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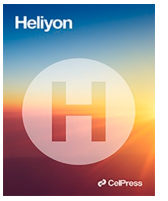

Understanding the promising role of antibody drug conjugates in breast and ovarian cancer

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ABSTRACT

A nascent category of anticancer therapeutic drugs called antibody-drug conjugates (ADCs) relate selectivity of aimed therapy using chemotherapeutic medicines with high cytotoxic power. Progressive linker technology led to the advancement of more efficacious and safer treatments. It offers neoteric as well as encouraging therapeutic strategies for treating cancer. ADCs selectively administer a medication by targeting antigens which are abundantly articulated on the membrane surface of tumor cells. Tumor-specific antigens are differently expressed in breast and ovarian cancers and can be utilized to direct ADCs. Compared to conventional chemotherapeutic drugs, this approach enables optimal tumor targeting while minimizing systemic damage. A cleavable linker improves the ADCs because it allows the toxic payload to be distributed to nearby cells that do not express the target protein, operating on assorted tumors with dissimilar cell aggregation. Presently fifteen ADCs are being studied in breast and ovarian carcinoma preclinically, and assortment of few have already undergone promising early-phase clinical trial testing. Furthermore, Phase I and II studies are investigating a wide variety of ADCs, and preliminary findings are encouraging. An expanding sum of ADCs will probably become feasible therapeutic choices as solo agents or in conjunction with chemotherapeutic agents. This review accentuates the most recent preclinical findings, pharmacodynamics, and upcoming applications of ADCs in breast and ovarian carcinoma.

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1. Introduction

Anywhere in the body, aberrant cells can develop uncontrollably and cause cancer. Malicious, tumor, or cancer cells are all expressions used to describe these aberrant cells. It is possible for these cells to invade healthy body tissues. Numerous tumors and the aberrant cells that lead to the emergence of cancer tissue can be distinguished further based on the name of the tissue that those anomalous cells originated from (for example, lung cancer, colorectal cancer, and breast cancer). The uncontrolled division of unrepaired or injured cells gives rise to cancer cells and these cells frequently move apart from this initial lump of cells, relocate, and reconcile in other organs where they can resume the unchecked growth sequence. Any aspect leading to an aberrant body cell's growth is to be feasibly carcinogenic. Although several cancers have undisclosed reasons, some may develop due to environmental or lifestyle sparks or many may develop owing to a person's genetic framework [1]. The varieties of cancer, where they are found, and how far along they are dictating the treatment options and methods. Some of the earliest and most desired treatment techniques include chemotherapy, radiotherapy, surgery, and radiation-based surgical instruments. The potential of innovative cancer therapy strategies is highlighted by the side effects of conventional cancer treatment [2]. The troublesome aftereffects of carcinoma management are only justifications for seeking out some better treatment choices [3–8]. In addition, ADCs have the capability to change the nature of cancer treatment, in contrast to conventional methods, which include the killing of healthy cells. Cytotoxic medication can be released selectively through ADCs, sparing the healthy cells. Advanced anti-tumor treatments known as antibody drug conjugates use antibodies connected to an anticancer drug (payload) with a linker. Major goal of ADCs is to precisely distribute antineoplastic agents to the cancer site with the least amount of systemic exposure possible. Antibody drug conjugates are like a miracle cure for cancer cells. ADCs is made up of three basic constituents: a cytotoxic drug, an antibody, and a linker protein that holds the other two components well together [9–11]. Typical cancer medicines have a relatively low therapeutic index and are not targeted, which has negative impacts on healthy cells like hair follicles, oral, digestive, and reproductive system cells. ADCs has less adverse effects than standard medicines including chemotherapy, radiation therapy, and surgery because of its target specificity and broad therapeutic index [12]. The evolution of ADCs generally encounters the following three provocations: Drug linker unreliability may cause the delivery of the drug into the bloodstream. Higher drug loading per antibody fragment is required since it will improve effectiveness, according to expectations [13]. ADCs can be made in a variety of forms, such as lysine-conjugated, cysteine-conjugated, or site-specific ADCs, depending on the conjugation chemistry [13–17]. FDA has approved five ADCs for curing HER2-positive metastatic breast cancer, hairy cell leukemia, lymphomas, and lymphomas. The hematologic malignancies were the ones that were most significantly impacted. ADCs have been shown to have a therapeutic advantage in solid tumors. ADCs are a fast-developing medicinal area that is now the subject of numerous clinical investigations [18]. The aim of ADCs is circumventing chemoresistance at the same time minimizing systemic harm by using antibody-cancer antigen interactions to transport anti-neoplastic medicines straight away to tumor cells. As the science of targeted treatment advances, further research of target antigens will probably be a substantial improvement in the

Table 1
ADCs currently under clinical investigations.

DRUG	TARGET	PAYLOAD	MOA	PHASE	REFERENCES
CX-2009	CD166	DM4	Microtubule Inhibitor	I/II	[25]
SYD985	HER2	Duocarmycin	DNA Alkylating Agents	III	[26]
ARX-788	HER2	MMAF	Suppresses Cellular Proliferation	II	[27]
RC48	HER2	MMAE	Inhibits Tubulin Polymerization	II	[28]
ALT-P7	HER2	MMAE	Inhibits Tubulin Polymerization	I	[29]
MEN1309/OBT076	CD205	DM4	Microtubule Inhibitor	I	[30]
Fs-1502	HER2	MMAF	Microtubule Inhibitor	I	[29]
Sgn-liv1a	LIV-1	MMAE	Microtubule Inhibitor	I	[31]
DS-1062	TROP2	DXd	Topoisomerase Inhibitor	I	[32]
B003	HER2	DM1	Alters Microtubule Dynamics	I	[33]
Mirvetuximab soravtansine	Folate Receptor α	Soravtansine (Maytansinoid DM4)	Microtubule Inhibitor	III	[34]
STRO-002	Folate Receptor α	Proprietary 3-aminophenyl hemiasterlin agent: SC209	Proprietary Tubulin-targeting Payload	I	[35]
MORAb-202	Folate Receptor α	Eribulin mesylate	Microtubule Inhibitor	I	[36]
XMT-1536	NaPi2b	Proprietary auristatin derivative (auristatin FHPA)	Microtubule Inhibitor	I/II	[37]
Lifastuzumab vedotin (LIFA/ DNIB0600A)	NaPi2b	MMAE	Microtubule Inhibitor	II	[38]
Tisotumab vedotin (HuMax-TF-ADC,or TF-011-MMAE)	TF	MMAE	Microtubule Inhibitor	III	[39]
Anetumab Ravtansine (BAY 94–9343)	Mesothelin	Ravtansine/DM4	Microtubule Inhibitor	II	[40]
DMOT4039A (RG7600)	Mesothelin	MMAE	Microtubule Inhibitor	II	[41]
BMS-986148	Mesothelin	Duocarmycin Related	Alkylation of DNA	I/II	[42]
Sofituzumab vedotin (DMUC5754A)	MUC16	MMAE	Microtubule Inhibitor	I	[43]
Anti-MUC16 TDC (DMUC4064A)	MUC16	MMAE	Microtubule Inhibitor	I	[44]

management of chronic, platinum-resistant disease. The choice of linker strikes a delicate equilibrium between therapeutic value or toxicity and distribution, serving as a major predictor of biodistribution, therapeutic efficacy, and pharmacokinetics. The linker used determines the drug to antibody ratio (DAR), which is a critical element impacting therapeutic toxicity, with a higher DAR translating to higher toxicity. While a large DAR boosts the ADCs efficacy, its pharmacokinetics and dispersion may be negatively impacted [19–21]. The greater hydrophobicity brought on by a higher DAR has been partially blamed for this improved clearance. To get beyond this barrier and boost the DAR with bioavailability equivalent to that of an unchanged antibody, hydrophilic linker molecules have been produced [20]. ADCs with a high DAR also have greater plasma clearance and are more likely to aggregate, which reduces bioavailability. Improved biodistribution is predicted to result from ongoing attempts to perfect linker chemistry [22]. The target antigen and cells' cellular density determines how much number of ADCs effectively penetrates the cell and its metabolism [23]. Choosing patients who gets benefitted from ADCs therapy based on the expression of tumor-specific antigens is crucial to maximizing the therapeutic response [24]. This review recapitulates comprehensively the etiology of breast and ovarian cancer and the ADCs as treatment regimens for breast and ovarian cancer (see Table 1).

1.1. Pharmacological aspects of ADCs

The action mechanism depends on incorporation of cytotoxic payload after antibody attachment to the target of cell facade and the consequent linker breakage Convoluted mechanisms are involved in how ADCs exert their therapeutic effects (Fig. 1) [45]. The naked antibody, as well as the coupled antibody, are established in the circulation after delivery of an ADCs and may independently generate anticancer activity. The antigen-binding fragment (Fab) of monoclonal antibodies can influence antitumor activity after goal involvement prior to the cytotoxic payload is unconfined into the cancerous cells. Relevance for ADCs that are attacking oncogenic antigens, are reported as T-DM1 and T-DXd [46,47]. The Fc constituent of an ADCs is well acknowledged for countless monoclonal antibodies, it attracts immune effector cells and effect killing of neoplastic cells through ADCP, CDC, or ADCC, serving as an immunotherapeutic method [46–48]. Following target identification, the ADC-antigen composite enters the cell by antigen-dependent endocytosis of receptor-mediated endocytosis. As a result, the degree of target internalization and antigen-binding affinity may have an impact on the ADCs effectiveness [49]. The liberation of the liberated cytotoxic warhead keen on cytosol, which causes apoptosis and cell fatality, depends on the activities of the lysosomes and endosomes [50]. Finally, membrane-permeable payloads have the potential to cause cytotoxic action in the surrounding cells despite the target antigen's articulation. The "bystander effect" is essential to the effectiveness of ADCs and is dependent on the linker qualities revealed above [51].

2. Etiology of breast cancer

The aberrant cells that cause this type of cancer are the most prevalent because they can infect neighboring tissues and divide out of control. On a molecular level, it is a heterogeneous disease that involves the activation of the progesterone and estrogen, and the (HER2). First stage tumors are treatable, but advanced, metastatic breast cancer is inoperable with the treatments that are currently available. Surgery, radiation therapy, and systemic therapy techniques are used in the treatment [52]. Test results determine the

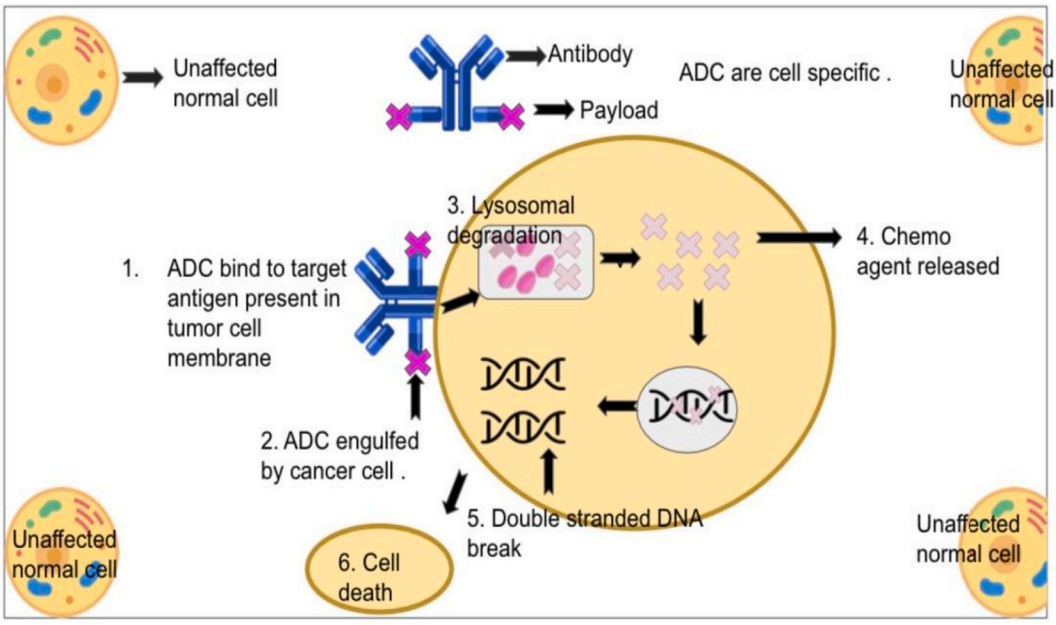

Fig. 1. Graphic representation of MOA of antibody drug conjugate inhibiting tumor cells.

hormone receptor status and hormone therapy medication treatment is ineffective for certain tumors. TNBC (Triple-Negative Breast Cancer) cells do not produce enough or any HER2 protein and lack estrogen and progesterone receptors. Compared to most other breast cancer types, triple-negative breast cancers develop and spread speedily. The breast tumors diverge into invasive and non-invasive breast cancers according to its site. Non-invasive breast cancer is a tumor not multiplied beyond the lobule where it originally appeared. Glandular carcinoma only affects the milk lobules; it does not spread to the adjoining tissues of the breast [53]. Whereas in situ ductal carcinoma only influences the breast vessel and is the utmost pervasive. In contrast, Invasive breast cancer occurs when aberrant cells segregate the lobules with the milk ducts in the breast tissue [54]. Carcinoma can proliferate from the milk ducts to various regions via the blood [55]. ILF proliferates in the milk glands, and frequently expands within the body [56]. Infiltrating ductal carcinoma commences in the milk lobules, proliferates, and intrudes the fatty tissues of the breast, and most likely spreads to other regions of the body [57,58]. A low-grade neoplasm is tubular carcinoma of the breast and is relatively scarce. It comprises well-differentiated tubular structures with open lumina. Breast cancer progresses once cancer cells plug lymphatic channels in the breast [59,60].

2.1. Human epidermal growth factor 2 (HER2) receptor

HER2 is a membrane tyrosinase kinase and oncoprotein located in the long arm of chromosome 17. Around 20–30 % of breast tumors overexpose the HER2. A more antagonistic ailment, a higher reappearance rate, and temporary endurance time are all linked to HER2 overexpression [61–64]. The appearance of hormone receptors and HER2 affect the treatment plan and prospects of survival and recovery from disease on tumor cells [65,66]. Amplification of the ERBB2 gene results in overexpression of HER2 in HER2-positive malignancies [67,68]. Amplification and overexpression are most common HER2 abnormalities in breast cancer. Advancements in targeting HER2 include further use of ADCs by altering linker, payload, or antibody scaffold to optimize the efficacy. It is a key target in the treatment of breast cancer because it is known to fuel tumor growth and progression. Roughly lobular carcinoma (15–20 %) are HER2-positive biologically, which is linked to a worse prospect of survival and recovery from disease and increased metastasis risk [69–71].

2.2. ADCs treatment regimes: FDA approved drugs and under CLINICAL trials

2.2.1. Sacituzumab govitecan

Sacituzumab govitecan (Trodelvy) targets trophoblastic cell surface antigen 2 (Trop-2). It comprises SN-38, an active product of metabolism of irinotecan, a humanized monoclonal antibody with a hydrolysable linker [72]. These medications are used for the TNBC (Triple-Negative Breast Cancer) adult patients with two preceding treatments for metastatic illness [73]. The FDA approved this drug after the trial's findings [74]. A DNA topoisomerase I inhibitor that is aimed at Trop-2 serves as the drug's mechanism of action [75]. Per antibody structure, 7–8 SN-38 molecules are typical. Topoisomerase I is inhibited by SN-38 which serves as a cytotoxic payload [76]. It cleaves and reanneal the DNA double helix The DNA strands break when this enzyme is blocked, which causes cell death [77]. A hydrolysable CL2A linker is used to attach SN-38 (7-ethyl-10-hydroxycamptothecin) to the humanized monoclonal immunoglobulin [78,79]. The payload SN-38 is liberated into the tumor site due to the cleavable characteristics of this linker [80]. This enables the delivery of the payload and, hence, the bystander effect, the anticipated decrease of both the targeted tumor and nearby cells [81]. Trop-2 is a target of sacituzumab govitecan and glycoprotein [82]. Trop-2-(trophoblastic cell surface antigen 2) has greater expression in a wide variety of malignancies, when compared to normal tissue. SN-38 linked to the antibody conjugate can circulate in an inactive form as it is shielded from deactivation via glucuronidation resulting in reduced toxicity than SN-38 with irinotecan therapy. Negative symptoms were reported like diarrhea and neutropenia, but they may be controlled with supportive care.

2.2.2. FAM-Trastuzumab deruxtecan-nxki [enhertu]

It was approved for curing metastatic HER2 positive milk duct tumor with past anti-her 2 based regimens. FDA granted expedited approval in the year 2019 [83]. DESTINY-Breast 01 study demonstrated T-remarkable DXd's anticancer effect in patients perceived a lot of previous therapy, this accelerated approval was granted [84,85]. A tetrapeptide linker links the antibody and the cytotoxic payload Deruxtecan [86,87] which is a topoisomerase inhibitor that promotes DNA destruction by establishing stable complex with DNA [88]. According to animal evidence, T-DXd has a diminutive $t_{1/2}$ which further decreases off-target toxicity [89]. Impressive response rates and encouraging early survival data are present. Numerous new clinical trials have been initiated because of its effectiveness in an array of HER2 delivering and mutant solid lumps, and it may find wider application. The MOA of Trastuzumab deruxtecan (T-DXd) entails internalization after binding to HER2 tumor cells and cleavage of intracellular linker by lysosomal enzymes. DXd enters the nucleus after being released, destroys the DNA, and induces apoptotic cell death. High DAR has been reported of Trastuzumab deruxtecan, higher than that of earlier ADCs [90]. The linker's stability in this context seems to allow for outstanding efficacy without experiencing any significant negative consequences [88]. Patients receiving T-DXd face a significant risk of interstitial lung disease (ILD)/pneumonitis, which requires constant monitoring and management in accordance with advised standards. For the best management, early identification, diagnosis, and action are crucial [91].

2.2.3. Trastuzumab emtansine

It is the foremost ADC to target HER2 receptor. It is a combination of trastuzumab with DM1 (Mertansine) which is acquired from maytansine and is the anti-neoplastic agent that was initially confined from Maytenus ovatus plant and depicted antineoplastic properties [92,93]. It was authorized for treatment-resistant metastatic breast cancer in 2013 established on the outcomes of the

EMILIA trial, a sizable phase III trial. The first clinical trial testing T-DM1 was announced in 2010, while preclinical findings pertaining to it were published in 2008. Five years after the initial publication, FDA approved T-DMI. This innovative drug's surprisingly quick development reflects the demand for and interest in targeted therapies that preserve healthy tissues while delivering increased efficacy over conventional cytotoxic [94]. It is a lysine conjugated ADC, in this exposed e-amino groups are used to bind with drug. Trastuzumab has 4 N-terminal groups and 88 lysines, which could be altered during the conjugation process [95,96]. Each trastuzumab molecule is adjoined to approximately 3.5 DM1 fragments, and medication is at least partially bound to 70 lysine sites [97]. A thioether linker, MCC is used to attach each DM1 molecule to trastuzumab [98–100]. T-DM1 is degraded in the lysosome and as a result DM1 is released [101,102]. After leaving the lysosome, some metabolites containing DM1 prevent the formation of microtubules, ultimately leading to cell death [103]. The adverse effects associated with TDM-1 were generally mild and patients were able to pursue treatment with sustained treatment effects [104].

2.2.4. Praluzatamab Ravtansine [CX-2009]

An anti-CD166 mAb is allied with a protease-cleavable linker to DM4, and a peptide cover constitutes Cx-2009. The peptide mask restricts target affining in healthy tissue and circulation [105]. DM4 is the payload that is derived from maytansine that has strong antimitotic properties since it may prevent microtubule assembly at nanomolar doses [106–108]. Safety profile was detected by administrating escalating doses every week.

2.2.5. SYD985

It comprises of the monoclonal HER2 targeting antibody trastuzumab that is conjugated to synthetic duocarmycin by means of cleavable valine-citrulline peptide [109,110]. Duocarmycin attaches to the DNA chain and alkylate it irreversibly [109]. These drugs are cytotoxic, and they change the nucleic acid structure killing cells in both dividing and non-dividing cells [111].

2.2.6. ARX-788

It comprises monoclonal HER2 targeting antibody that is conjugated to monomethyl auristatin F by means of the para-acetyl-phenylalanine which is an amino acid linker [111]. The conjugation is site specific which elevates the therapeutic window, payload stability and optimizes half-life [112]. ARX788 significantly reduced tumor development in xenograft models that had high and low HER2 expression. The positive preclinical results uplifted its research and progress for the therapy of patients. To boost linker stability, AS269 was designed with a diminutive, NH-PEG4 linker allied to the N-terminus of monomethyl auristatin F. By interfering with tubulin polymerization, the synthetic auristatin derivative MMAF suppresses cellular proliferation [113]. ARX788, a homogenous, incredibly stable, and powerful site-specific anti-HER2 ADC of the next generation has been created [114].

2.2.7. RC48 (RC48-ACD, HERTUZUMAB-VC-MMAE)

It is a humanized anti-HER2 antibody hertuzumab that is allied to MMAE by a protease-sensitive valine-citrulline dipeptide sequence, it provides adequate stability [115]. MMAE, an effective antimitotic agent that hinders cell distribution by jamming the polymerization of tubulin prompting cell death by G2/M phase arrest [116]. MMAE is a very effective anti-cancer microtubule-targeting agent that has been licensed for its utilization in three antibody drug conjugates and is being developed for use in several additional ADCs. It displayed encouraging activity with tolerable safety, suggesting prospective applications [117].

2.2.8. ALT-P7 (HM2/MMAE)

It comprises of trastuzumab HM2 coupled to monomethyl auristatin E in a definitive manner [118]. MMAE hinders cell division by jamming the polymerization of tubulin prompting cell death by G2/M phase arrest [119–121]. Toxicokinetic analysis suggested that there was no accumulation of ALT-P7 upon repeated injection.

2.2.9. MEN1309/OBT076

It comprises of a new anti-CD205 human antibody linked to the microtubule disruptor DM4 by a cleavable SPDB linker. DM4 is the payload that is derived from maytansine that has strong antimitotic properties since it may prevent microtubule assembly at nanomolar doses [106,107]. Mass spectrometric analysis showed that CD205 was significantly expressed in several solid tumors from various histotypes. The durable and soft to moderate CD205 demonstration in tumor cells was specifically and powerfully targeted by MEN1309 cytotoxic effects. In numerous TNBC, MEN1309/OBT076 demonstrated robust anticancer activity that led to long-lasting responses and full tumor regressions, independent of antigen expression levels [108]. OBT076 is an investigational ADC for treating tumors that express this target antigen, such as ovarian, bladder, lung, and gastric cancers and her2 negative breast cancer. Leading healthcare facilities around the United States will conduct the phase I trial. OBT076 is anticipated to be crucial in helping OBT fulfil its promise to support cancer patients, particularly those with high-risk breast cancer.

2.2.10. Trastuzumab monomethyl auristatin F (FS-1502)

It comprises the monoclonal antibody trastuzumab that is allied to dynamic microtubule inhibitor monomethyl auristatin, an auristatin analog. The trastuzumab scaffold attaches to HER2 on the surface of tumor cell. After incorporation, the MMAF hinders the cell division by jamming the polymerization of tubulin prompting cell death by G2/M phase arrest [122].

2.2.11. SGN–LIV1A

It is a new ADC that targets the zinc transporter LIV-1 (SLC39A6). SGN-LIV1A is a powerful microtubule-disrupting compound that

is associated to a humanized antibody through a linker that is proteolytically cleavable. Cancer cells that produce LIV-1 exhibit unique in vitro cytotoxic activity towards SGN-LIV1A. Combines the action of a strong anti-mitotic agent (MMAE) with the antibody's specificity to create a cytotoxic substance that is directed at LIV-1 [123]. When used to treat LIV-1-expressing cell lines and tumors, SGN-LIV1A exhibits potency and specificity in both the lab and in animals [124].

2.2.12. DS-1062

It consists of anti-TROP2 which is humanized monoclonal antibody that is linked with a four-peptide constructed linker to a payload which is an inhibitor of topoisomerase. DS-1062 attaches with the TROP2 receptor on tumor cell surface. After internalization, lysosomal enzymes degrade the linker and liberate the DXd payload. Elevated TROP2 expression is correlated with poor survival of patient, tumor cell growth and proliferation. TROP2 is a hopeful target for therapeutic development in various tumors [125–130].

2.2.13. Anti-HER2-DM1 ADC B003

B003 attaches superficially to HER2 of tumor cell when administered, the DM1 moiety is released after internalization, the dm1 moiety attaches to tubulin this revamp microtubule dynamics and cancer cell proliferation that overexpress HER2 and prevent cell division. Conjugation – undisclosed [33].

3. Etiology of ovarian cancer

The genesis of ovarian cancer is not proven, however numerous possibilities have been suggested. According to the "incessant ovulation hypothesis," which was first put forth by Fathalla, epithelial neoplasms are thought to develop because of repeated ovulation, which causes mild laceration to the ovarian epithelium and predisposes it to pernicious transformation. Periods of oligomenorrhea should be protective, according to this notion. Indeed, the vulnerability of ovarian cancer is relatively low in parous women and in women who have taken oral contraceptives. However, it has been demonstrated that, with some exceptions, the risk of ovarian cancer increases with various markers of ovulatory time, which can be roughly calculated as the sum of the times a woman was pregnant, breastfed, or used an oral contraceptive during her lifetime. According to the ovulation theory, women who ovulate rarely should have a lower chance of developing ovarian cancer; nevertheless, past investigations have found either no change in risk or an increase in risk among infertile women. The etiology of ovarian cancer pathogenesis has also been linked to a hypergonadotropic condition, or higher gonadotropin levels, according to animal experiments that have linked high gonadotropin production to ovarian cancers. In the scenario that Cramer put up, the ovary is predisposed to developing cancer through continuous gonadotropin stimulation. In one study, low serum gonadotropin levels were linked to an increased risk of ovarian cancer, although few studies have directly evaluated the relationship between gonadotropin levels and risk [131]. The surface epithelium, germ cells, and stroma are the three main cell types of the ovary from which cancers can develop. Epithelial ovarian cancer starts from the ovary and is pervasive type whereas germ cell ovarian cancer is atypical and emerges from the reproductive ovarian cells. On the other side, stromal cell ovarian cancer is very rare and emerges from connective tissues cells in contrast to small cell carcinoma which is a tremendously infrequent type. Ovarian malignancies are classified as epithelial in around 90 % of cases; they can also be classified as serous, endometrioid, or mucinous. Epithelial cancer cell types have been shown to exhibit some etiologic heterogeneity; nevertheless, the differences between the cell types are not well understood, and in epidemiologic investigations, epithelial malignancies are usually lumped together. Like borderline tumors, or malignancies with minimal potential for malignancy, they are typically associated with invasive illness and show unique clinical behavior but lack a defined origin. Each ovary normally ovulates every other month after menarche. Folic and luteal cysts during ovulation are common and do not seem to increase the risk of cancer. Although there is conflicting data, it has been proposed that cancer is caused by microscopic inclusion cysts. Ovarian function terminates and the organs shrivel at menopause. Age-specific markers of normal ovarian function are correlated with the age-specific risk of ovarian cancer, but the correlation is not as strong. Constipation, elevated pelvic pressure, or frequent urination are common nonspecific symptoms that women with ovarian cancer report with seeking diagnosis [132].

3.1. Treatment regimes

3.1.1. Mirvetuximab soravtansine (Mirv)

It is among the foremost ADC to acquire traction in management of platinum-resistant ovarian cancer [133]. It consists of a humanized FR-binding monoclonal antibody which is connected to DM4 through a cleavable disulfide linker [134]. Each antibody molecule is coupled to a median of three to four molecules of DM4, which, by inhibiting microtubule dynamics, functions as a powerful antimitotic agent, Functional stimulation by mirvetuximab soravtansine, high similarity obligatory to surface-expressed FR (Folate receptor) is followed by internalization and degradation [135]. Through endocytosis, the combined molecule is internalized, followed by transportation to the lysosomes, where ADCs is liberated. The lipophilic maytansinoid analogues have strong antimitotic outcomes, preventing tubulin polymerization and microtubule fabrication and causes cell death. Notably, the last two hydrophobic derivatives can kill nearby cells without regard to the presence of the antigen by diffusing from tumor cells that express the antigen [136]. *In vivo*, if FR expression on tumor cells is diverse or where tumor infringement of the ADCs fragment may be restricted, this effect, known as "bystander," death, is advantageous. As part of their anticancer activity, diffuse cytotoxic metabolites may also have an impact on neo vasculature or tumor microenvironment cells [137]. A phase 3 experiment called FORWARD I compares Mirv to conventional treatment for platinum-resistant ovarian cancer. Patients whose FR expression was somewhat high were included. Depending upon the proportion of cells at a 10× magnification, FR expression was assessed using a 10X scoring system. This was distinct from earlier

research that used a PS2+ scoring system and both a percentage of stained cells to assess staining intensity. The outcomes were shown at ESMO 2019 [34]. It is suggested that the novel antibody-drug combination mirvetuximab soravtansine may establish a new quality of therapy for affected people with folate receptor α-positive and platinum-impervious ovarian cancer [42].

3.1.2. STRO-002

ADC STRO-002 (Sutro Biopharma, Inc.) has started clinical studies and targets FR. An amalgamation of an anti-FR monoclonal antibody and SC209, a hemiasterlin derivative, has been created (STRO-002). In this conjugation, an enzymatically cleavable linker was used [138]. STRO-002 internalizes quickly into target positive cells, binds to FolRα with strong affinity, and cytotoxin 3-aminophenyl hemiasterlin is released, which targets tubulin (SC209). Comparing SC209 to other tubulin-targeting payloads, P-gp drug pumps have a lower potential for drug efflux from SC209. STRO-002 does not exhibit non-specific cytotoxicity towards FolR-negative cell lines, but when target positive cells were co-cultured including target negative cells, bystander destroying of the target negative cells was seen [139]. In both patient-derived xenograft (PDX) and FolR-expressing xenograft models, a single dosage of STRO-002 significantly inhibited tumor development. As FR receptors are overexpressed in animal models of ovarian and endometrial carcinomas, this formulation has shown effective targeting, suggesting that it may be a potential therapy choice for both neoplasms, displaying tumor growth suppression [140]. STRO-002 had a 23 % overall disease control rate, with 1/13 patients seeing a partial response and 2/13 experiencing stable illness (NCT03748186) [35]. STRO-002 was reasonably safe at dosages between 0 and 5 mg/kg, according to preliminary findings, without exceeding the maximum tolerated dose. The most frequent negative side effects included exhaustion, motion sickness, reduced appetite, and drowsiness, all of which were mild in intensity. The use of this formulation for the therapy of ovarian cancer is promising, as evidenced by the fact that nearly 50 % of the patients showed feedback to therapy in the form of stable disease or a partial response [141].

3.1.3. MORAb-202

That MORAb-202, are the first antibody conjugates targets solid tumors that are FR-positive. The experimental agent is made up of Eisai's in-house created anticancer drug eribulin (Halaven®) and the industry's internal developed anti-carcinomic drug farletuzumab, a humanized IgG1 monoclonal antibody that interacts to the FR. MORAb-202 is a glycosylated membrane protein that assaults the folate receptor (FR), also identified as FOLR1. Since it is mostly unavailable in normal tissues but overexposed in epithelial malignancies likewise in breast, lung and ovarian cancer, an appealing target for ADCs [142]. The microtubule dynamics inhibitors of the halichondrin class, which have a brand-new method of action, include the eribulin payload. It is a simplified and synthetically generated form of the natural substance halichondrin B, obtained from the marine sponge. A lysosomal protease-sensitive cleavable linker is present in MORAb-202 [36]. Eribulin operates by suppressing the growing phase of microtubule dynamics, which stops cell division [143].

3.1.4. XMT-1536

An exclusive humanized anti-NaPi2b antibody allied to Dolaflexin makes up XMT-1536. The Dolaflexin platform is used to combine a specific humanized antibody with AF–HPA payload molecules to create XMT–1536. Auristatin F (AF), an active, very low-permeable metabolite of the antimitotic chemical AF-HPA, is slowly absorbed intratumorally and causes regulated bystander killing [144]. The SLC34A2 gene encodes the transmembrane sodium phosphate transporter protein known as NaPi2b, articulated in both healthy and malignant tissue. NaPi2b participates in phosphate transport in healthy lung tissue, and mutations in SLC34A2 are correlated to testicular and pulmonary microlithiasis [145]. In accordance with the higher DAR, it demonstrated superior anticancer efficacy than lifastuzumab-vedotin in primary patient-derived xenograft models for ovarian cancer [146]. Dose escalation included patients with tumor types known to express NaPi2b.Participants with cisplatin unaffected ovarian tumor are being volunteered. In the UPLIFT portion of this trial, participants with high-grade serous ovarian cancer that is platinum-resistant are being recruited. The pharmacokinetics of the medication and ADCs activity will also be evaluated in addition to safety evaluations. For the UPLIFT cohort for a subset of locations, a QTc sub-study has been introduced [37].

3.1.5. Lifastuzumab vedotin (LIFA/DNIB0600A)

SLC34A2, is a tumor-linked antigen that is the target of the lifastuzumab vedotin antibody. SLC34A2 may diligently transport phosphate into cells by taking part in Na + cotransport as part of its biological activity. Numerous biological processes in cells are influenced by phosphate (Pi). Additionally, SLC34A2 has been linked to the formation of various malignancies since it has been found to be articulated in tumor of ovary and papillary thyroid carcinoma. Monomethyl auristatin E (MMAE, vedotin), the drug's toxic component, prevents cell mitosis by preventing tubulin polymerization. Due to its extreme toxicity, it is frequently conjugated with monoclonal antibodies to enable targeting and cannot be utilized as a therapeutic medication alone [147]. The MMAE-monoclonal antibody conjugate is stable in extracellular fluid, but when the complex attaches to certain tumor antigens, the protease hydrolyses the linker releasing MMAE. Then, MMAE attaches to microtubules and prevents the protein polymerization there, which prevents the partition of tumor cells. Patients with platinum-resistant ovarian cancer were exposed to LIFA (Genentech, Inc.) in a randomized phase II study. In this study, multicenter, open-label research, patients with PROC, primary peritoneal cancer, or fallopian tube cancer were assessed to PLD for safety and effectiveness [38].

3.1.6. TISOTUMAB VEDOTIN (HuMax-TF-ADC or TF-011-mmae)

It is used in the antibody-drug combination tisotumab vedotin, which targets the intracellular signaling system but has no effect on TF's procoagulant action. As internalization using this target antigen appears to be more effective than internalization using other

ADCs target antigens, TF is a suitable ADCs target. This is thought to be partly because tumor cells have a high TF turnover rate [148]. Humans and a number of other animals express the highly evolutionarily conserved glycoprotein known as tissue factor (TF). The tissue factor (F3) gene, coagulation factor III, which codes for human TF, is translated into TF (pre-mRNA). As a result of substituent splicing, three mRNA splice variants of TF are expressed: alternatively spliced (as)TF, full-length (fl)TF, and a fourth form known as TF-A. flTF isoform is formed with the translation of flTF and asTF. a procoagulant protein, and soluble as TF, with limited prothrombogenic prospective but significant proangiogenic, prosurvival activity, and cell proliferation-facilitating action. The TF-A mRNA splice modification does not translate into a protein due to the termination sequences in alternative exon 1A, which cause an early translation to stop. Human endothelial cells and several cancer cell lines have both shown TF-A mRNA expression. However, it is still unclear what TF-A does in the body [39]. FlTF and asTF have significant roles in cancer biology, including thrombogenicity, tumor development, angiogenesis, survival, invasion, metastasis, and signaling. They are expressed in various kinds of cancer cells and tumors. Additionally, both TF isoforms have a role in other pathologies such cardiovascular illnesses. To treat cancer patients, tisotumab vedotin, which targets certain TF isoforms, offers fresh possible therapeutic alternatives. Tisotumab vedotin exhibits its standard ADCs actions in addition to targeting and inhibiting TF. It attaches to TF, triggering internalization and lysosome trafficking inside the cell [149]. The intracellular release of MMAE caused by the subsequent enzymatic breakdown of tisotumab vedotin causes cell death by disrupting microtubules. Additionally, the production of MMAE in the tumor microenvironment results in the bystander death of cancer cells nearby. TV was experienced on patients with advanced or metastatic solid tumors (ovary, endometrial, cervix, esophagus, prostate) known to express tissue factor. Innova TV 208, a phase II study, evaluated TV in patients, in this experiment, a dose-dense schedule in addition to every three weeks of dosing has been tested [39].

3.1.7. ANETUMAB ravtansine (BAY 94–9343)

It targets mesothelin. The derivative of maytansine inhibitor DM4 is connected to G1 anti-mesothelin antibody by anetumab ravtansine, also recognized as BAY 94–9343, using a reducible linker of disulfide. Anetumab ravtansine is internalized and the disulfide linker is broken, liberating the DM4 payload after binding to mesothelin on tumor cells. After DM4 attaches to tubulin, microtubule polymerization is disrupted, which leads to cell cycle arrest and death. When DM4 is released into the tumor microenvironment, nearby dividing cells are accidently killed [150]. Anetumab ravtansine was found to be extremely cytotoxic to pancreatic, ovarian, mesothelin-expressing mesothelioma cell lines in preclinical research. Pre-clinical findings showed significant action both as a monotherapy and with the potential for additional anti-proliferative reactions when paired with PLD for cells expressing mesothelin [151,40].

3.1.8. DMOT4039A (RG7600)

It targets mesothelin which is a glycoprotein that coats various bodily cavities (such as the peritoneum or pleura) and aids in cell attachment. In 70–85 % of epithelial ovarian carcinomas, it is overexpressed. Individuals with untreatable, PROC participated in phase I trial. Phase II dosages were established weekly and every three weeks dosing were compared [152,41].

3.1.9. BMS-986148

The tumor associated antigen mesothelin is the target of and is bound to by the monoclonal antibody portion of the anti-mesothelin ADC BMS-986148. Through a yet unidentified mode of action, the cytotoxic drug kills or stops the cellular growth of tumor cells that express mesothelin after internalization. All mesotheliomas and several other malignancies overexpress mesothelin, whereas normal tissue hardly expresses it. It is being studied in patients with advanced solid malignancies during phase I/IIa. In this trial, BMS and nivolumab are being combined. The combo treatment showed a controllable safety profile and was tolerated. Serious TRAEs were recorded in 23 % of individuals receiving combination treatment (NCT02341625) and 18 % of those receiving monotherapy [153].

3.1.10. SOFITUZUMAB vedotin (DMUC5754A)

It targets MUC16, the expression of MUC16, formerly known as CA125, has been linked to the development of the illness. It has been widely utilized as a biomarker for ovarian cancer. The structure and roles of this protein in essential processes, such as epithelial protection and human carcinogenesis, have been uncovered through significant advances. Mucin expression in resting, normally polarized cells is tightly regulated, and it is only permitted on the exposed epithelia's apical membranes. Mucins are produced throughout the cell surface once loss of cell polarity occurs during carcinogenesis. They can interact with many growth factor receptors, which are generally only found on the basolateral surface, and modify their downstream signaling in different malignancies. MUC16 has been found to be abnormally overexpressed in several neoplastic cells. Ligands of MUC16 have become capable targets for therapeutic intervention, because of their aberrant overexpression and functional participation [43]. Sofituzumab vedotin coheres to MUC16 on cancer cells surface, internalizes the conjugate by endocytosis, and releases its cytotoxic payload MMAE following lysosomal breakdown. It also contains a human anti-nectin-4 antibody allied to the MMAE. A synthetic antineoplastic agent is MMAE. It cannot be used as a medicine by itself because of its toxicity; instead, it is typically combined with a mAb that guides it to the cancer cells. Microtubules are broken down by MMAE, which also causes tumor cells to die [42].

3.1.11. ANTI-MUC16 TDC (DMUC4064A)

It contains a monoclonal antibody against human mucin 16 coupled to MMAE, a potent microtubule disruptor with potential anticancer efficacy. After delivery, anti-MUC16/MMAE ADC DMUC4064A coheres to MUC16 displayed on the surface of tumor cells. Upon internalization, the MMAE moiety hinders cell division by jamming the polymerization of tubulin prompting cell death by G2/M phase arrest. This causes G2/M phase halt and programmed cell death. MUC16, a glycoprotein from the mucin family, is overexpressed in

several tumor cells and is essential for the growth of tumor cells [42,44].

3.1.12. Adcs under clinical research for the cure of breast and ovarian cancer

The table embraces all the ADCs discussed in this review [certified and under clinical progress]. The information includes regarding the target, payload, mechanism of action and their phase registered with clinicaltrial.gov.

4. Conclusion

ADCs represents an encouraging approach to treat neoplasm, by showing targeted delivery, this lowers the systemic toxicity. This approach utilizes a mAb allied to a lethal payload via chemical linker that is directed at a target antigen expressed on surface of neoplastic cell. ADCs cohere to receptors present on tumor cells and then the tumor cell indurates the ADCs and the cytotoxic freight is liberated into the cell. The conventional cancer medicines have relatively low therapeutic index and are not targeted, which cause serious adverse effects on healthy cells, ADCs have less adverse effects due to target specificity and their broad therapeutic index. The precise selection of antibody, payload, linker would be needed to prepare a successful ADC. There are many ADCs that are currently in clinical evaluation as explained above. Despite difficulties in ADCs design, the future of this nascent category appears to be very bright since more clinical trials and research on ADCs would open door to addressing problems with antibody, cytotoxic payload, linker stability and other issues.

5. Future perspectives

ADCs are an accessible therapeutic option for a variety of cancer types. The industry is increasingly moving away from traditional technologies and toward newer, more reliable techniques to develop such complicated products as more and more ADCs enter clinical trials. This covers methods for investigating brand-new tumor antigens, payloads, linkers, and cutting-edge conjugation technologies, all with the intention of expanding the therapeutic window of ADCs. Additionally, several conjugation platforms are currently in use to improve ADCs stability in circulation while retaining effective payload release. ADCs' intricacy presents difficult analytical problems, particularly when hydrophobic payloads are used. Modern analytical methods are necessary and are always developing to keep up with the explosive expansion of ADCs development. To accurately characterize product features and ensure production consistency both during product creation and throughout its lifecycle, the right analytical techniques must be applied. The combination of many ADCs in the clinical pipeline with other recognized treatment classes is being studied. The cumulative clinical data and the details provided here about the product's quality are influencing how ADCs will be developed in the future. To optimize ADCs design and manufacturing in the direction of next-generation innovative cancer medicines, Potential correlations amid good eminence attributes and the safety and effectiveness profile of individual products will undoubtedly be helpful as more data becomes publicly available.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Ritchu Babbar: Conceptualization. **Vanya:** Data curation. **Aarti Bassi:** Data curation. **Rashmi Arora:** Investigation. **Ankur Aggarwal:** Investigation. **Pranay Wal:** Data curation. **Sunil Kumar Dwivedi:** Data curation. **Salma Alolayan:** Data curation. **Monica Gulati:** Data curation. **Celia Vargas-De-La-Cruz:** Investigation, Data curation. **Tapan Behl:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Shreesh Ojha:** Writing – original draft, Data curation, Conceptualization.

Declaration of competing interest

None

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