	25%	36%
Disease control	75%	42%	46%	43%
Median PFS	5.8	3	3.1	3.1

Abbreviation: PFS: progression free survival

Busch et al. (2011)[581]

Busch et al. (2011)[581] was a retrospective chart audit of patients who received two lines of therapy for metastatic renal cell carcinoma. Patients were included if they have received both everolimus or a receptor tyrosine kinase inhibitor after the failure of an initial receptor tyrosine kinase inhibitor. Forty-six patients were treated initially with sunitinib (11) or sorafenib (35).

Table 215: Information from Busch et al. (2011)[581]

Protocol	**Sunitinib**		**Sorafenib**	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	35	11	11	35
Median PFS	5.5 months	4 months	10.5 months	4.1 months

Abbreviation: PFS: progression free survival

Herrmann et al. (2011)[643]

Herrmann et al. (2011)[643] investigated the impact of sequential treatment with sorafenib and sunitinib in renal cell carcinoma. A retrospective review identified 89 patients. There was no statistical difference between the two groups with a median survival of 28.8 months.

Table 216: Information from Herrmann et al. (2011)[643]

Protocol	**Sorafenib**		**Sunitinib**	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	33	54	54	33
Overall response rate	21.4%	17.6%	27.3%	17.6%
Median PFS	9.3	3.8	9.8	3.4

Abbreviation: PFS: progression free survival

Park et al. (2011 [642]

Park et al. (2011)[642] was a retrospective study of second and third line therapy in gastric cancer. The protocols were FOLFIRI and taxanes with 5-FU. Poor prognosis was associated with a shorter time to progression in the first line of therapy.

Table 217: Information from Park et al. (2011)[642]

Protocol	**FOLFIRI**		**Taxanes**	
Line of therapy	**2**	**3**	**2**	**3**
Numbers	18	32	32	18
Complete response	0%	0%	0%	0%
Partial response	11%	9%	6%	6%

Protocol	FOLFIRI		Taxanes	
Line of therapy	**2**	**3**	**2**	**3**
Overall response rate	11%	9%	6%	6%
Stable disease	28%	31%	47%	17%
Disease control	39%	41%	53%	22%

Abbreviation: FOLFIRI: a protocol consisting of 5-fluorouracil, leucovorin and irinotecan

Porta et al. (2011)[262]

Porta was a retrospective review of patients receiving sorafenib and sunitinib for renal cell carcinoma. One hundred and eighty-nine patients were identified in the retrospective review. First line therapy for each agent was similar (sunitinib 7.8 months median PFS and sorafenib 8.4 months). Second line therapy produced a statistically significant difference between the two therapies (sunitinib 7.9 months vs sorafenib 4.2 months). There was no discussion of the overall survival or toxicity associated with the treatments in first or second line.

Table 218: Information from Porta et al. (2011)[262]

Protocol	Sorafenib		Sunitinib	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	90	99	99	90
Median PFS	8.4	4.2	7.8	7.9

Abbreviation: PFS: progression free survival

Buchler et al. (2012)[641]

Buchler et al. (2012)[641] was a review of patients who had been treated sequentially with both sunitinib and sorafenib for metastatic renal cell carcinoma. 260 patients were identified. There was no statistically significant difference between PFS_{02} between the two groups (a median of 17.7 months for the group receiving sunitinib first and a median of 18.8 months for the group receiving sorafenib first). Median overall survival was 35 months in the group who received sunitinib first and 30 months in the group who received sorafenib first. Patients spent significantly less time on the pharmaceutical given in second line.

The article commented on toxicity. The authors noted that the number of adverse events was lower in second line treatment than in first line, but the results were not adjusted for the time spent in each state.

Table 219: Information from Buchler et al. (2012)[641]

Protocol	Sorafenib		Sunitinib	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	122	138	138	122

Protocol		Sorafenib		Sunitinib
Line of therapy	**1**	**2**	**1**	**2**
Median cycles	5.7	3.2	6.3	4.3
Adverse events	Yes	Yes	Yes	Yes

Hong et al. (2012)[574]

Hong et al. (2012)[574] was a retrospective review of NSCLC patients who received second and third line therapy with pemetrexed or a tyrosine kinase inhibitor (TKI). 83 patients were identified, 45 who received tyrosine kinase inhibitors followed by pemetrexed and 38 with the opposite sequence. The sequence of a tyrosine kinase inhibitor followed by pemetrexed was found to result in a significantly longer median survival time (23.6 months versus 16.2 months). The response of tyrosine kinase inhibitors was found to be higher in second line therapy than third line therapy.

Table 220: Information from Hong et al. (2012)[574]

Protocol		EGFR TKI		Pemetrexed
Line of therapy	2	3	2	3
Numbers	45	38	38	45
Overall response rate	44%	34%	13%	20%
Stable disease	11%	29%	32%	42%
Disease control	56%	63%	45%	62%
Median PFS	8 months	7.6 months	4.2 months	6.9 months

Abbreviation: EGFR: epithelial growth factor receptor; PFS: progression free survival; TKI: tyrosine kinase inhibitor

Stenner et al. (2012)[261]

Stenner et al. (2012)[261] was a combination of an empirical study and a meta-analysis. It was conducted in patients with renal cell carcinoma. A retrospective analysis was conducted for patients who had received the tyrosine kinase inhibitors, sorafenib and sunitinib in sequence. The results were pooled with the other results present in the literature. Stenner et al. (2012)[261] itself contributed 21 patients to the pooling. The total pool consisted of 853 patients. There was a statistical difference between the two sequences, sorafenib followed by sunitinib had a PFS_{02} of 15.4 months compared to 12.1 months for the reverse sequence.

Table 221: Information from Stenner et al. (2012)[261]

Protocol		Sorafenib		Sunitinib
Line of therapy	**1**	**2**	**1**	**2**
Numbers	10	11	11	10
Median PFS	5.39	3.71	12.71	6.01

Abbreviation: PFS: progression free survival

Zhang et al. (2012)

Zhang was a study published in 2012 in the Chinese Journal of Oncology.[638] Only the abstract was available in English. It was conducted in patients with NSCLC. 83 patients were included and appeared to be a retrospective chart audit. The results were similar to those presented in Hong.[574] Second line tyrosine kinase inhibitors followed by pemetrexed were associated with a statistically significantly longer progression free survival time and median survival time than the reverse sequence. There was no full-text available in English and this study was not included in the analysis.

Busch et al. (2013)[637]

Busch et al. (2013)[637] was a retrospective comparison of two different treatment sequences for renal cell carcinoma. For each the first line therapy was the same, a vascular endothelial growth factor inhibitor. However, the next two lines of therapy were reversed in the two arms, a receptor tyrosine kinase inhibitor (rTKI), the most common being sunitinib, and a mammalian target of rapamycin inhibitor (mTORi), the most common being everolimus. There was a breakdown of toxicity by the line of therapy.

Table 222: Information from Busch et al. (2013)[637]

Protocol		**rTKI**		**mTORi**
Line of therapy	**2**	**3**	**2**	**3**
Numbers	62	41	41	62
Complete response	0%	0%	0%	0%
Partial response	5%	2%	5%	5%
Overall response rate	5%	2%	5%	5%
Stable disease	35%	49%	49%	44%
Disease control	40%	51%	54%	48%
Median PFS	4.1	3.7	5.4	3.6
Adverse events	Yes	Yes	Yes	Yes

Abbreviations: mTORi: mammalian target of rapamycin inhibitor; PFS: progression free survival; rTKI: receptor tyrosine kinase inhibitor

Fiala et al. (2013)[636]

Fiala et al. (2013)[636] considered the sequence of pemetrexed and erlotinib in second and third line treatment for NSCLC. Fifty-seven patients were included in the retrospective analysis. The population was defined as having wild type EGFR that progressed on standard first line therapy. It is notable that the two arms were unbalanced in terms of smoking status, with 77% being current smokers in the group that received pemetrexed first and 39% being current smokers in the erlotinib first group. Both progression free survival and overall survival were

improved with the sequence erlotinib and then pemetrexed compared to the reverse sequence. The median overall survival was 7.9 months in the group that received pemetrexed initially and 26.3 months in the group that received erlotinib initially. There was no discussion of toxicity.

Table 223: Information from Fiala et al. (2013)[636]

Protocol	Pemetrexed		Erlotinib	
Line of therapy	**2**	**3**	**2**	**3**
Numbers	31	26	26	31
Median PFS	1.5	3.1	2.9	1.8

Abbreviation: PFS: progression free survival

Alimohamed et al. (2014)[655]

A prospective data collection of renal cell carcinoma was undertaken in Canada. The treatment sequences used for renal cell carcinoma were recorded. Among a larger set of treatments were the sequence sunitinib followed by sorafenib and the reverse sequence.

Table 224: Information from Alimohamed et al. (2014)[655]

Protocol	Sunitinib		Sorafenib	
Line of therapy	**1**	**2**	**1**	**2**
Numbers	257	152	152	257
Median PFS	7.6	5.2	7.3	3.6

Abbreviation: PFS: progression free survival

Jonasch et al. (2014)[659]

Jonasch et al. (2014)[659] was a retrospective study published in Current Medical Research and Opinion. Physicians from a nationwide panel contributed up to 15 patients whose files were reviewed. A larger number of treatments were given but the sequence of VEGF TKI (the most common being sunitinib) and an mTOR (the two most common being everolimus and temsirolimus) was given as was the reverse. There was no individual piece of information that was available in both lines of therapy.

Polkowska et al. (2017)[697]

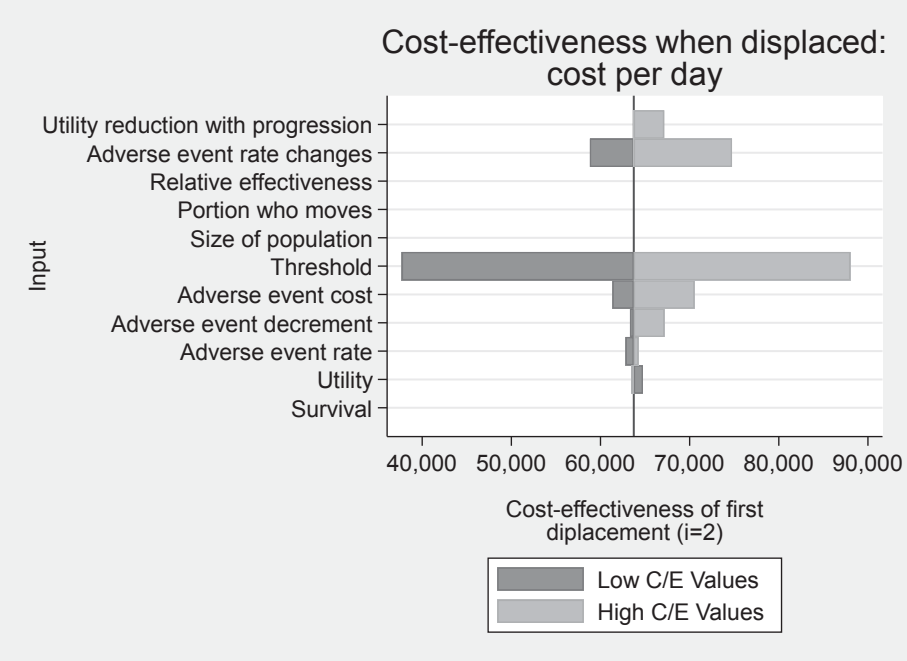
Polkowska et al. (2017)[697] was a retrospective analysis of melanoma treatment in Poland between 2012 and 2016. Included in the treatments were classic chemotherapy and vemurafenib. Other treatments were involved, and the analysis conducted in the publication did not ensure that the treatments were reversed. No information was available by line of therapy.

Appendix G: Parameters and detailed sensitivity analysis

Sensitivity analysis of Section 7.1

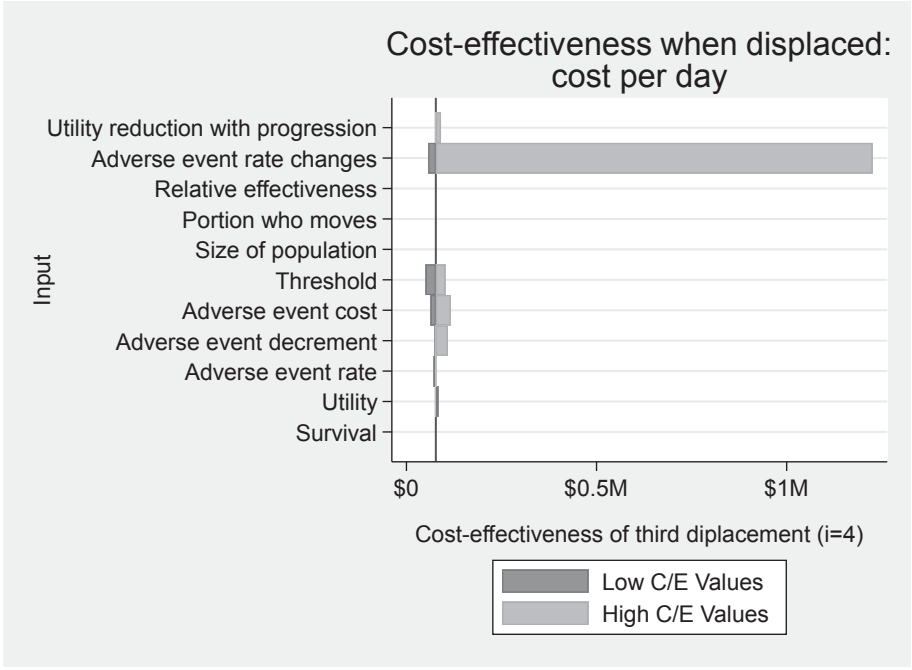
The one-way sensitivity analysis for the cost-effectiveness of the cost per day payment mechanism is demonstrated for one displacement (into the second line of therapy [i=2]) and for three displacements (into the fourth line of therapy [i=4]). The tornado diagram shows the relative changes in cost-effectiveness compared to the calculated cost-effectiveness ratio for one displacement ($63 733) or three displacements ($77 381). A lower threshold for decision-making resulted in a lower cost-effectiveness ratio after displacement. After being displaced three times in the fourth line of therapy the increase in rate of adverse events occurring with displacement has the largest impact on the predicted cost-effectiveness. The cost-effectiveness of the cost per day model was unaffected by alterations in the estimated relative effectiveness.

The size of the population had the largest impact on the estimation of net monetary benefit with one displacement into the second line of therapy (Figure 51 [i=2]). With the third displacement into the fourth line of therapy (i=4), the higher rate of adverse events modelled had a larger impact than the increased size of population.



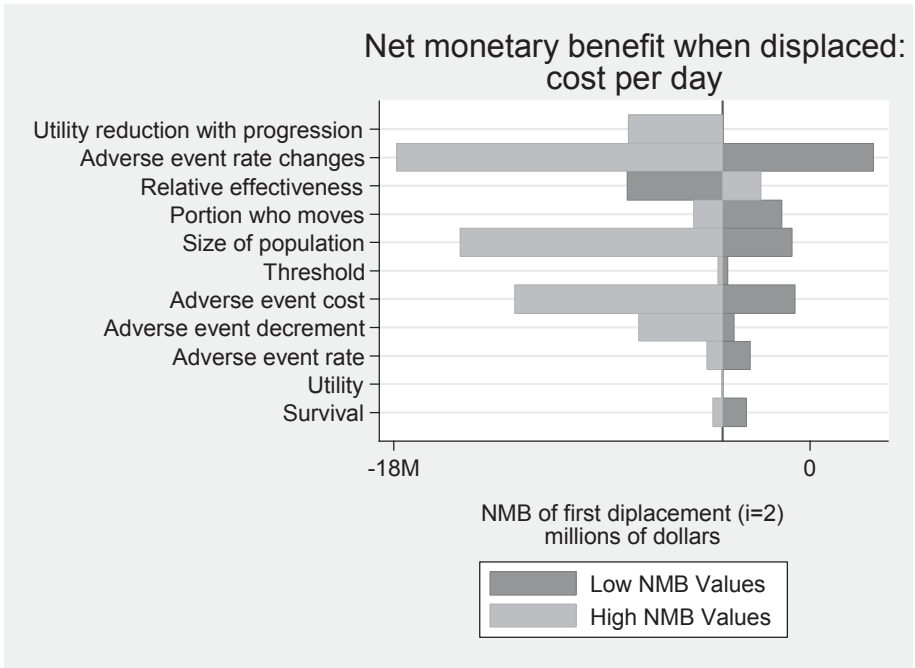
Abbreviation: C/E: cost-effectiveness

Figure 49: One-way sensitivity analysis of cost-effectiveness (cost per day model) (i=2)



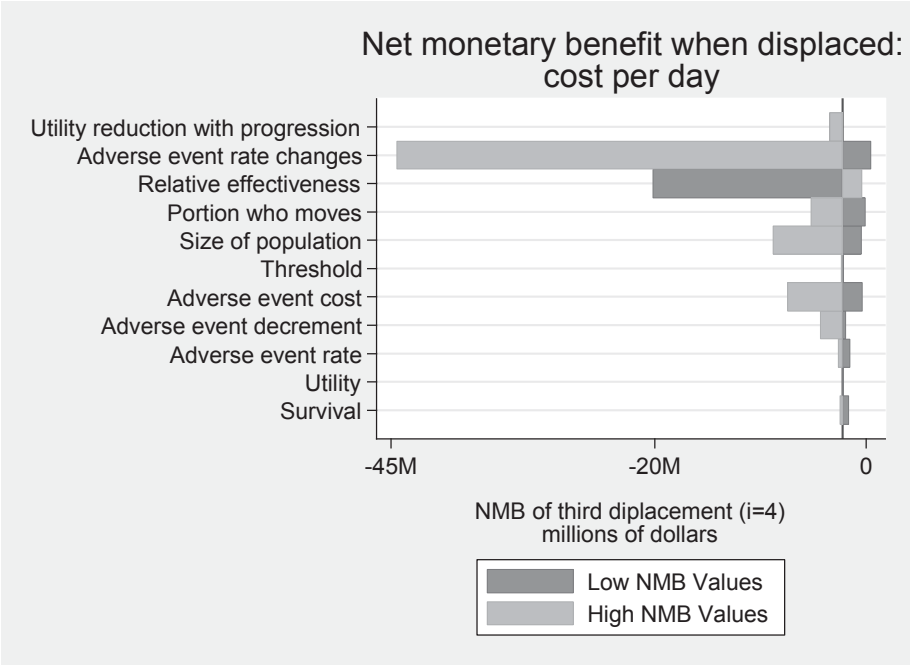
Abbreviation: C/E: cost-effectiveness

Figure 50: One-way sensitivity analysis of cost-effectiveness (cost per day model) (i=4)



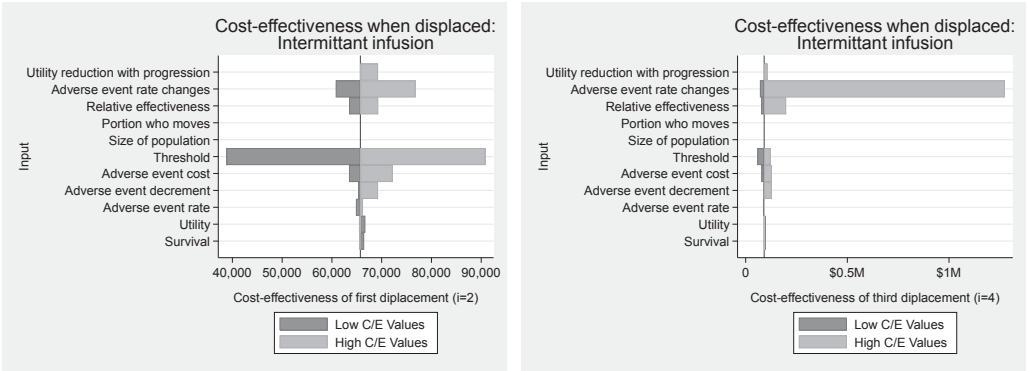
Abbreviation: NMB: net monetary benefit

Figure 51: One-way sensitivity analysis of net monetary benefit (cost per day model) (i=2)



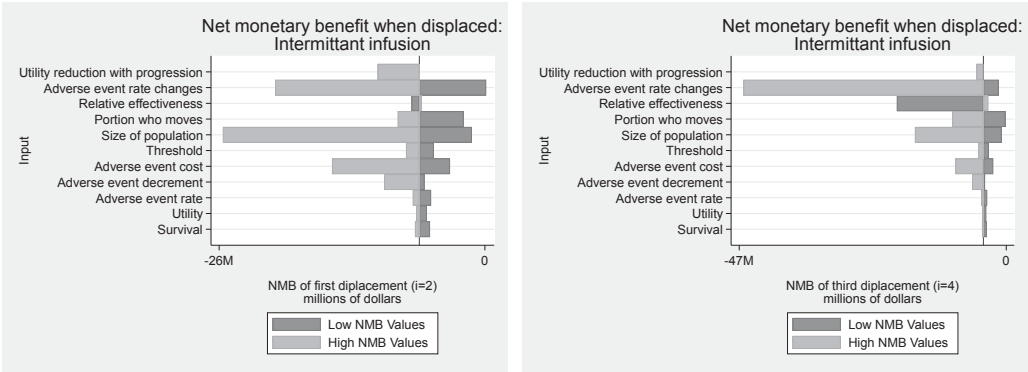
Abbreviation: NMB: net monetary benefit

Figure 52: One-way sensitivity analysis of net monetary benefit (cost per day model) (i=4)



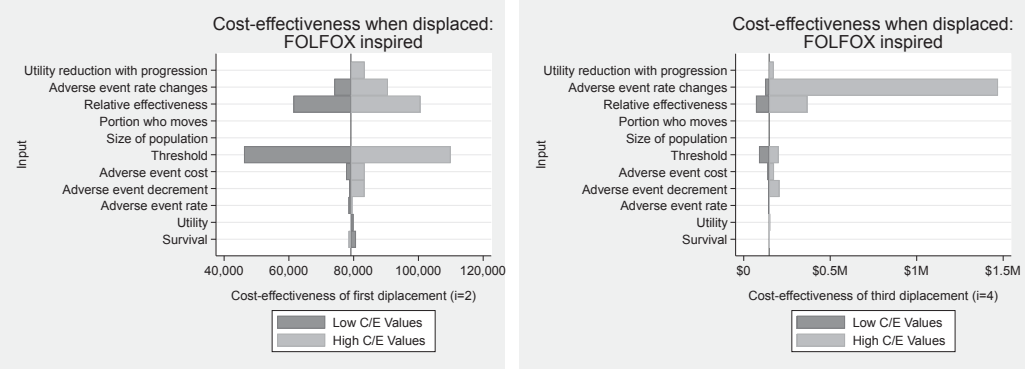
Abbreviation: C/E: cost-effectiveness

Figure 53: One-way sensitivity analysis of cost-effectiveness (intermittent infusion) (i=2,4)



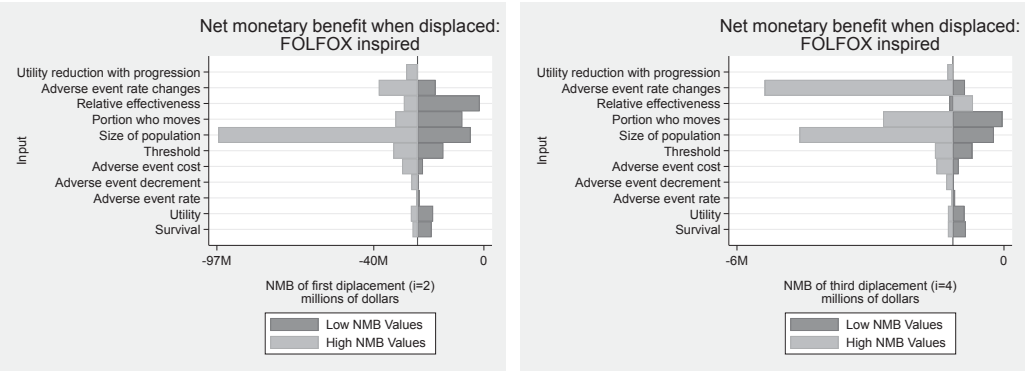
Abbreviation: NMB: net monetary benefit

Figure 54: One-way sensitivity analysis of net monetary benefit (intermittent infusion) (i=2,4)



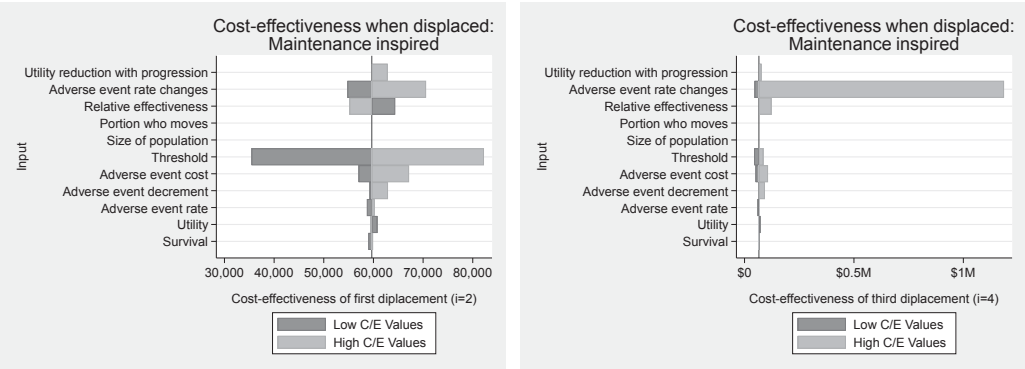
Abbreviation: C/E: cost-effectiveness

Figure 55: One-way sensitivity analysis of cost-effectiveness (FOLFOX model) (i=2,4)



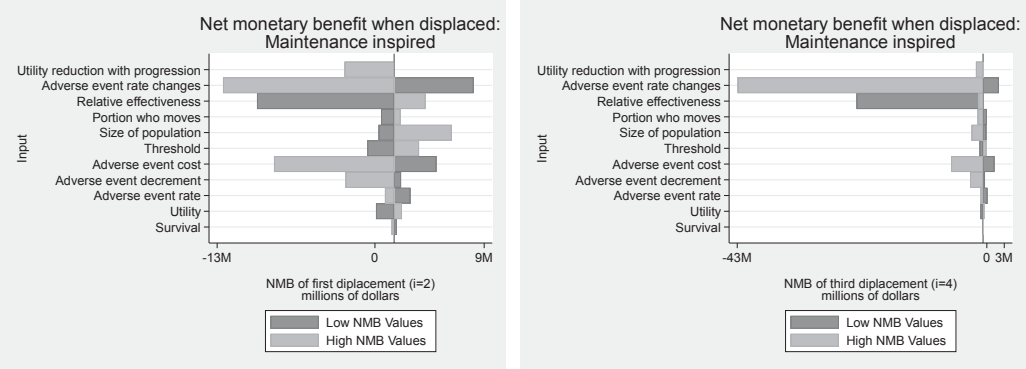
Abbreviation: NMB: net monetary benefit

Figure 56: One-way sensitivity analysis of net monetary benefit (FOLFOX model) (i=2,4)



Abbreviation: C/E: cost-effectiveness

Figure 57: One-way sensitivity analysis of cost-effectiveness (maintenance model) (i=2,4)



Abbreviation: NMB: net monetary benefit

Figure 58: One-way sensitivity analysis of net monetary benefit (maintenance model) (i=2,4)

Parameters for probabilistic sensitivity analysis

Table 225: Parameters and model inputs for probabilistic sensitivity analysis

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
			Cancer type and survival			
Cancer	All cancers	Multivariate	To determine the cancer type for the protocol	Assumption	Only the three cancer types in the EoCC were modelled	"Cancer"
Median progression free survival in first line of survival	Breast	Mean 9.95 months Range 5.7 to 14.2 months	Converted to hazard rate using assumption of exponential distribution	Assumption	All survivals were assumed to have exponential distribution	"medianPFS01" "hazardrate" "meanPFS01"
	CRC	Mean 10.75 months Range: 9.4 to 12.1 months		Assumption	All survivals were assumed to have exponential distribution	
	NSCLC	Mean 5.7 months: Range: 3 to 8.4 months		Assumption	All survivals were assumed to have exponential distribution	
Reduction in effectiveness into second line	All	Mean increase in HR by a multiple of 1.869 and a 95% CI of 1.646 to 2.123	A normal distribution was assumed for the logged mean and standard deviation, the resultant estimate was then converted back as an exponential	Assumption based on meta-analysis	All survivals were assumed to have exponential distribution	"newchangeeff"
Post-progression survival	All	Mean of 3 months				"ppsurvival01" "ppsurvival12"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
			Utilities			
Utility	Breast	Mean value of 0.724 and standard deviation of 0.038776	Converted into beta distribution	Upper and lower limits of first line treatment.[284]		"utility"
	CRC	Mean value of 0.8 and standard deviation 0.04	Converted into beta distribution	Reported health state utilities for Stage IV.[276]		
	NSCLC	Mean value 0.573 and standard deviation 0.067	Converted in beta distribution	Reported health state utilities		
Utility reduction with increase line of therapy	All	-	-	-	Not included in the base model, available for further modelling	"utilitydecrement"
Utility decrement with adverse event	All	Mean value 0.15, standard error was 0.02	Converted into a beta distribution	[286]		"utilitydec"
Utility of post-progression survival	All	Mean value 0f 0.55, standard error of 0.04	Converted into a beta distribution			"pputility01" "pputility12"
Adverse event rate in initial line of therapy (per month)	All	Average of 66% with a standard deviation of 0.11	Converted into beta distribution	To ensure that negative numbers were avoided		"adverseevents"
Increase in adverse events per period	All	Relative risk of 0.88, predictive interval of 0.65 to 1.19	Converted into log values and random variable produced then converted back			"changeae"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
			Resource use			
Number of tests used when progression occurs	All	Mean value of 2	Random Poisson with mean value of 2	Poisson		"progresstest"
Pharmaceutical use in first line of therapy	All	Determined by mean PFS				"pharmaceutical"
			Costs			
Adverse event cost	All	Median cost of $11 311 (logged 9.334), with standard error of 0.174 on logged distribution	Log normal distribution used, given the log of costs gives of more normal distribution, attributed per adverse event. Mean costs adjusted by inflation.	Pearce.[288]		"adverseeventcost"
Monitoring costs	All	Mean cost $178.85 for non-infusion	Attributed at the start of every month (not cycle)			"moncost1"
Infusion costs	For intermittent and FOLFOX type	Mean cost $83.3	Attributed at the start of every cycle (not month)			"moncost23"
Progression cost	All			Random selection of test costs	The cost was assumed to be the same in first and second line treatment	"progressioncost01" "progressioncost12"
Palliative care costs	All	Mean of $21 642 and standard deviation of $346 was used.	Attributed when progression occurs	Gamma distribution (3908.02,5.537846)	The cost was assumed to be the same in both alternatives in	"deathcost01" "deathcost12"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
					second line and in first line treatment	
Type of payment schedule	All	Daily (38.1%) Periodic (23.8%) FOLFOX inspired (38.1%)	Multivariate	Mutually exclusive probabilities, requirement to add to sum to 1	Analysis of last 20 PBAC submissions (Table 59)	"Paymentmech"
Cycle length	Daily	Monthly	No distribution		Assumed based on accessing pharmaceutical	Nil
	Periodic	Mean of 2.5 weeks	10% probability of 1 40% probability of 2 40% probability of 3 10% probability of 1	Mutually exclusive probabilities, requirement to add to sum to 1		"cyclelength"
	FOLFOX inspired	Mean of 2.5 weeks	10% probability of 1 40% probability of 2 40% probability of 3 10% probability of 1	Mutually exclusive probabilities, requirement to add to sum to 1		"cyclelength"
Maximum number of cycles with multiple pharmaceuticals	For FOLFOX inspired payment schedule only	-	Random integer below the mean progression free survival with four as minimum			"FOLFOXlength"
Portion of FOLFOX type with no continuation		50%		No distribution		"randomcontinue"
Relative cost of FOLFOX type with continuation		Mean 0.02533, standard deviation of 0.02533	Converted into a beta distribution	The cost of the additional pharmaceuticals in		"FOLFOXratio"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
				the FOLFOX group that cease		
Decrease in usage of pharmaceutical with adverse events	All					
Threshold	All	Mean $60 866 Standard deviation $10 000	Used to generate a price in the first line of therapy	Assumption	Inflating the estimate for life saving treatment estimated by Harris et al. (2008) by health inflation gave estimate of $60.866 in AUS $ (2015)	"threshold"
Parameters associated with determination of population size						
Size of population	Breast	Mean of 8 330 and standard deviation of 914	Normal distribution	Assumption	Based on mortality rate and estimates of the proportion of the prevalent population who may develop metastatic disease	"population"
	CRC	Mean of 4 964 and standard deviation of 298	Normal distribution	Assumption		
	NSCLC	Mean of 6 303 and standard deviation of 649	Normal distribution	Assumption		
Change of targeted agents	All	Mean 57.1%	No distribution used	Probability, therefore a requirement to be between zero and one	Analysis of last 20 PBAC submissions (Table 59)	"drugtupe"
Portion of population who use a targeted agent	All	Mean of 30.1% and standard deviation of 0.203	Converted into a beta distribution	Proportion, therefore a requirement to be between zero and one	Proportion of population for targeted agent	"biofactor"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
Proportion who move line of therapy	All	Mean 60%, standard deviation 0.144	Converted into a beta distribution	Requirement to be between zero and one		"portion"
			Microsimulation			
Individual progression free survival in first line	Microsimulation only	The protocol hazard rate was used		Assumed exponential distribution		"surv01"
Individual progression free survival in second line	Microsimulation only	The protocol hazard rate was multiplied by the reduction in effectiveness		Assumed exponential distribution		"surv12"
Individual post-progression survival	Microsimulation only	The post-progression survival was calculated independently for post-first line and post-second line treatment		Assumed exponential distribution		"pps01" "pps12"
Number of adverse events	Microsimulation	Survival multiplied by protocol risk		Assumed Poisson distribution		"numae01" "numae12"
Cost of adverse events	Microsimulation	Protocol cost of adverse events	Calculated for each individual	Gamma		"costae"
Post-progression palliative care cost	Microsimulation only	Dependent on length of post-progression survival	4/7 of cost for survival equal to one month or less, 6/7 of cost for survival equal to two months or less, additionally 1/7 of cost per month in excess of 2 months		Based on results of Langton et al. (2016).[200]	

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
Number of individuals who received second line therapy	Microsimulation only	-	Each individual had the same probability of moving to second line of therapy modified by their potential post-progression survival	Not applicable		"random"
Specific individual moving a line of therapy	Microsimulation only		Each individual had the same probability of moving to second line of therapy modified by their potential post-progression survival	Not applicable		"secondlinetreatment"
Individual utility	Microsimulation only	Mean from protocol used, standard deviation of 0.15 used, unless the utility was greater than 0.9, then 0.05 was used		Assumed beta distribution	Standard deviation used	"utility01s" "utility12s" "utilitydecs" "utilitypps01" "utilitypps12"
Individual pharmaceutical usage and monitoring use	Microsimulation only			The distribution of survival in the first and second lines of therapy		"pharmuse01" "pharmuse12s" "monitorc01s" "monitorc12s"
Correlation of post-progression	Microsimulation only	The post-progression survival of the alternative of no second line			The has the effect of reducing the difference in survival	"pps01g12"

Parameter	Type	Mean value (and distribution)	How used	Source of distribution	Notes	Name in model
survival and the use of a second		treatment was correlated with the chance of receiving second line treatment			for those who receive treatment	
Variables used in the sensitivity analysis						
Disease cost		$1 000	Increased the monitoring (monthly cost) by $1 000	N/A		"moncost1"
Lower utility in second line of therapy		0.039	Decreased utility in second line of therapy	N/A	From difference between first and second line treatment in Riesco-Martinez et al. (2016)[4]	"utilitydecrement"
Adverse events						
Reduction in post-treatment period after second line treatment		2	The post-progression survival after the second line of therapy was reduced		The cost associated with mortality was left unchanged	

Abbreviations: CI: confidence interval; CRC: colorectal cancer; EoCC: Elements of Cancer Care; NSCLC: non-small cell lung cancer; PFS: progression free survival

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