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The emerging role of antibody-drug conjugates in urothelial carcinoma

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Abstract

Introduction: In December 2019, the US Food and Drug Administration granted accelerated approval to the novel nectin-4-targeting antibody-drug conjugate, enfortumab vedotin, for the treatment of platinum-refractory and immune checkpoint blockade-refractory locally advanced or metastatic urothelial carcinoma. Antibody-drug conjugates represent a new therapeutic modality in urothelial cancer; and beyond nectin-4, agents targeting Trop-2, HER2, and EpCAM are also in clinical development.

Areas covered: This review outlines the biologic rationale and the clinical development of novel antibody-drug conjugates for the treatment of urothelial cancer across the spectrum of disease from non-muscle-invasive bladder cancer through treatment-refractory metastatic disease.

Expert opinion: The high response rates observed with enfortumab vedotin – both as monotherapy and in combination with checkpoint blockade immunotherapy – suggest this and other antibody-drug conjugates may have efficacy similar to or even exceeding that of traditional cytotoxic chemotherapy. Ongoing clinical development of antibody-drug conjugates in urothelial cancer will address the optimal combination or sequencing strategy with anti-PD-1/L1 immunotherapy and platinum-based chemotherapy.

Keywords

Antibody-drug conjugate; Bladder cancer; Enfortumab vedotin; HER2; Immunotherapy; Nectin-4; Pembrolizumab; Sacituzumab govitecan; Urothelial

1. Introduction

While advanced urothelial cancer remains an area of high unmet need, the treatment landscape has been rapidly evolving over the past several years(1–8). In addition to the

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Declaration of interest

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regulatory approval of five different checkpoint inhibitors as well as FGFR targeted therapy, in December 2019 the United States Food and Drug Administration (FDA) granted accelerated approval the novel antibody-drug conjugate, enfortumab vedotin (EV) for the treatment of advanced urothelial carcinoma. While antibody-drug conjugates are regularly used in the treatment of hematologic malignancies(9–11) and breast cancer(12, 13), EV is the first antibody-drug conjugate to gain approval for the treatment of urothelial cancer. Structurally, EV is comprised of a monoclonal antibody directed against nectin-4 – an antigen overexpressed in the vast majority of urothelial cancers – coupled via a protease-cleavable linker to the cytotoxic microtubule-disrupting agent monomethyl auristatin E(14). While EV has now entered routine clinical care for patients with treatment-refractory advanced urothelial cancer, ongoing clinical development seeks to improve the efficacy of this agent via novel combinations and to move EV into earlier lines of therapy. This review will focus on the clinical development of EV as well as other novel antibody-drug conjugates for the treatment of urothelial cancer (Table 1).

2. Urothelial Carcinoma

Urothelial cancer is the 4th most common cancer among men in the United States and the 8th leading cause of cancer-associated deaths among American males(15). Most urothelial cancers begin in the bladder and are non-muscle invasive at diagnosis(16). Non-muscle invasive bladder cancer (NMIBC) is typically managed by TURBT and usually followed by intravesical therapy such as bacillus Calmette-Guérin (BCG)(17). Although the majority of these patients respond to available therapies, some high-risk patients will go on to develop locally-recurrent disease, at which point the standard of care has been radical cystectomy(18), a procedure associated with significant morbidity, quality of life and lifestyle changes, and a nontrivial mortality(19). While non-muscle invasive bladder cancer has historically been the purview of urologic surgical oncologists, checkpoint blockade immunotherapy has recently demonstrated encouraging activity(20), and in January, 2020, pembrolizumab was FDA-approved for high-risk BCG-unresponsive NMIBC. The role for medical oncologists in the management of NMIBC may very well continue to evolve in the coming years.

Muscle-invasive bladder cancer (MIBC) is associated with a relatively high rate of lymph node spread and distant metastasis (21–23). For this reason, a standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy(24). Despite these interventions, approximately half of patients will ultimately develop recurrent metastatic disease post-operatively(22, 23). Furthermore, up to half of all MIBC patients will forgo cystectomy in favor of trimodality therapy with maximal transurethral resection and chemoradiation(25), and still many others are not candidates for neoadjuvant cisplatin-based chemotherapy on the basis of renal insufficiency, sensorineural hearing loss, or peripheral neuropathy and have surgery alone(26). The limitations of perioperative systemic therapy highlight an area of significant unmet medical need and an avenue for future clinical drug development.

Prior to the advent of immune checkpoint blockade, the median overall survival with platinum-based chemotherapy alone was just 12–16 months(27, 28). While checkpoint

blockade immunotherapy offers the hope of durable long-term responses among a small subset of patients, response rates to anti-PD-1/L1 immunotherapy are modest (approximately 20%)(1–4), and responses to platinum-based chemotherapy last only 6–9 months, with few long-term survivors(27, 28). While the front-line therapeutic landscape may actively evolve in the coming months to years to embrace combination chemoimmunotherapy(29), the current standard of care for most patients remains platinum-based chemotherapy. At present, only cisplatin-ineligible patients whose tumors express high levels of PD-L1 or patients ineligible for even carboplatin are eligible for front-line checkpoint blockade monotherapy (pembrolizumab or atezolizumab) (30).

Following progression on platinum-based chemotherapy, five different PD-1/L1 antibodies are approved in the United States regardless of tumor PD-L1 expression(2, 4–7). More recently in April, 2019, the FDA granted accelerated approval to the small molecule FGFR inhibitor erdafitinib for patients whose tumors harbor oncogenic mutations or fusions in FGFR3 or FGFR2(8). Ongoing clinical development in mUC will focus on optimizing the sequencing and combination of these agents with standard platinum-based chemotherapy. Nevertheless, therapeutic options remain limited for patients who progress despite platinum-based chemotherapy and especially for patients who progress despite both chemotherapy and immunotherapy.

Antibody-drug conjugates are being increasingly utilized across multiple cancers, including leukemia, lymphoma, breast cancer, and now urothelial cancer. The antibody drug conjugate enfortumab vedotin (EV) was recently FDA approved, and several others targeting different antigens are in development. This review will highlight the available preclinical and clinical data on EV and other ADCs in clinical development and discuss possible opportunities for future development of ADCs in the treatment of urothelial cancer.

3. Antibody-Drug Conjugates

Antibody-drug conjugates are monoclonal antibodies directed against cancer cell surface proteins. These antibodies are linked to a potent cytotoxic agent. By delivering cytotoxic agents preferentially to the tumor, ADCs are capable of achieving high effective intratumoral drug concentration and efficient cancer cell killing with lower systemic distribution and off-target effects. There are three basic components to an ADC - the antibody, the linker, and the cytotoxic payload. The increased efficacy and tolerability of an ADC construct relative to a corresponding traditional cytotoxic agent depends upon both the specificity of the monoclonal antibody as well as the stability of the linker. The optimal target antigen should be highly expressed on tumor cells and minimally expressed elsewhere throughout the body, and binding of the target antigen should catalyze the endocytosis of the ADC(31). In contrast to typical targeted therapies which generally act to inhibit an oncogenic driver, ADCs may exert antitumoral effects by targeting even surface proteins which are not directly promoting cell growth and proliferation so long as they are highly and selectively expressed within the tumor microenvironment and are able to facilitate internalization(32).

In addition to antigen selection and antibody design, the nature of the chemical linker is key to both stability of the ADC construct as well as intratumoral release of the cytotoxic

payload. Linkers may be nominally classified as either cleavable or non-cleavable. Non-cleavable linkers are generally very stable in the circulation and maintain a physical connection between the warhead and an amino acid residue following intracellular lysosomal degradation of the ADC construct, both of which promote very precise delivery to antigen-expressing cells. On the other hand, cleavable linkers, while generally less stable in circulation, allow release the small molecule cytotoxic payload intracellularly where it may subsequently diffuse into the tumor microenvironment and exert anti-cancer effects upon neighboring cells irrespective of target antigen expression, a phenomenon known as the bystander effect(31). Ongoing work in the biomolecular engineering of ADCs is focusing on further optimizing linkers to maintain circulatory stability – thereby minimizing the toxicities of systemic distribution – while allowing for intratumoral cytotoxin release and bystander killing.

In addition to the technological advances which have allowed for the development of more effective ADC linkers, the nature of the cytotoxic agents has also evolved. Prior generations of ADCs utilizing conventional chemotherapeutic agents failed to generate sufficient efficacy at tolerable doses. However, recent ADC development has relied on more highly potent cytotoxins that can not be administered systemically(33). Since there are a limited number of target antigens on any given cancer cell and each ADC constitutes a finite number of cytotoxic molecules, the effective intratumoral drug concentrations are quite low(34). As such, the ideal cytotoxic payload should have very high potency – with IC50 in the nanomolar or even picomolar scale(35). In addition, the cytotoxic agent must be able to overcome multidrug resistance protein 1 (MDR1) - mediated efflux, an established mechanism of resistance to ADC therapy(36, 37).

As of publication, there are seven ADCs currently FDA-approved for the treatment of cancer. A drug called gemtuzumab ozogamicin was the first ADC to be approved by the US FDA on an accelerated basis in 2000. Gemtuzumab ozogamicin is comprised of a monoclonal antibody to CD33, which is highly-expressed on the majority of acute myelogenous leukemia (AML) cells, conjugated via an acid-cleavable hydrazone linker to a potent antitumor antibiotic calicheamicin, a drug which acts by inducing double-stranded DNA cleavage at specific motifs(38). While gemtuzumab ozogamicin was granted accelerated approval on the basis of response rates observed in a phase II trial in patients with CD33-positive relapsed AML(39), this agent was subsequently withdrawn from the market owing to increased deaths observed in a confirmatory phase III trial(40). Nevertheless, continued efforts to modify the dosing regimen and minimize toxicity resulted in more encouraging survival data(41, 42), and on this basis in 2017 the US FDA re-approved gemtuzumab ozogamicin for the treatment of AML.

ADCs are also beginning to take on a more prominent role in the management of lymphoid malignancies. Brentuximab vedotin is a CD30-specific ADC which is currently approved for the treatment of Hodgkin’s lymphoma, anaplastic large cell lymphoma, and peripheral T cell lymphoma. Structurally, brentuximab vedotin is an anti-CD30 monoclonal antibody conjugated to the anti-microtubule agent monomethyl auristatin E (MMAE) via a protease-cleavable linker(43). On the basis of high response rates in early phase clinical trials(44–46), brentuximab vedotin was approved by the US FDA in 2011 and continues to be investigated

for expanded use among other CD30-positive lymphomas. More recently, inotuzumab ozogamicin was approved by the FDA in 2017 for the treatment of relapsed or refractory B cell precursor acute lymphoblastic leukemia (B-ALL). Approval was based on a randomized phase III trial of inotuzumab ozogamicin versus standard intensive chemotherapy which found a clinically and statistically significant increase in complete response rate of 80.7% with inotuzumab ozogamicin versus just 29.4% with standard therapy(11). Finally, polatuzumab vedotin, a CD79b targeted ADC, was shown in a randomized phase II study to confer an increased response rate (40% versus 18%) when added to standard bendamustine and rituximab for the treatment of relapsed or refractory diffuse large B cell lymphoma, and was granted accelerated approval in 2019(47).

Until recently, the use of ADCs in solid tumors was limited to the treatment of HER2-positive breast cancer with the ADC trastuzumab emtansine, also known as T-DM1. Trastuzumab emtansine is comprised of monoclonal HER2 antibody trastuzumab and the anti-microtubule cytotoxic payload emtansine (also known as derivative of maytansine, or DM1) conjugated via a non-cleavable thioether linker(48). The efficacy of trastuzumab emtansine was demonstrated in a phase III trial of trastuzumab-refractory metastatic HER2-positive breast cancer, in which T-DM1 was associated with improved progression-free and overall survival(13). Subsequently, the KATHERINE study demonstrated that among HER2-positive breast cancer patients with residual disease at the time of mastectomy despite neoadjuvant therapy, adjuvant T-DM1 was associated with improved outcomes relative to adjuvant trastuzumab(49), and T-DM1 is now approved for HER2-positive breast cancer in both the metastatic and adjuvant settings. More recently, investigators have also reported promising results with the use of trastuzumab deruxtecan for the treatment of HER2-positive breast cancer. Trastuzumab deruxtecan – also known as DS-8201 – is a trastuzumab-based ADC, however unlike T-DM1, trastuzumab deruxtecan delivers a DNA topoisomerase I inhibitor cytotoxic warhead attached to a protease cleavable peptide linker(50). The safety and efficacy of trastuzumab deruxtecan were demonstrated in a multicohort phase I study of patients with advanced treatment-refractory HER2-positive breast and gastric cancer(51). Of note, responses were even observed in HER2-low tumors, which may suggest the occurrence of bystander killing, ADC uptake in low antigen-expressing tumor cells, or marked potency of the cytotoxin – all mechanisms which are distinct from that of unconjugated antibodies such as trastuzumab. In a subsequent pivotal single-arm phase II study of very heavily pretreated metastatic HER2-positive breast cancer patients, trastuzumab deruxtecan achieved a remarkable 61% objective response rate, with ongoing responses lasting 14.8 months which compared quite favorably to historical controls(12). On the basis of high response rates and durability of responses, in December, 2019, the FDA granted accelerated approval to trastuzumab deruxtecan for advanced HER2-positive breast cancer.

4. Enfortumab Vedotin for Advanced Urothelial Cancer

Nectins are a class of immunoglobulin-like proteins play a critical role in cellular adhesion and intracellular communication, and have recently been demonstrated to influence key oncogenic processes such as cellular growth, invasion, and survival(52–54). Nectin-4 is highly expressed across several carcinomas, including gastric(55), breast(56), lung(57), and

bladder(14, 58). Interestingly, nectin-4 serves as an entry receptor for the measles virus, which may hold future implications for oncolytic virus therapy(59).

EV is an ADC comprised of a fully humanized IgG1 antibody to nectin-4 which is conjugated via a protease-cleavable linker to the highly potent microtubule disrupter MMAE. EV-101 was a multicohort phase I dose escalation and expansion study of EV monotherapy for the treatment of refractory nectin-4-expressing solid tumors, including advanced urothelial cancer (60). EV was administered on days 1, 8, and 15 of each 28-day cycle until unacceptable toxicity or disease progression. The first report of suggested activity emerged at ASCO 2016, when initial data were presented on 44 evaluable patients with advanced urothelial cancer refractory to at least one prior line of systemic therapy (61). EV was generally well-tolerated, with only two dose-limiting toxicities observed. A total of 10 patients achieved an objective response (27.8%). Responses were observed across a range of dose levels from 0.5 mg/kg to 1.25 mg/kg, and 1.25 mg/kg was selected for the recommended dose for an expansion cohort of mUC patients refractory to both platinum-based chemotherapy and checkpoint blockade immunotherapy. Mature results of 112 patients with immunotherapy and platinum refractory mUC treated at the 1.25 mg/kg dose level indicate a 43% confirmed objective response rate, including five complete responses(60). The most common treatment-related adverse events were fatigue (53%) and alopecia (46%); 38% of patients developed a peripheral sensory neuropathy.

The efficacy of EV for treatment-refractory mUC was further demonstrated in a registrational phase II study. EV-201 is an ongoing international single-arm multi-cohort trial of EV monotherapy for patients with locally advanced or metastatic urothelial cancer who had progressed despite prior platinum-based chemotherapy and anti-PD1/L1 immune checkpoint blockade (Table 2) (62). Patients with treatment-refractory mUC were enrolled in two cohorts: cohort 1 included patients who had progressed despite both platinum-based chemotherapy as well as anti-PD-1 or anti-PD-L1 immune checkpoint blockade, and cohort 2 includes cisplatin-ineligible patients refractory to immunotherapy. While cohort 1 has already been reported, enrollment continues for cohort 2. EV was administered at a dose of 1.25 mg/kg on days 1, 8, and 15 of each 28-day cycle until unacceptable toxicity or disease progression. A total of 125 mUC patients across 51 centers in the United States and Japan were treated on cohort 1 and exhibited a number of poor prognostic features – most notably, a preponderance of visceral metastases (90%), including 42% with liver metastases and a median of 3 prior systemic therapies. Despite these adverse characteristics, 44% achieved a confirmed objective response by blinded independent central review, including 15 (12%) patients with a complete response. The median duration of response was 7.6 months. At a median follow-up of 10.2 months, the estimated progression-free survival was 5.8 months, which compares favorably to historical controls(27). As in the phase I experience, EV was generally well-tolerated. The most common treatment-related adverse events were fatigue (50%) and alopecia (49%). A sizable minority (40%) of patients developed peripheral sensory neuropathy, though only 2% of these were grade 3 or greater. The most common grade 3 or 4 adverse events were neutropenia (8%) and anemia (7%), and 4% of patients developed febrile neutropenia, though growth factor support was not routinely implemented. Hyperglycemia occurred in 11% of patients, including a single patient with grade 4 hyperglycemia, though this effect was reversible in the majority of cases.

While cross-study comparisons are fraught, it is worthwhile to consider the response rates to more traditional anti-microtubule chemotherapies in contemporary studies. In the randomized phase 3 studies of second-line pembrolizumab(4) or atezolizumab(63) in metastatic platinum-refractory mUC, second-line anti-microtubule chemotherapy with traditional paclitaxel, docetaxel or vinflunine achieved objective response rates of 11–13%, and complete responses were rare. In the post-platinum post-checkpoint inhibitor setting, data are more limited, though a recent randomized study reported a 11% objective response rate with docetaxel(64). On the basis of the high objective response rate in a patient population with severely limited therapeutic options, in December, 2019, the FDA granted accelerated approval to enfotumab vedotin for the treatment of advanced urothelial cancer refractory to platinum-based chemotherapy and to checkpoint blockade immunotherapy.

EV-301 is the ongoing international randomized phase III trial of EV for the treatment of advanced urothelial cancer designed to support full US FDA approval and global registration (Table 3)(65, 66). Approximately 550 patients with locally advanced or metastatic urothelial cancer who have previously been treated with both platinum-based chemotherapy as well as an immune checkpoint inhibitor will be randomized 1:1 to receive either EV monotherapy or investigator choice chemotherapy with either paclitaxel, docetaxel, or – in the European Union – vinflunine. Patients will be treated until unacceptable toxicity or disease progression, and the study is powered for a primary endpoint of overall survival.

In parallel to the development of EV for treatment-refractory mUC, investigators have also explored the use of EV in earlier lines of treatment. There is strong preclinical evidence to suggest that brentuximab vedotin (another MMAE ADC), unlike its corresponding unconjugated antibody, is capable of inducing an endoplasmic reticulum stress response and immunogenic cell death with activation of antigen presenting cells in vitro(67). Given the potential for the induction of immunogenic cell death and the established role for PD-1/L1 blockade in mUC, investigators have sought to evaluate the feasibility of combining EV with anti-PD1/L1 immunotherapy. EV-103 (NCT03288545) is a multicohort phase 1b dose escalation and expansion study of EV in combination with the PD-1 antibody pembrolizumab (68–70). Patients are required to have checkpoint blockade-naïve mUC and be either platinum refractory or ineligible. At the 2020 ASCO Genitourinary Cancers Symposium, updated preliminary data were presented on the combination of EV at the selected dose of 1.25 mg/kg plus pembrolizumab (200 mg) in the first-line setting for cisplatin-ineligible patients with mUC(71). The combination was generally well-tolerated, and the safety profile roughly mirrored that of EV monotherapy, with the most common treatment-related adverse events being fatigue (58%), alopecia (53%), and peripheral sensory neuropathy (53%). A total of four patients (9%) discontinued treatment owing to toxicity, two of whom developed grade ≥3 peripheral neuropathy. With regard to efficacy, 33 patients achieved a confirmed objective response for a response rate of 73.3%. Furthermore, 93% of patients achieved some degree of tumor shrinkage within the target lesions. This objective response rate, while based on a small phase II study, compares quite favorably to the 44% response rate observed with traditional chemoimmunotherapy with gemcitabine + platinum + atezolizumab in IMvigor130(41). Importantly, responses seem to be durable, with the median duration of response not yet reached at 10.4 months of follow-up among responders. Based on the efficacy observed in EV-103, investigators have recently initiated a

randomized phase III study (EV-302, NCT04223856) of EV and pembrolizumab with or without platinum-based chemotherapy for the first-line treatment of locally advanced or metastatic urothelial cancer.

5. Sacituzumab Govitecan: A Novel Trop-2 Targeting Antibody-Drug Conjugate

In addition to the clinical development of the nectin-4 targeting EV, investigators have also studied the Trop-2 targeting ADC sacituzumab govitecan in advanced urothelial cancer. Sacituzumab govitecan is an ADC comprised of a monoclonal antibody against Trop-2 conjugated via a pH-sensitive cleavable linker to SN-38, the active metabolite of irinotecan(72). Also known as trophoblast cell-surface antigen, Trop-2 is a transmembrane calcium signal transducing glycoprotein implicated in cell growth and migration and shown to be overexpressed in a wide variety of epithelial cancers including urothelial cancer(73–80). The DNA topoisomerase I inhibitor, irinotecan has been widely used for the treatment of various cancers for decades. While irinotecan has antineoplastic activity as is, it is also metabolized *in vivo* to the more potent SN-38 which demonstrates activity even at nanomolar concentrations(81).

Sacituzumab govitecan (SG) was first evaluated in a phase I dose escalation study in multiple solid tumors(82). The most common treatment-related adverse event was neutropenia, which necessitated dose reductions at the 12 mg/kg dosing level; 10 mg/kg was selected for further study. At the 2019 ASCO Genitourinary Cancers Symposium, updated data were presented from the phase I/II experience with sacituzumab govitecan in patients with platinum-refractory (or ineligible) mUC who had progressed despite at least one prior systemic therapy(83–85). Among the 45 patients treated on protocol, SG achieved a promising 31.1% objective response rate. TROPHY-U-01 is an ongoing multicohort single-arm phase II study of SG in mUC(86). Patients with mUC are enrolled in two cohorts: cohort 1 is comprised of patients with disease progression despite prior platinum-based chemotherapy and anti-PD-1/L1 immunotherapy. Cohort 2 is enrolling platinum-ineligible patients refractory to checkpoint blockade. At last update, 35 patients had been treated in cohort 1, and investigators reported an objective response rate of 29%, including 2 complete responses(86). The most significant toxicity was myelosuppression, with neutropenia occurring in 66% (26% with grade 4 neutropenia) and febrile neutropenia in 11%, though only nine of 35 patients received growth factor support. Other common treatment-related adverse events were alopecia (74%), and diarrhea (57%). Enrollment is ongoing with a planned accrual of 100 patients per cohort.

6. Targeting HER2 in Metastatic Urothelial Cancer

HER2 (human epidermal growth factor receptor 2) is a member of the Erbb family of receptor tyrosine kinases which have long been known to mediate cancer cell growth and invasion via constitutive activation of the mitogen-activated protein kinase signaling pathway. While HER2 has been successfully targeted in breast(87) and gastric cancer(88), there is no FDA-approved HER2 targeted therapy for urothelial cancer. However, genomic profiling (89–91) and immunohistochemistry(92) consistently show urothelial cancer to

exhibit high rates of HER2 amplification, mutation and overexpression. Specifically, HER2 gene amplification is identified in approximately 7% of 412 MIBC tumors in The Cancer Genome Atlas cohort (89, 90), and 7% of 387 mUC tumors in the MSK IMPACT cohort(93). However, the presence of gene amplification does not correlate perfectly with overexpression of the cell surface receptor; in fact genomic assays likely underestimate the degree of protein overexpression(94). Immunohistochemical assessment of a large clinical sequencing cohort across multiple tumor types actually found that bladder cancer exhibits the highest prevalence of HER2 overexpression (12%) relative to all other histologies, including breast and gastric cancer(92).

On the basis of the high frequency of HER2 overexpression, investigators have pursued HER2 as a therapeutic target in urothelial cancer. A single-arm phase II study investigated the combination of trastuzumab plus carboplatin and gemcitabine for the treatment of HER2-overexpressing mUC(95). While the combination achieved a 70% response rate and median progression-free survival of 9.3 months, the addition of trastuzumab was associated with three therapy-related deaths as well as two cases of grade 3 cardiotoxity. Subsequently, a randomized phase II study tested the hypothesis that the addition of trastuzumab to platinum-based chemotherapy in the first-line setting would confer a progression-free survival advantage among patients with HER2-overexpressing mUC(96). Among 563 screened patients, 75 (13%) were HER2 ≥2+ by immunohistochemistry (IHC) and HER2-amplified by fluorescence in situ hybridization (FISH) and were eligible for enrollment. Unfortunately, there was no difference in response rate, progression-free, or overall survival despite the addition of trastuzumab to gemcitabine and platinum, though interpretation is limited by the high prevalence of carboplatin-treated patients (48%) and small sample size. A more recent multicohort phase II study examined the efficacy of trastuzumab plus pertuzumab in the platinum-refractory setting(97). Patients with platinum-refractory mUC with HER2 amplification, overexpression, or mutation as defined by next-generation sequencing (10/12), and/or FISH (2/12), and/or IHC (2/12) were eligible. Among 12 evaluable patients, responses were observed in 25% (2 partial responses, 1 complete response); however, excluding the three patients enrolled via a somatic HER2 mutation, the response rate among patients with HER2 amplification or overexpression was 33% (3/9).

While the naked HER2 antibodies have not shown particularly strong efficacy in HER2+ mUC, the development of novel ADCs has reinvigorated the clinical development for HER2 targeted therapies in this disease. At the 2018 ASCO Annual Meeting, data were presented on a novel HER2-targeting ADC, RC48(98, 99). In a dose escalation and expansion study of RC48 across multiple HER2 overexpressing solid tumors, investigators reported an objective response rate of 33.3% among 24 evaluable patients, including a partial response in one of two HER2+ mUC patients(98). Concurrently, investigators reported on the results of a phase Ib study of RC48 for the treatment of HER2+ metastatic breast cancer, demonstrating a 37% objective response rate among 30 evaluable patients(99). The most common adverse events were transaminase elevation (50%), neutropenia (33%, including 10% grade ≥3 neutropenia), and peripheral neuropathy (23%). A dose of 2.0 mg/kg every 2 weeks was subsequently selected for a single-arm phase II trial in HER2+ urothelial cancer(100). Preliminary data demonstrate encouraging efficacy in HER2+ mUC with an objective response rate of 51% among 43 evaluable patients. Interestingly, subgroup analyses reveal

that the response rate did not differ considerably between IHC 2+ tumors which were FISH+ versus FISH-, suggesting efficacy at lower levels of HER2 expression than might be expected based upon prior clinical experience with trastuzumab in breast cancer(101). Phase II clinical development of RC48 for the treatment of mUC is ongoing.

While RC48 is the only HER2-targeted ADC with publicly available data in urothelial cancer, an ongoing multicohort phase II study is investigating the efficacy of trastuzumab deruxtecan (DS-8201)(12) in combination with the PD-1 antibody nivolumab among patients with HER2+ breast cancer as well as HER2+ platinum-refractory, checkpoint blockade-naïve mUC(102). Interestingly, treatment with another HER-2 directed ADC, trastuzumab emtansine, was shown in an orthotropic murine model to induce intratumoral T lymphocyte infiltration and render these normally immunoresistant tumors susceptible to checkpoint blockade immunotherapy(103). This trial is enrolling two separate cohorts of mUC based upon HER2 positivity: a cohort of the traditionally-defined HER2+ by IHC 2+ or 3+ as well as a smaller cohort of IHC 1+ patients to explore efficacy at lower HER2 expression levels. These novel antibody-drug conjugates – if shown to be consistently effective – have the potential to move urothelial cancer to the forefront of clinical drug development in HER2+ diseases.

7. Intravesical Therapy for Non-Muscle Invasive Disease

While the majority of novel therapeutics in urothelial cancer in recent years have been developed in the metastatic setting, systemic pembrolizumab has recently gained FDA approval for high-risk BCG-refractory NMIBC(20). While systemic ADCs have not been investigated for the treatment of NMIBC, intravesical therapy with oportuzumab monatox is currently in clinical development for NMIBC. Oportuzumab monatox is an ADC-like fusion protein immunotoxin comprised of a truncated, pro-inflammatory form of the pseudomonas aeruginosa exotoxin A conjugated to a humanized single chain variable fragment (scFv) against epithelial cell adhesion molecule (EpCAM)(104). EpCAM is a transmembrane glycoprotein which is highly expressed across a wide range of carcinomas, including squamous cell carcinoma of the head and neck and urothelial cancer(105). Unfortunately, these therapeutic agents are associated with the development of neutralizing antibodies in vivo, limiting their efficacy as systemic therapeutics, and thus investigators have relied on intratumoral modes of drug delivery(106).

A phase I dose escalation study was also carried out with intravesical oportuzumab monatox in NMIBC(107). A total of 64 patients with BCG-refractory (or BCG-ineligible) NMIBC grade 2 or 3 and stage Ta or T1 or patients with carcinoma in situ were enrolled. Treatment was well-tolerated, and the maximum tolerated dose was not reached. Encouragingly, 39% of patients achieved a complete response at twelve weeks by cystoscopy and cytology. To better characterize the efficacy of this agent, investigators carried out a two-cohort phase II study of oportuzumab monatox (OM) in BCG-refractory urothelial carcinoma in situ(108). Cohort 1 received an induction of 6 weekly doses intravesical OM, while cohort 2 received a twelve-dose induction; all patients were eligible for up to three maintenance cycles. Toxicities were generally mild and related to direct irritation of the bladder. Of 45 evaluable patients, 20 (44%) achieved a complete response, which is noteworthy given the lack of

effective cystectomy-sparing local therapies in the BCG-refractory setting and the potential for immune-mediated adverse events with systemic anti-PD-1 immunotherapy. Unfortunately, only 16% of responses were ongoing at last follow-up (18–25 months), with a median time to recurrence of 274 days and 408 days in cohorts 1 and 2, respectively. A phase I trial is underway investigating the safety of intravesical OM in combination with the systemic PD-L1 antibody durvalumab (NCT03258593).

8. Conclusion

Antibody-drug conjugates represent a class of emerging therapeutics which are beginning to demonstrate efficacy across a range of cancers, including leukemia, lymphoma, breast cancer, and urothelial carcinoma. EV, the nectin-4 targeted ADC recently garnered accelerated approval from the US FDA for the treatment of platinum-refractory and checkpoint blockade-refractory metastatic urothelial cancer on the basis of high response rates observed in a phase II trial. In parallel to the confirmatory randomized phase III study, EV is being combined with immunotherapy and with platinum-based chemotherapy. The combination of EV plus pembrolizumab has demonstrated a notable 73% objective response rate in the first-line metastatic setting among cisplatin-ineligible patients, and most of these responses appear durable. Ongoing and future clinical trials will determine how to best combine and sequence EV with checkpoint blockade immunotherapy and platinum-based chemotherapy.

Although EV is the only FDA-approved antibody-drug conjugate for urothelial cancer, promising data are emerging for other antibody-drug conjugates. Sacituzumab govitecan is a Trop-2 targeted antibody-drug conjugate which has demonstrated a 29% response rate among cisplatin-ineligible patients refractory to checkpoint blockade in a phase II trial. Additionally, urothelial cancer is associated with one of the highest rates of HER2 overexpression of any cancer. The HER2 targeted antibody-drug conjugate RC48 has demonstrated an impressive response rate in the metastatic setting, and data on trastuzumab deruxtecan – a HER2 targeting antibody-drug conjugate recently approved for metastatic HER2+ breast cancer – in combination with the PD-1 antibody nivolumab are eagerly anticipated.

9. Expert Opinion

Antibody-drug conjugates promise the ability to deliver high concentrations of potent cytotoxic agents to the tumor microenvironment while minimizing systemic distribution and associated toxicities. Over the past decade or so, improvements in biomolecular engineering have allowed the development of novel antibody-drug conjugates with improved antibody specificity, linker stability, and cytotoxic potency. These agents have begun to demonstrate clinically meaningful efficacy with relatively favorable toxicity profiles and have entered routine clinical care for patients with leukemia, lymphoma, breast cancer, and now urothelial carcinoma. EV has demonstrated clear efficacy in advanced urothelial cancer – both as a monotherapy in the platinum-refractory and checkpoint blockade refractory setting as well as in the frontline cisplatin ineligible setting in combination with pembrolizumab. While regulatory approval has only been granted for treatment refractory metastatic disease, the

combination of EV with pembrolizumab appears immensely promising and was granted FDA Breakthrough Therapy designation based on the reported data. It is possible that this will lead to approval of this combination for cisplatin ineligible patients in the near future, and may portend an effective platinum-free first-line option for patients with metastatic urothelial carcinoma.

Among cisplatin-eligible patients, IMvigor130 may significantly alter the first-line treatment landscape. While the trial has met its primary endpoint with respect to progression-free survival with atezolizumab plus gemcitabine and platinum versus gemcitabine and platinum, overall survival data are not yet mature, and this triplet regimen has yet to gain regulatory approval. With ongoing follow-up, it is possible that overall survival will reach statistical significance in favor of chemoimmunotherapy, and this regimen may become an established standard of care for mUC in the first-line setting. EV-302 is a randomized first line phase III trial about to launch that will compare EV plus pembrolizumab with or without platinum versus gemcitabine plus platinum; there is no chemoimmunotherapy arm. This may complicate the oncology community's ability to assess the impact of EV-302. Finally, the high response rates observed in EV-103 (and EV-201) clearly suggest that EV is capable of consistent and clinically meaningful tumor shrinkage. This efficacy, in conjunction with good tolerability, suggest a potential role for EV in the neoadjuvant setting, where cisplatin-based chemotherapy remains the only therapeutic option. Future clinical development will seek to incorporate EV or other antibody-drug conjugates into earlier lines of therapy.

In addition to the exciting late-stage development for EV, there are exciting data emerging for other antibody-drug conjugates in advanced urothelial cancer. Sacituzumab govitecan is the best-studied and has demonstrated responses in almost 1/3 of cisplatin-ineligible patients with checkpoint blockade refractory disease. While SG is accompanied by more myelosuppression, future development of this agent may benefit from more routine use of growth factor support.

HER2 represents an exciting area of clinical investigation in urothelial cancer. While studies of naked HER2 antibodies proved to be somewhat disappointing, the advent of novel HER2 targeted antibody-drug conjugates may finally allow for therapeutic targeting of HER2 in urothelial carcinoma. This prospect is especially exciting given the relatively high prevalence of HER2 overexpression in urothelial cancer. Unlike targeting HER2 with trastuzumab, which generally requires genomic amplification to achieve efficacy, RC48 (and perhaps trastuzumab deruxtecan also) has demonstrated efficacy in IHC 2+ FISH- tumors, suggesting that protein expression – even at modest levels – may be sufficient to drive response to HER2 targeted antibody-drug conjugates by virtue of a robust bystander effect.

While some antibody-drug conjugate targets are ubiquitous (e.g. nectin-4), others, such as HER2 may require careful biomarker studies to define the optimal threshold for response. Future clinical drug development in urothelial cancer should aim to leverage the proven technologic advances of ADC construction and expand the field of targetable cell surface peptides to create novel effective therapeutics.

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Article highlights:

- Enfortumab vedotin – an antibody-drug conjugate comprised of a monoclonal antibody to nectin-4 conjugated via a protease-cleavable linker to the microtubule disruptor monomethyl auristatin E – is an established treatment for patients with metastatic urothelial cancer which has progressed despite platinum-based chemotherapy and immune checkpoint blockade.
- Ongoing research will best determine how and when to combine enfortumab vedotin with anti-PD-1/L1 immunotherapy and/or platinum-based chemotherapy; the combination of enfortumab vedotin plus the PD-1 antibody pembrolizumab is associated with high objective responses that appear durable in phase Ib testing.
- A number of other antibody-drug conjugates are under investigation and appear promising, including the Trop-2 targeted agent sacituzumab govitecan and the HER2 targeting agents RC48 and trastuzumab deruxtecan.

Table 1.

Molecular characteristics of select novel antibody-drug conjugates.

ADC	Target Antigen	Chemical Linker	Cytotoxic Compound	Development Status
Enfortumab vedotin	Nectin-4	Protease-cleavable	MMAE	Approved for mUC
Sacituzumab govitecan	Trop-2	Acid-labile	SN-38	Phase II in mUC
Trastuzumab deruxtecan	HER2	Protease-cleavable tetrapeptide	deruxtecan	Phase I
RC48	HER2	Cathepsin-cleavable	MMAE	Phase II mUC
Gemtuzumab ozogamicin	CD33	Acid-cleavable hydrazone	calicheamicin	Approved for AML
Brentuximab vedotin	CD30	Protease-cleavable	MMAE	Approved for lymphoma (HL, ALCL, PTCL)
Inotuzumab ozogamicin	CD22	Acid-cleavable	calicheamicin	Approved for B-ALL
Polatuzumab vedotin	CD79b	Protease-cleavable	MMAE	Approved for DLBCL
Trastuzumab emtansine	HER2	Non-cleavable thioether	emtansine	Approved for HER2+ breast cancer

Table 2.

Clinical data supporting accelerated regulatory approval of enfortumab vedotin in advanced urothelial cancer

Trial	Design	Setting	Number of Patients	ORR	Median Duration of Response	Median Progression-Free Survival	Median Overall Survival
EV-101	Single-Arm Phase I	Platinum-and Checkpoint Blockade-Refractory	112	45% (11% CR, 34% PR)	7.5 months	6.6 months (estimated)	12.3 months (estimated)
EV-201 (Cohort 1)	Single-Arm Phase II	Platinum- and Checkpoint Blockade-Refractory	125	44% (12% CR, 32% PR)	7.6 months	5.8 months (estimated)	11.7 months (estimated)

Table 3.

Ongoing trials of novel antibody-drug conjugates in advanced urothelial cancer.

	Trial	Design	Setting	Arm(s) / Cohort(s)	Primary Endpoint(s)
Nectin-4 / Enfortumab vedotin	EV-302 (NCT04223856)	Randomized Phase III	Front-line, Cisplatin-Eligible	1) EV + Pembro 2) Gem/Cis or Gem/Carbo 3) EV + Pembro + Cis or Carbo	PFS & OS
	EV-201 (Cohort 2) (NCT03219333)	Single-Arm Phase II	Platinum-Naïve and Cisplatin-ineligible	EV monotherapy	ORR
	EV-301 (NCT03474107)	Randomized Phase III	Platinum- and Checkpoint Blockade-Refractory	1) EV monotherapy 2) Chemotherapy (docetaxel, vinflunine, or paclitaxel)	OS
	EV-103 (NCT03288545)	Multicohort Phase I/II	Multiple *	1) EV monotherapy 2) EV + Pembro 3) EV + Pembro + (Cis or Carbo) 4) EV + Cis 5) EV + Carbo 6) EV + Gem	Safety & ORR
	MORPHEUS mUC (NCT03869190)	Multicohort Phase I/II	Platinum-Refractory	Atezo + EV	ORR
Trop-2 / Sacituzumab govitecan	TROPHY-U-01 (NCT03547973)	Single-Arm Multicohort Phase II	Checkpoint Blockade Refractory and Platinum-Refractory or Ineligible	Sacituzumab Govitecan	ORR
Her-2	NCT03523572	Multicohort Phase Ib	Platinum-Refractory	Trastuzumab Deruxtecan + Nivo	Safety & ORR
	NCT04073602	Single Arm Phase II	Chemotherapy-Refractory	RC48-ADC monotherapy	ORR

* Two cohorts of MIBC will assess pCR rate