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ORIGINAL RESEARCH

Cost-effectiveness of osimertinib versus standard EGFR-TKI as first-line treatment for locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer in Australia

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ABSTRACT

Objectives: To assess the cost-effectiveness of osimertinib versus standard epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), gefitinib or erlotinib, as first-line treatment for patients with locally advanced or metastatic EGFR mutation-positive non-small cell lung cancer in Australia from a healthcare system perspective.

Methods: A partitioned survival model comprising three mutually exclusive health states with a five-year time horizon was developed. Model inputs were sourced from the pivotal trial (FLAURA) and published literature. Incremental cost-effectiveness ratios (ICERs), in terms of cost per quality-adjusted life-year (QALY) gained and cost per life-year (LY) gained, were calculated. Uncertainty of the results was assessed using deterministic and probabilistic sensitivity analyses.

Results: Compared with standard EGFR-TKIs, osimertinib was associated with a higher incremental cost of A$118,502, and an incremental benefit of 0.274 QALYs and 0.313 LYs. The ICER was estimated to be A$432,197/QALY gained and A$378,157/LY gained. The base-case ICER was most sensitive to changes in cost of first-line osimertinib, time horizon, and choice of overall survival data (interim versus final analysis).

Conclusions: At a willingness-to-pay threshold of A$50,000/QALY, first-line osimertinib is not cost-effective compared with standard EGFR-TKIs in Australia based on the current published price. To achieve acceptable cost-effectiveness, the cost of first-line osimertinib needs to be reduced by at least 68.4%.

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KEYWORDS
Osimertinib; non-small cell lung cancer; EGFR mutation; economic evaluation; cost-effectiveness

1. Introduction

In 2018, lung cancer was one of the most commonly diagnosed cancers worldwide which represented 11.6% of all newly diagnosed cancer cases and was the leading cause of cancer deaths with an estimated total of 1.76 million deaths [1]. In Australia, lung cancer ranked fifth in terms of cancer diagnosis and was responsible for the highest number of cancer deaths in 2019 [2]. In patients diagnosed with stage III and IV lung cancer, the 5-year survival rate (2012–2016) was only at 17.1% and 3.2% [2]. Therefore, there remains a significant unmet medical need in the treatment of advanced lung cancer in Australia.

In Australia, patients diagnosed with locally advanced or metastatic non-small cell lung cancer (Stage IIIB or IV; referred to hereafter as advanced NSCLC) would undergo mutation testing to assess for targetable mutations such as epidermal growth factor receptor (EGFR) [3]. The results of the mutation testing allow clinicians to select the most appropriate first-line treatment for these patients, such as EGFR tyrosine kinase inhibitors (EGFR-TKIs) which works by preventing cancer cells with the EGFR mutation from growing and multiplying [4]. The first-generation EGFR-TKIs, gefitinib and erlotinib, were listed on the Pharmaceutical Benefits Scheme (PBS, the national formulary for publicly subsidized medicines) as first-line treatment for advanced NSCLC in January 2014 and have been the standard of care since.

Unlike the reversible first-generation EGFR-TKI, osimertinib is an irreversible third-generation EGFR-TKI, which selectively targets both EGFR-TKI–sensitizing and EGFR T790M resistance mutations. Osimertinib is currently listed on the PBS for patients with advanced NSCLC who have progressed on or after prior EGFR-TKI therapy and whose tumors have tested positive for a T790M mutation (i.e. second-line treatment). T790M mutation is a common mutation, which develops following treatment resistance to first-line EGFR-TKI therapy [5].

In a recently completed Phase III trial (FLAURA) in the first-line setting, osimertinib was shown to significantly improve progression-free survival (PFS) and overall survival (OS) compared with reversible first-generation EGFR-TKIs in patients with EGFR mutation-positive advanced NSCLC [6,7]. Osimertinib was considered by the Pharmaceutical Benefits Advisory Committee (PBAC) as a first-line treatment at its July 2019 meeting; however, was not recommended for

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reimbursement due to immature OS data and lack of cost-effectiveness [8]. The economic model submitted for consideration was not published and was based on immature OS results from the interim analysis [6].

This study aims to assess the cost-effectiveness of osimertinib versus standard EGFR-TKIs, gefitinib or erlotinib, as first-line treatment for patients with EGFR mutation-positive advanced NSCLC in Australia from a healthcare system perspective. This is the first published economic evaluation conducted in the Australian setting utilizing the most recent OS data that was published in January 2020 [7].

2. Methods

2.1. Choice of model

Partitioned survival and Markov models are commonly used in disease areas which can be represented by mutually exclusive health states such as cancer [9]. Partitioned survival model (PSM) is similar to Markov model in that it follows a cohort moving through each health state over time. However, the key difference between the two models is the variable used to determine how quickly the movement occurs between each health state. PSM uses a set of non-mutually exclusive survival curves, while Markov relies on transition probabilities. Both modeling techniques have been extensively used to inform policy decision-making [10].

The main advantage of the PSM approach is the ease in constructing the model using summary data from the published Kaplan-Meier charts [10]. By using the survival data from the graph, the probability of death during the trial period could be accurately replicated. A fundamental limitation of this approach is the risk that the extrapolated PFS curve may cross and lie above the extrapolated OS curve due to the absence of a structural relationship [10]. Therefore, the PFS and OS curves of the intervention and comparator should be plotted on the same graph for visual inspection.

As the Kaplan-Meier charts with summary data of PFS and OS for FLAURA were published, PSM was utilized in this study.

2.2. Model structure

The PSM consisted of three mutually exclusive health states (progression-free [PF], progressive disease [PD] and death) and was developed using TreeAge Pro Healthcare (Version 2020 R1.2, TreeAge Software, Williamstown, MA, USA). The model structure was aligned with the outcomes of PFS and OS reported in FLAURA and reflected the underlying progression of the disease (Supplementary Figure 1). In the model, all patients with EGFR mutation-positive advanced NSCLC initiated in the PF state, receiving treatment with either osimertinib or standard EGFR-TKIs (gefitinib or erlotinib). In each cycle, patients may stay in the PF state or move to PD state or death state. No patients were allowed to return to the PF state from PD or death, nor from death to PF state.

The model adopted an Australian healthcare system perspective, which dictates that only direct healthcare costs should be included. A time horizon of 5 years was chosen for the base-case analysis, consistent with the time horizon for the other first-line treatment submissions previously considered and accepted for this disease [11–13]. A monthly cycle length (i.e. 30 days) was selected to align with the pack sizes of all treatments and reflects the rate of disease progression. As per local guidelines, a discount rate of 5% annually was included for future costs and benefits [14]. Half-cycle correction was not required for PSM as the model maps state membership directly to the survival functions on a continuous basis.

2.3. Model inputs

2.3.1. Clinical data

In FLAURA, a total of 556 eligible patients were randomly allocated to either osimertinib or gefitinib/erlotinib in a 1:1 ratio (279 versus 277 [66% gefitinib/34% erlotinib]) [6]. The primary outcome was PFS, while OS was a key secondary outcome. The clinical data input for the model was based on the PFS and OS data from FLAURA. The FLAURA trial was previously considered to be applicable to the Australian population [8]. In January 2020, the results of the final analysis of OS were published, which addressed the issue of immature OS data from the interim analysis [7]. In the final analysis, the median duration of follow-up was 35.8 months in the osimertinib arm and 27 months in the standard EGFR-TKI arm [7]. The median duration of follow-up in FLAURA was shorter than the model's base-case time horizon; thus, extrapolation of the survival data was necessary. This was achieved by fitting a parametric model to the reconstructed Kaplan-Meier survival data.

Firstly, the probability of survival at each time point for PFS and OS curves was extracted from the published Kaplan–Meier charts using a graph digitizer software (WebPlotDigitizer version 4.2[1]), as the individual patient data (IPD) were not publicly available due to confidentiality. Subsequently, the IPD were reconstructed from the extracted data of the published Kaplan-Meier charts using the Hoyle and Henley methodology since both the survival probabilities and the number of patients at risk were available [15]. This method assumed that censoring within each time interval is constant.

With the reconstructed IPD, log-cumulative hazard plots were computed in R software to assess the proportional hazard (PH) assumption (i.e. parallel lines for intervention and comparator). The computed log-cumulative hazard plots showed that the PH assumption for OS was violated; therefore, the survival curves for osimertinib and standard EGFR-TKI were modeled independently for PFS and OS (Supplementary Figure 2–3).

Next, the survival curves were fitted to the reconstructed data using the 'flexsurv' package in R by the method of maximum likelihood [16]. The fitted parametric distributions include exponential, Weibull, Gompertz, generalized gamma, log-normal, and log-logistic (Supplementary Figures 4–7). Finally, the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) goodness-of-fit statistics for each parametric distribution obtained from R, in addition to visual inspection and external data, were used to compare and select the parametric distribution which has the best fit (Supplementary Tables 1–2).

Visual inspection and AIC/BIC values for PFS showed that Weibull, log-logistic, and generalized gamma distributions were the optimal fit in both arms. Although log-normal distribution had the lowest AIC/BIC for osimertinib PFS, this distribution was excluded as fitting different types of distribution to different treatment arms require greater justification [20]. For OS, Weibull and log-logistic distributions were the optimal fit in both arms.

While the above approaches ensure the parametric distribution chosen for the model had the best fit to the observed data (i.e. internal validity), they do not indicate how suitable it is in the extrapolation period. In order to reduce the uncertainty, published literature reporting long-term survival data from first-line standard EGFR-TKI trials and real-world data were used to validate the selected distribution. This comparison should only be indicative due to heterogeneity across all sources. This could only be performed on the comparator arm since osimertinib is a new intervention for this indication.

For PFS, the data from Ding et al. 2017 were considered the most relevant since it was conducted in the Australian setting [21] (Supplementary Table 3). At 5 years, the proportion of PF patients was 0%, which supported the use of Weibull distribution in the base-case. Further, the proportion of PF patients at 1-year and 2-year for Weibull distribution was comparable to the trial data. Sensitivity analysis using generalized-gamma distribution was conducted, while log-logistic distribution was excluded due to its overestimation compared with Australian external data at 5 years and trial data at 2 years.

Given that the OS data from the final analysis of FLAURA were relatively complete (i.e. up to around 4 years), prediction using parametric distribution was only required for a small portion in the base-case. Further, external data were less informative as the treatment paradigm in second-line has changed in recent years due to the availability of osimertinib as second-line treatment for patients with T790M mutation who progressed on first-line EGFR-TKI. For consistency, Weibull distribution was chosen for OS in the base-case while log-logistic distribution was tested in the sensitivity analysis.

The proportion of patients in the PF and PD states by treatment groups were informed by Kaplan-Meier trial-based data for PFS and OS up to 18 months and 45 months and then were sourced from extrapolated data up to 60 months (Supplementary Figures 8–9). Trial-based data were utilized to the time points where the number of remaining patients at risk became too small for reliable estimation. There were less than 50 patients beyond 18 months for PFS or 45 months for OS data.

The extrapolated OS curves crossed at a later timepoint beyond the base-case time horizon of 60 months. The curves crossing could probably be attributed to the effect of subsequent therapies on OS as patients in the standard EGFR-TKI arm could initiate second-line osimertinib after progression and confirmation of T790M-positive mutation, consistent with current clinical practice [22]. Nevertheless, multivariate sensitivity analyses were conducted for time horizon of 7.5 and 10 years, by aligning the OS curves to follow either the osimertinib arm or standard EGFR-TKI arm after the point of convergence.

The OS and PFS curves, including extrapolated data, were plotted on the same graph for each treatment arm to assess whether the PFS curve cross and lie above the OS curve; which showed that this did not occur for the chosen parametric distributions (Supplementary Figures 10–11).

2.3.2. Costs

The direct medical costs included in this study were the cost of medicines, medical services, adverse events-related, subsequent therapies (post-progression) and terminal care (Table 1). Subsequent therapies cost included drug acquisition, administration, and T790M mutation testing (Supplementary Table 4). Historical costs were adjusted for inflation to estimate current prices (2020) using the Australian Institute of Health and Welfare price index [23].

In FLAURA, patients could continue treatment beyond disease progression if there was perceived clinical benefit. However, the current PBS continuation restriction criteria for erlotinib and gefitinib state that 'Patient must not have progressive disease', which preclude treatment beyond disease progression [24]. Therefore, the cost of medicines and medical services were applied up to disease progression in the model to align with the Australian setting.

The cost of first-line osimertinib in the model was based on the published price of osimertinib in the second-line setting (proxy cost). In the second-line setting, osimertinib is subject to special pricing arrangements (SPA) with a published and an effective price. The difference between the two prices is managed through a rebate arrangement [24]. As the effective price is confidential, the published price was used in the base-case with assumed effective prices explored in the sensitivity analysis.

For the comparator, both erlotinib and gefitinib are listed on the PBS. As erlotinib has a marginally lower price compared with gefitinib (A$1,151.77 versus A$1,211.45 per pack of 30 tablets), erlotinib price was used to represent standard EGFR-TKIs [24].

Of the patients who progressed and received subsequent therapies in the osimertinib arm, it was assumed that all patients received platinum-based chemotherapy. Of the patients who progressed and received subsequent therapies in the standard EGFR-TKI arm, it was assumed that 50.9% received platinum-based chemotherapy and 49.1% received second-line osimertinib based on the proportions observed in FLAURA [7].

T790M mutation testing cost was only applied to patients who progressed and received subsequent therapies in the standard EGFR-TKI arm. Patients treated with first-line osimertinib are unlikely to receive treatment with osimertinib again in subsequent lines which negates the need for a T790 mutation testing. Further, there is no evidence to support the repeated use of osimertinib in both first- and second-line settings.

2.3.3. Utilities

In FLAURA, quality of life outcome was measured using the non-preference-based EORTC QLQ-LC13 and QLQ-C30 questionnaires [25]. The utility values or health preference scores were

Table 1. Costs and utilities input for the model.

Costs Resource item	Unit	Unit cost	Osimertinib	Standard EGFR-TKI	Distribution	Source
Medicines						
Osimertinib (Proxy Item 11622Q)	80 mg tablet, 30's	A$7,962.12	Per cycle until progression	-	Gamma	[24]
Erlotinib (Item 10014C & 11259N)	250 mg tablet, 30's	A$1,151.77	-	Per cycle until progression	Gamma	[24]
Medical services						
Consultation specialist (Item 105)	Per visit	A$44.35	Once per cycle until progression		Gamma	[17]
Full blood examination (Item 65070)	Per service	A$16.95	Once per cycle until progression		Gamma	[17]
Liver function test, urea and electrolytes (Item 66512)	Per service	A$17.70	Once per cycle until progression		Gamma	[17]
CT scan[a] (Item 56807)	Per service	A$560.00	Once every three cycles until progression		Gamma	[17]
Adverse events – Grade ≥3 adverse events (>2% difference)						
Rashes and acnes[b] (Weighted average of DRG J67A & J67B)	Weighted average cost	A$2,847	One-off cost at the initial cycle 1.1% (3/279)	One-off cost at the initial cycle 7.2% (20/277)	Gamma	[18]
Subsequent therapies cost						
Post-progression therapies	Weighted average cost	Osimertinib: A$1,265.96 EGFR-TKI: A$22,895.70	One-off cost from PF to PD		Gamma	Supplementary Table 4
Terminal care cost						
End of life and palliation before death	Average cost	A$49,166	One-off cost from PD to dead		Gamma	[19]
Utilities[c]			Mean (SD)			
PF			0.77 (0.02)		Beta	[26]
PD			0.64 (0.03)		Beta	[26]
Death			0.00		-	-

EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; PD, progressive disease; PF, progression-free; TKI, tyrosine kinase inhibitor
a Applied in the model as A$560/3 per month cycle
b Applied in the model by multiplying the average cost with the probability of event occurring
c Adjusted to per month cycle in the model

not reported; therefore, the utility values for the model were sourced from published literature. Labbe et al. (2017) assessed the quality of life of patients with metastatic lung cancer, including EGFR-mutation positive, using the EQ-5D-3L questionnaire [26]. The utility values applied in the base-case were based on the UK algorithm, while the Canadian algorithm was tested in the sensitivity analysis (Table 1). Similar to costs, health utilities were allocated based on disease progression status rather than treatment status. In the model, the utility values applied were assumed to be equal in both arms [25].

The disutilities attributed to adverse events were not incorporated in the base-case. This was a conservative assumption as osimertinib was shown to have a similar safety profile with a lower incidence of Grade ≥3 adverse events compared with standard EGFR-TKIs. Nonetheless, the impact of incorporating AE-related disutilities was explored in the sensitivity analysis.

2.4. Cost-effectiveness analysis

The cost-effectiveness of osimertinib was expressed as incremental cost-effectiveness ratio (ICER), in terms of cost per quality-adjusted life-year (QALY) gained and cost per life-year (LY) gained. The ICER was then compared with a willingness-to-pay threshold to determine if the intervention was cost-effective. In Australia, there is not an explicit threshold; however, the often-cited threshold of A$50,000/QALY was adopted in this study [27].

2.5. Sensitivity analyses

A series of univariate and multivariate deterministic sensitivity analyses (DSA) were conducted to test the robustness of the base-case ICER (Supplementary Table 5). Probabilistic sensitivity analysis (PSA) was performed by using beta distribution for utilities and gamma distribution for costs (second-order Monte Carlo simulations, 2,000 iterations).

Since the published price of second-line osimertinib was used as a proxy cost for first-line osimertinib in the model, scenario analyses were conducted to determine the percentage of rebate which would be needed to reduce the ICER to A$50,000/QALY. This was performed by varying the cost of osimertinib, which resulted in different subsequent therapies costs applied to the standard EGFR-TKI arm (Supplementary Table 6).

3. Results

3.1. Base-case analysis

In the base-case analysis, the incremental cost was estimated to be A$118,502 with an incremental effectiveness of 0.274 QALYs and 0.313 LYs (Table 2). This corresponded to an ICER of A$432,197/QALY gained and A$378,157/LY gained. The results demonstrate that osimertinib was associated with higher cost and greater benefit compared with standard EGFR-TKIs. At a willingness-to-pay threshold of A$50,000/QALY, the use of osimertinib is not cost-effective.

Table 2. Base-case results.

	Osimertinib	Standard EGFR-TKI	Incremental
Costs	$192,377	$73,875	A$118,502
QALYs	2.062	1.788	0.274
		ICER (QALY)	A$432,197
LYs	2.896	2.583	0.313
		ICER (LY)	A$378,157

EGFR, epidermal growth factor receptor; ICER, incremental cost effectiveness ratio; LY, life year; QALY, quality-adjusted life year; TKI, tyrosine kinase inhibitor

3.2. Sensitivity analyses

3.2.1. Deterministic sensitivity analysis

A summary of the DSA results is presented in Supplementary Table 7. A Tornado diagram summarizing the results of one-way DSA is shown in Figure 1. Overall, the base-case ICER was most sensitive (>20% difference) to changes in the cost of first-line osimertinib, the time horizon, and the choice of OS data (interim analysis versus final analysis). The ICER was least sensitive to changes in the cost of subsequent therapies in the osimertinib arm and inclusion of disutilities (<1% difference).

3.2.2. Probabilistic sensitivity analysis

The PSA produced a mean ICER of A$430,042/QALY, similar to the base-case ICER of A$432,197/QALY. The cost-effectiveness plane illustrates that all 2,000 iterations were in the North-East quadrant, indicating that osimertinib was more costly and more effective than standard EGFR-TKIs (Figure 2). The probability of being cost-effective was 0% (all iterations were above A$50,000/QALY). The cost-effectiveness acceptability curve shows that osimertinib could become cost-effective if the willingness-to-pay threshold is greater than ~A$430,000/QALY (Figure 3).

3.2.3. Scenario analysis

At a willingness-to-pay threshold of A$50,000/QALY, the percentage of rebate which would be required for first-line osimertinib to be cost-effective ranges from 68.4% to 78.4% (depending on the percentage of rebate currently in place in the second-line setting) (Supplementary Table 8).

4. Discussion

At a willingness-to-pay threshold of A$50,000/QALY, the use of osimertinib as a first-line treatment in patients with EGFR mutation-positive advanced NSCLC is not cost-effective. The high ICER was attributed to the high incremental cost (A$118,502), which was primarily driven by the cost of medicines, with a relatively small gain in incremental benefit (0.274 QALYs and 0.313 LYs). The average cost of medicines per patient for first-line osimertinib was estimated to be A$153,241, compared with A$14,339 for standard EGFR-TKI. Due to the significant improvement in PFS, patients in the osimertinib arm spent a longer time in the PF state receiving treatment than patients in the standard EGFR-TKI arm. If the cost of first-line osimertinib was reduced by 50%, the ICER decreased by 63.4% to A$158,088/QALY.

The results from the sensitivity analyses are worth discussing. Using a longer time horizon of 7.5 and 10 years, the ICER

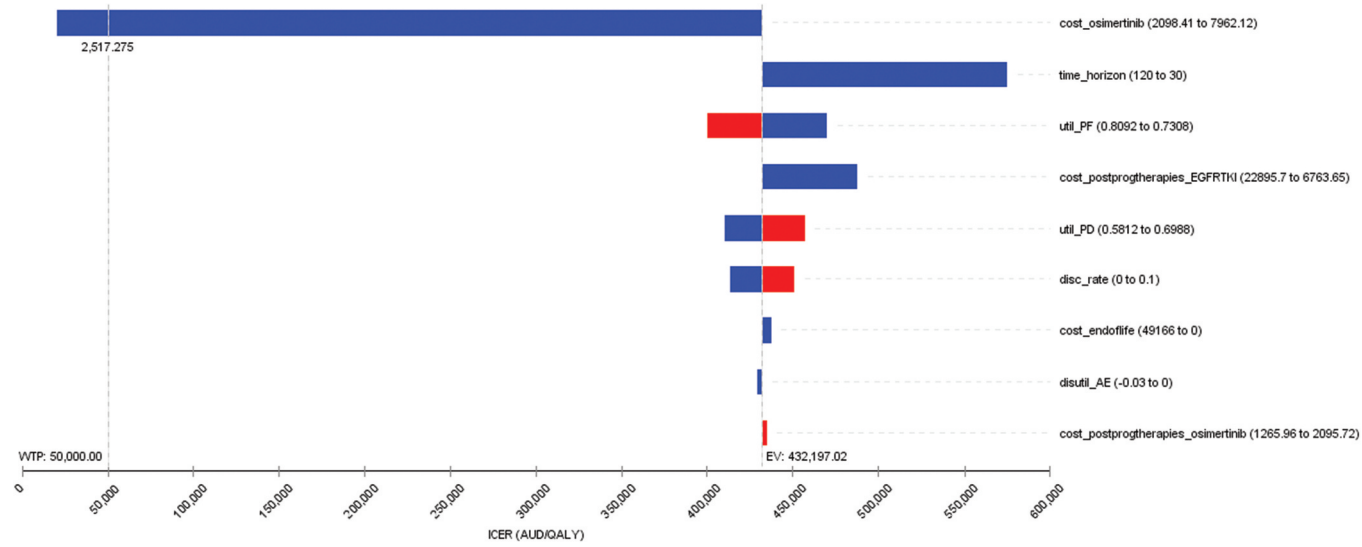

Figure 1. Tornado diagram of one-way deterministic sensitivity analysis.

Note: Blue bar section represents the parameter range from the low uncertainty value to the base case, while the red bar section represents the parameter range from the base case to the high uncertainty value

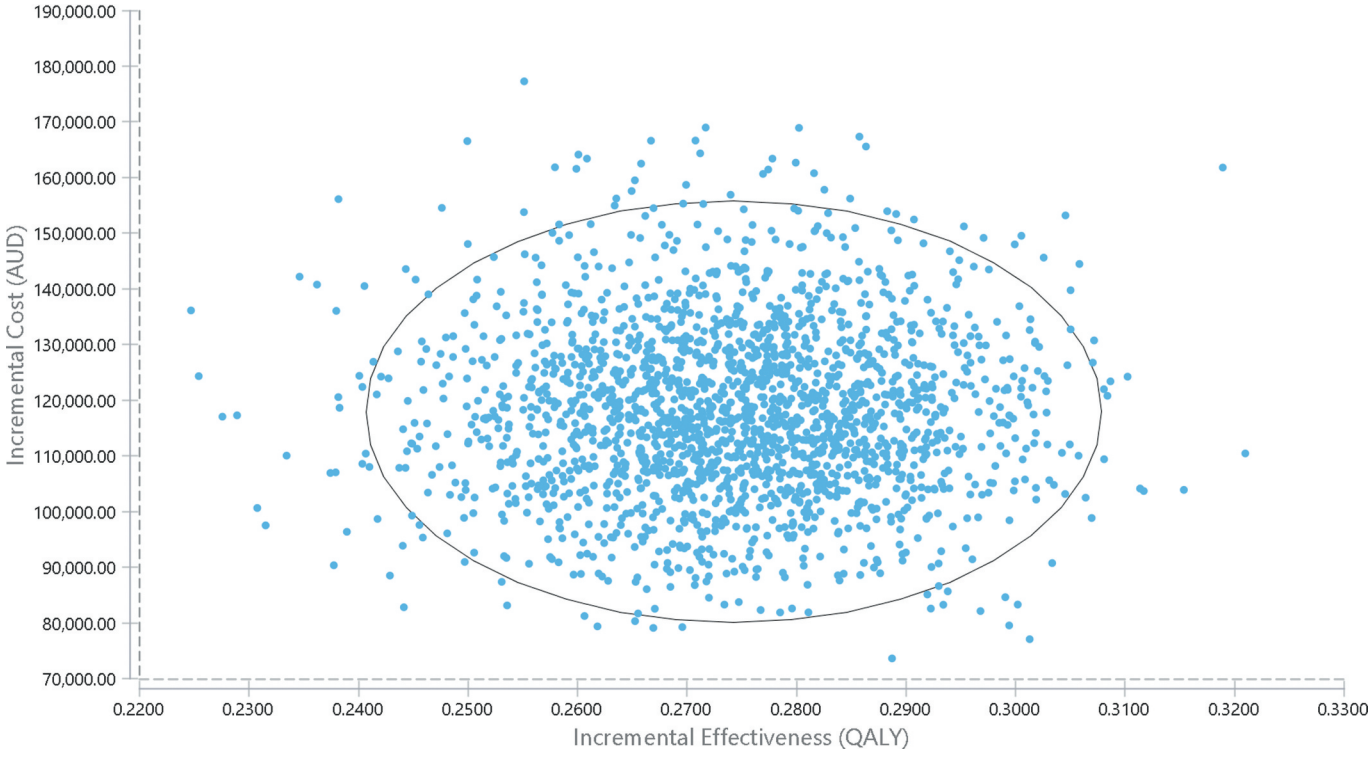

Figure 2. Cost-effectiveness plane from the probabilistic sensitivity analysis.

increased to A$438,598/QALY (+1.5%) and A$463,470/QALY (+7.2%), respectively. The increase in ICER by using a longer time horizon was expected given that the extrapolated OS curve of standard EGFR-TKI crossed and lay above the osimertinib curve at around 72-month time point, reducing the overall incremental benefit. This is supported by the computed log-cumulative hazard plot for OS, which demonstrated that the lines of both arms were converging. The convergence could be attributed to the better post-progression outcomes experienced by a proportion of patients in the standard EGFR-TKI arm who received second-line osimertinib treatment [28]. This proportion was assumed to be 33.5% based on FLAURA and is within the expected range of between 29.1% and 58.8% [8].

A series of multivariate sensitivity analyses were conducted using the OS data from the interim analysis over

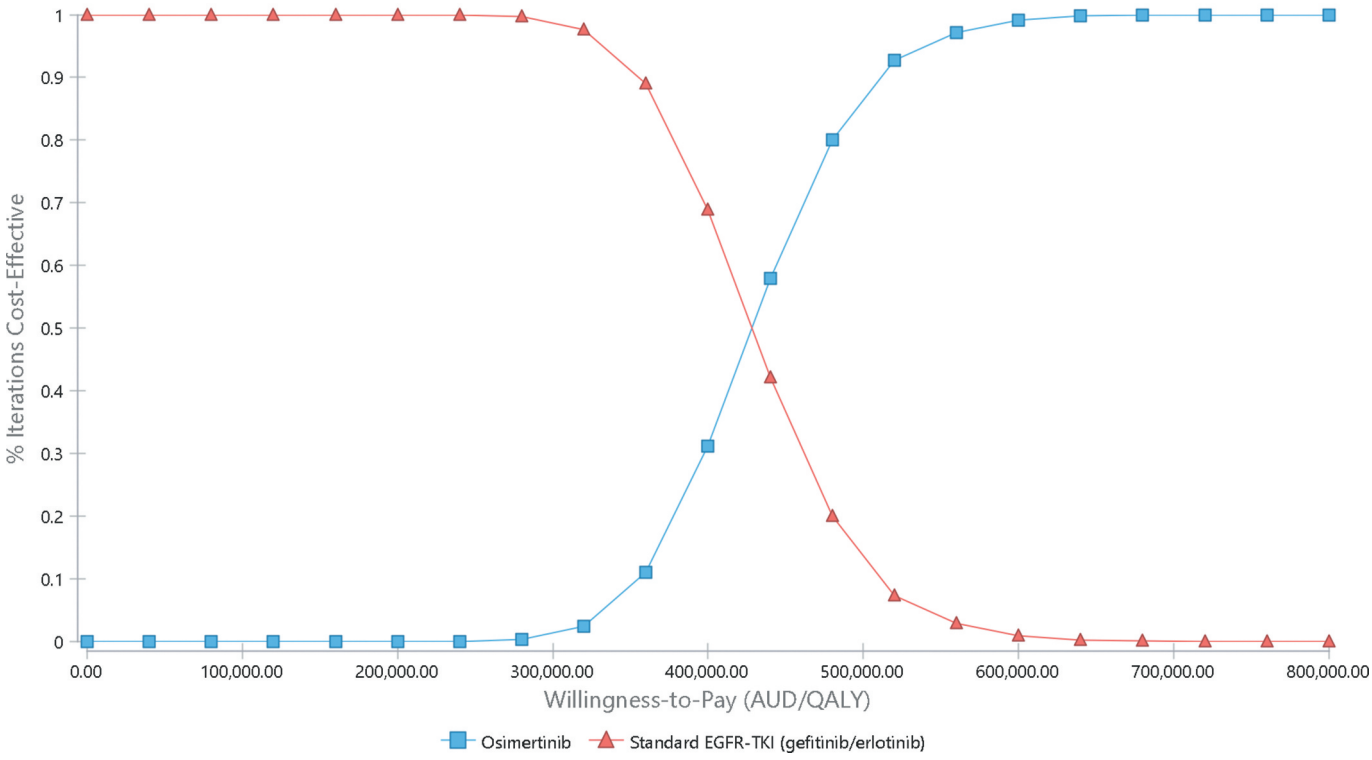

Figure 3. Cost-effectiveness acceptability curve.

a time horizon of 5 years, 7.5 year, and 10 years. In all scenarios, the ICER was reduced to A$347,556/QALY (−19.6%), A$275,291/QALY (−36.3%), and A$254,465/QALY (−41.1%) over the respective time horizons. For a 5-year time horizon, the incremental cost was estimated to be A $115,000, while the incremental benefit was 0.331 QALYs. This suggests that the incremental benefit was overestimated by using the OS data from the interim analysis, which consequently underestimated the true ICER [29]. The hazard ratio of OS reported in the interim analysis was 0.63 (95% CI, 0.45 to 0.88, p = 0.007), while in the final analysis, it was 0.80 (95.05% CI, 0.64 to 1.00, p = 0.046), demonstrating that the magnitude of survival benefit was lower than expected [6,7].

The first-generation EGFR-TKIs, gefitinib and erlotinib, were recommended for reimbursement at an ICER of A$15,000-A$45,000/QALY [11,12]. In the July 2019 submission, an SPA was proposed for osimertinib; however, the percentage of rebate offered was confidential [8]. Based on the scenario analyses conducted, this percentage should range from 68.4% to 78.4% for osimertinib to be considered cost-effective, depending on the percentage of rebate currently in place for osimertinib in the second-line setting.

To our knowledge, this is the first study conducted in the Australian setting utilizing the OS data from the final analysis. Accordingly, this study addresses one of the key concerns highlighted in the July 2019 meeting (i.e. immature OS data). Further, the PSM chosen for this study is the same type of model submitted for consideration [8].

The findings from our study were consistent with a recent cost-effectiveness study conducted by Aziz et al. (2020) which also uses the OS data from the final analysis [30]. The study assessed the use of osimertinib in the same population from a Singaporean healthcare system perspective. The authors reported a base-case ICER of S$418,839/QALY with an incremental cost of S$133,633 and an incremental benefit of 0.319 QALYs over a 10-year time horizon [30]. There are several other published studies, which assessed the cost-effectiveness of osimertinib for the same indication; however, these were conducted using the immature OS data from the interim analysis [31–36]. Of note, the study by Ezeife et al. (2018) was conducted from a Canadian healthcare system perspective, which has a similar healthcare system to Australia [31]. The authors reported an ICER of C$223,133/QALY over a 10-year time horizon [31], similar to the results from our multivariate sensitivity analyses. In our study, the cost of first-line osimertinib was shown to be the key driver of the model, consistent with the findings from most of the published studies.

There are several limitations to this study. First, the IPD were not publicly available; therefore, it had to be reconstructed and estimated. Using the reconstructed survival data, a range of parametric distributions were fitted to the curves to estimate long-term PFS and OS. Several steps were taken to ensure the choice of parametric distribution for extrapolating the data is plausible from internal and external validity perspectives. Second, the utility values had to be sourced from published literature since they were not reported in FLAURA. In addition, sensitivity analysis was performed using the utility values from an alternative source to examine the robustness of base-case results. Third, the comparator chosen for this study was first-generation

EGFR-TKIs, consistent with the comparator arm in FLAURA. While afatinib, a second-generation EGFR-TKI, could be considered a relevant comparator, these three EGFR-TKIs (i.e. afatinib, gefitinib, and erlotinib) were considered to be clinically non-inferior to each other [13]. As such, gefitinib and erlotinib can be deemed representative of the EGFR-TKIs currently used in practice. Lastly, costs and utilities were allocated based on disease progression status rather than treatment status. This assumption was made to reflect clinical practice in the Australian setting, which do not allow treatment beyond disease progression.

5. Conclusion

Despite the observed clinical benefit in FLAURA, the results of this study demonstrated that osimertinib is not cost-effective compared with first-generation EGFR-TKIs based on the current published price. To achieve acceptable cost-effectiveness, a reduction in the requested price of osimertinib would be necessary. Further, this study highlighted the importance of relying on mature OS data to reliably measure the comparative benefit of competing treatments and ultimately the ICER. The findings from this study will support the decision-making in funding the use of osimertinib for this indication in Australia. Consequently, patients affected by this debilitating disease could potentially have access to a more effective treatment option resulting in improved health outcomes.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants, or patents received or pending, or royalties.

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