

Targeted Treatment of Locally Advanced and Metastatic Urothelial Cancer: Enfortumab Vedotin in Context

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Abstract: Enfortumab vedotin (EV) is a novel antibody–drug conjugate that is the first in class to be FDA-approved for use in patients with treatment-refractory urothelial cancer. Enfortumab is comprised of an antibody targeting nectin-4, widely expressed in urothelial cancers, with an monomethyl auristatin E (MMAE) chemotherapy payload. To date, trials in urothelial cancers refractory to platinum-based chemotherapy, and or checkpoint inhibitors, have shown the drug is very active, with overall responses ranging from 40% to 52%. This includes patients with visceral metastasis, a known predictor of poor prognosis. EV is fairly well tolerated, including in patients who are not candidates for cisplatin, a common urothelial cancer population with significant unmet need. Side effects such as skin toxicity, fatigue, and blood sugar elevations are generally manageable with supportive care and dose modifications. Peripheral neuropathy is common and can be dose-limiting in responding patients, and rare serious skin toxicities have been reported. Trials in various disease states and in combination with checkpoint inhibitors and other agents are ongoing, with additional indications likely in the future for EV in urothelial cancer.

Keywords: antibody-drug conjugate, urothelial cancer, metastatic, treatment refractory

Introduction

Management of Advanced Urothelial Cancer

Platinum-based chemotherapy has been the mainstay of treatment for locally advanced and metastatic urothelial cancer treatment for decades, with a median overall survival of just over a year with platinum regimens.^{1–7} The checkpoint inhibitor immunotherapy class of agents is active for treatment in the second line and beyond setting post platinum progression.^{8–12} Use of checkpoint therapy is now approved in the maintenance setting as well for patients with clinical benefit (complete or partial response, or stable disease) post frontline platinum, leading to an additional survival benefit of 21.4 months vs 14.3 months compared to post-chemotherapy observation alone.¹³ Despite the success of immunotherapy, many patients with advanced urothelial cancer do not benefit, and in a randomized trial pembrolizumab led to additional survival benefit of 3 months versus second-line chemotherapy in patients with progression post platinum.¹⁴

Patients with advanced urothelial cancer are on average 73 years old at diagnosis and typically have other medical comorbidities.^{15,16} Pre-existing heart disease, peripheral neuropathy, impaired functional status, and renal insufficiency, either at baseline or disease-related, are common. These factors often preclude the safe use of cisplatin, the most active frontline chemotherapy agent to date, for about half of patients with urothelial cancer.¹⁷ Furthermore, Gupta et al defined a group of patients with urothelial cancer with further unmet need, who have a combination of comorbidities that make them very poor candidates for carboplatin chemotherapy as well.¹⁸ For these frail patients, checkpoint inhibitor therapy with either atezolizumab or pembrolizumab is an alternative in the frontline setting to chemotherapy, regardless of PD-L1 biomarker status.^{8,9} For those with disease progression post anti-PD-1 or L1 therapies and or platinum chemotherapy,

targeted therapies are approved. For a minority of tumor biomarker-selected patients with FGFR3 mutation or FGFR2/3 fusion, erdafitinib is an option. In addition, data have been published supporting the expansion of the indication of sacituzumab govitecan for advanced treatment-refractory urothelial cancer. This review will focus on the data to date supporting the use of enfortumab vedotin for this population.

Antibody–Drug Conjugate – Enfortumab Vedotin

Antibody–drug conjugates (ADC) are an emerging class of cytotoxic drugs that link chemotherapeutic agents to highly specific monoclonal antibodies, delivering therapy more directly to cancer cells. This theoretically leads to less toxicity with directed drug delivery sparing normal tissues, and enhancing cancer response.¹⁹ Enfortumab vedotin is an ADC comprised of an human monoclonal antibody to nectin-4, linked to cytotoxic payload monomethyl auristatin E (MMAE), which is a microtubule-disrupting compound.²⁰ Nectin-4 is primarily expressed in embryo, placenta, and skin, and is overexpressed by a number of cancers, including urothelial and breast cancers.

Efficacy of Enfortumab – Clinical Studies

Phase I

The larger of two phase I studies was a trial in which patients with solid tumors expressing nectin-4 were treated in escalating weight-based doses of 0.5, 0.75, 1.0, and 1.25 mg/kg weekly on days 1, 8, and 15 in a 28 day cycle. It also included an expanded cohort of patients with urothelial cancers refractory to anti-PD-(L)1 therapies and or other therapies, treated at the phase I maximum tolerated dose (MTD) of 1.25 mg/kg on the same schedule.²¹ The majority of the patients with urothelial cancer in the study had prior platinum therapy, and 29% had ≥ 3 prior lines of prior treatment. Median nectin-4 testing by immunohistochemistry measured by H score was exceptionally high at 290 (range 0–300), and nectin-4 biomarker testing was ultimately withdrawn as an inclusion criterion, as high expression of nectin-4 was so prevalent. The median age was 67, and the majority of patients were white males, congruent with other studies in the advanced urothelial cancer population. At baseline, 41% had a glomerular filtration rate < 60 mL/min, and 77% had visceral disease, both reflective of the comorbidities and disease phenotype of the advanced treatment-refractory urothelial cancer population. Side effect profile included rash and peripheral neuropathy as the most common side effects, followed by gastrointestinal toxicity. Grade > 3 treatment-related events occurred in 34% of participants, the most common of which was hyperglycemia. Four patients experienced treatment-related fatality related to respiratory failure, infection, diabetic ketoacidosis, and multisystem organ failure.

Of the 112 patients with urothelial cancer treated at the 1.25 mg/kg MTD level, the objective response rate (ORR) was 43% including 5% of patients with complete response, with median duration of response 7.4 months. The authors reported responses ranging from 18.5% to 50% in the small number of patients treated at lower dose levels. At the time of reporting, the median PFS for patients treated at the 1.25 mg/kg dose level was 5.4 months, with median overall survival of 12.3 months.

In a much smaller trial, 17 Japanese patients with treatment-refractory urothelial cancer were randomized to receive either 1 or 1.25 mg/kg of enfortumab vedotin at the standard 28 day cycle length.²² Toxicities were similar to those reported in the prior EV phase I trial of rash and skin toxicity, neuropathy, gastrointestinal toxicity, as well as fever which was less common in the US cohort. The confirmed response rate was 35% including one patient with complete response, with median progression-free survival of 8.1 months. Compared to the US population, pK values measuring both enfortumab and the chemotherapy payload MMAE were similar to the US population. No dose or schedule modifications were recommended for the Japanese population in future studies.

Phase II EV-201

Cohort I

EV-201 was a trial which evaluated cisplatin-eligible and ineligible patients in 2 parallel single arm cohorts. Patients in cohort 1 were previously treated and experienced disease progression post platinum-based chemotherapy, either in the perioperative or frontline setting, and following a checkpoint inhibitor.²³ In this arm, 125 patients were treated with enfortumab vedotin at standard 1.25 mg/kg dosing on days 1, 8, and 15 every 21 days. Eligibility included ECOG ≤ 1 ,

and, as per all enfortumab trials, uncontrolled diabetes defined as hemoglobin A1C of $\geq 8\%$ was an exclusion. Patients were predominantly male with median age of 69 (40–84), and 35% had primary tumor located in the upper tract. Sixty-seven percent were reported to have pure urothelial cancer, with the remaining having some mix of variant histology. Ten percent had disease in lymph nodes alone, historically the phenotype of advanced urothelial cancer with the best prognosis, with 40% presenting with disease in liver.

Enfortumab vedotin was well tolerated with a median duration of 4.6 months on treatment, with a maximum duration of >15 months at the time of data cutoff, at a median 10.4 months' follow-up. The confirmed objective response rate (ORR) was 44% (95% CI, 35.1%–53.2%) by central review, including 12% with complete responses. These responses tended to be brisk (median 1.84 months to first response) with a median duration of response (DOR) of 7.6 months. Responses occurred irrespective of metastatic site, including the poorest prognostic category of liver metastasis, and in the most heavily pretreated patients. Side effects in this study were similar to those reported in the phase I studies, most commonly fatigue, alopecia, appetite change, taste disturbance, and neuropathy. Febrile neutropenia was a rare but reported grade ≥ 3 event, and peripheral sensory neuropathy was the most reported dose-limiting toxicity. Ongoing durable responses of treatment were reported.

Cohort 2

EV-201 cohort 2 enrolled patients with locally advanced or metastatic urothelial cancer who were ineligible for platinum-based therapy, with disease progression on or following prior immune checkpoint inhibitor therapy.²⁴ This cohort of 89 patients who were mostly chemotherapy-naïve were predominantly male with a median age of 75 years (68–78), and were treated with enfortumab vedotin at standard dose and schedule. In this cisplatin-ineligible population, 12% had baseline ECOG performance status 2, 13% with hearing loss, and the majority had some degree of renal impairment, including 69% with creatinine clearance <60 mL/min. In this cohort, 43% had upper tract cancers as the primary site of origin, 79% with visceral metastasis including 24% with liver metastasis.

The median duration of treatment on trial was 6 months (2.8–8.3 months). The confirmed ORR was 52% with 20% complete responses, with a median duration of response of 10.9 months. The authors note this is the highest ORR ever reported with a single agent in this treatment-refractory population. The most common treatment-related adverse effects were acute kidney injury, hyperglycemia, decreased appetite, hypotension, diarrhea, neutropenia, and skin reactions. Three patients died of treatment-related toxicity within 30 days of the last enfortumab administration, and one post 30 days. Notably the patients with reported treatment-related death had concomitant age (>75) or other contributing comorbidities, including obesity. Importantly in this weight-based dosed drug, dosing guidelines currently stipulate 100 kg dosing cutoff, so the highest per day dosing in obese patients is 125 mg total. As in prior studies, peripheral sensory neuropathy was a dose-limiting toxicity leading to discontinuation in 4% of subjects.

Phase III EV-301

The phase III EV-301 trial randomized patients with urothelial cancer post progression on chemo and a PD-1 or L1 inhibitor to enfortumab vedotin at standard dose and schedule, or to investigator-chosen chemotherapy.²⁵ The primary endpoint of this a global, open-label study was overall survival. Three hundred and one subjects were randomized to receive enfortumab vedotin or investigator's choice of docetaxel 75 mg/m², paclitaxel 175 mg/m², or vinflunine 320 mg/m², where available – all every 21 days). The median age of 68 years (30–88) was similar to populations in other EV trials, and the majority were men at over 77%. The percentage of subjects with visceral disease was high and well balanced in both groups over 77%. The majority of patients were enrolled from outside of the US. The study met the pre-specified primary endpoint with an improvement in median overall survival of 12.88 months (95% CI, 10.58 to 15.21) with EV compared to 8.97 months (95% CI, 8.05 to 10.74) in the chemotherapy arm, equating to a 30% reduction in the risk of death with enfortumab, $p=0.001$. Progression-free survival was also statistically significant at 5.55 vs 3.71 months in the enfortumab and chemotherapy arms, respectively. Similarly, confirmed ORR with enfortumab was 40.6%, consistent with prior studies and substantially higher than ORR with chemotherapy of 17.9% [95% CI, 13.7 to 22.8], $p<0.001$. Complete responses were less common at 4.9% and 2.7% in the enfortumab and chemotherapy cohorts,

respectively. In patients with complete or partial response, the duration of response was similar at 7.39 months on the enfortumab arm and 8.11 months on the chemotherapy arm.

Safety and tolerability of enfortumab and chemotherapy were consistent with prior reports of late-line therapies in urothelial cancer. Grade ≥ 3 adverse events were similar at 51.4% and 49.8% in the enfortumab and chemotherapy cohorts. Treatment-related rash is well known and was very common at 43.9% in the enfortumab group and 9.6% in the chemotherapy arm. Peripheral neuropathy was common in both groups, reported in 46.3% in those treated with enfortumab and 30.6% in those treated with chemotherapy. Treatment-related hyperglycemia was much more common in those treated with enfortumab at 6.4% versus 0.3% in the chemotherapy arm. Seven patients died of treatment-related adverse events in the enfortumab arm: multi-organ failure ($n=2$), hepatic failure ($n=1$), hyperglycemia ($n=1$), and infection-related ($n=3$); and three in the chemo arm: infection-related ($n=2$) and pancytopenia ($n=1$). Superior survival outcome of enfortumab in this randomized phase III trial led to full US FDA approval for enfortumab in July 2021.

Enfortumab Vedotin and Pembrolizumab

EV-I03 Cohort A – Dose Expansion

In a cisplatin-ineligible population of 45 patients with locally advanced or metastatic urothelial cancer, enfortumab vedotin at standard 1.25 mg/kg dosing was given on days 1 and 8 with pembrolizumab at flat 200 mg dosing on day 1 of a 21 day cycle.²⁶ Eligible patients were not cisplatin-treated based on one or more of ECOG PS ≤ 2 , impaired renal function defined as creatinine clearance ≥ 30 and < 60 mL/min, or hearing loss. Platinum allergy or platinum treatment in the perioperative setting > 12 months from enrollment was allowed. As noted in all previous studies, this was a male-predominant (80%) and older (median age 69 years) group with the majority (84.4%) with visceral metastasis, and liver metastasis in 31.1%, indicative of a very high-risk population. The investigator-reported response rate was high at 73.3%, with 15.6% with complete response to the combination. The majority (87.9%) were brisk and noted at first imaging assessment as reported in prior trials. The median progression-free survival was 12.3 months. The median duration of response was 25.6 months, and median overall survival was 26.1 months, importantly the highest ever reported in a frontline urothelial cancer trial.

Treatment-related adverse events were common, including peripheral neuropathy, fatigue, and alopecia. Peripheral neuropathy occurred in 62.2% and was the most common dose-limiting side effect. Rash is a common toxicity in both enfortumab and pembrolizumab treatment, and was frequent in this study at 66.7%, and appeared predominantly within the first cycles (median time to skin toxicity 0.7 months, IQR: 0.33, 4.1). The majority of these skin toxicities were grade ≤ 3 and one was grade 4. Immune-related adverse events were reported in 44% of subjects in this checkpoint combination study. One patient experienced grade 5 multi-system organ failure.

EV-I03 Cohort K – Enfortumab Vedotin With or Without Pembrolizumab

Data were presented on this cohort at the 2022 European Society of Medical Oncology (ESMO) Meeting, in which patients with urothelial cancer who were previously untreated and ineligible for cisplatin were enrolled. Like prior trials in the setting, most were cisplatin-ineligible due to renal insufficiency and $> 80\%$ had visceral metastases. These subjects were randomized to receive enfortumab 1.25 mg/kg on days 1 and 8 alone or in combination with pembrolizumab 200 mg on day 1. With enfortumab alone in this cohort, the confirmed ORR was similar to that reported in previous studies at 45.2% with complete response in 4.1%. In the combination arm, the ORR was 64.5%, with 10.5% rate of CR. The median duration of response was 13.2 months for enfortumab alone, and not yet reached for the combination. The incidence of skin toxicity was higher in the combination arm at 67.1%, while in the EV alone arm it was reported at 45.2%, congruent with prior EV single agent studies. Peripheral neuropathy was common in both 60.5% (EV+P) and 54.8% (EV) arms. Median 12 month survival rates were similar 80.7% (EV+P) and 70.7% (EV) in this first reporting, at a median follow-up time of approximately 15 months. The median duration of response was not yet reached in either arm.

Sequencing EV with Other Novel Agents

In addition to enfortumab vedotin, two other novel therapies have been approved for use in advanced urothelial cancer since 2019, with hopefully more novel agents on the horizon. These agents, the oral targeted FGFR2/3 inhibitor erdafitinib and ADC

sacituzumab govitecan, were developed before or in parallel timing with EV, therefore best sequencing of these three novel agents has yet to be determined.^{27,28} Only the approximate 15%–20% of patients with somatic FGFR3 mutations or FGFR2/3 fusions are acceptable candidates for targeted erdafitinib therapy. Similar to results seen in enfortumab trials, erdafitinib is active in patients with visceral and liver metastasis and led to an ORR of 40% in a phase II trial. One group performed a retrospective review of 60 patients treated with EV and compared response outcomes in those patients who did (13/60) or did not have tumors harboring these alterations; only one had prior therapy with an FGFR inhibitor.²⁹ The authors noted no difference in tumor response outcomes by presence or absence of FGFR alterations in this small retrospective cohort. This lack of outcome difference to EV between FGFR mutated and wild-type tumors was further supported by the real-world multi-institution UNITE dataset evaluating outcomes to EV, in which the ORR to EV in FGFR3 mutation or FGFR2/3 fusion-altered tumors was 57%.³⁰ Therefore there is no clear use of biomarker at this time that informs the sequence in which targeted FGFR2/3 inhibition should be used with other ADC in selected patients.

In the single arm phase II study supporting use of sacituzumab in patients with treatment-refractory urothelial cancer, 113 patients were enrolled. The authors reported that 10 (8.8%) and 2 (1.8%) had received prior enfortumab vedotin and erdafitinib, respectively. Again, since the population was heavily pretreated in this late line trial, visceral metastasis was common, and the ORR of sacituzumab was 27.4%. Of the 10 patients previously treated with enfortumab, there was a 30% ORR to sacituzumab, an early indication that there may not be cross-resistance between the agents. Finally Grivas et al reported at the ASCO GU conference in 2022 on the combination of sacituzumab with pembrolizumab in patients with platinum-refractory but checkpoint inhibitor-naïve metastatic urothelial cancer, which led to an ORR of 34%. Prior use of enfortumab was not reported in this dataset, but the median number of prior therapies was 1 (1–2). To date there is no clear data reported on platinum response post EV for patients treated in the frontline with EV or EV combinations. These real-world and trial update data are sure to emerge in the coming years, and hopefully will help establish best sequence of administration, and predictive biomarkers informing care for urothelial cancers.

The Role of Nectin-4 Biomarker Testing in Standard Practice

There is no role for nectin-4 biomarker testing in standard practice. To date, only a few of the reported enfortumab publications include nectin-4 biomarker information. In the larger of two phase I trials, the authors noted that responses appeared irrespective of reported nectin-4 expression, reported as immunohistochemistry (IHC) H score (range from negative at 0 to highest expression level at 300), which was low in several subjects. In the phase II trial of enfortumab vedotin post checkpoint therapy in cisplatin-ineligible patients, 80 of the 91 enrolled subjects had tissue for biomarker analysis.²⁴ The authors report nearly all (99%) had some expression of nectin-4 by IHC. Furthermore, nectin-4 expression was high, and similar among subjects with response to enfortumab (median H score 270/300) and those without response (Median H score 280/300). Nectin-4 biomarker data were also reported in the EV-103 Cohort A dataset of patients ineligible for cisplatin treated with enfortumab and pembrolizumab in the frontline setting.²⁶ In this trial, 39 subjects had adequate tumor sample for testing, 38 of which showed some expression of nectin-4. Here too, the authors noted no difference in mean nectin-4 IHC expression measured by H score in the patients who did or did not have tumor response to enfortumab vedotin. Finally no correlation was shown between nectin-4 expression and response to enfortumab or enfortumab and pembrolizumab in the frontline setting in the recently presented work on EV-103 Cohort K at ESMO 2022.

EV in Upper Tract Urothelial Cancer (UTUC)

UTUC is much less common than urothelial bladder cancer in all patients newly diagnosed with urothelial cancer, comprising about 5%–10% of all new urothelial cancer diagnoses annually. Stage for stage, UTUC tends to be a more aggressive tumor, presenting in later stages than bladder cancer, and more likely to be advanced at first presentation. Not surprisingly then, this relatively uncommon urothelial subtype represented 25%–43% of patients in prospective EV trials to date, which enroll patients with later-stage disease.^{21,23–25,31} (Table 1) Furthermore, as nephroureterectomy is a standard practice for patients with localized UTUC, many patients with recurrent UTUC also have concomitant renal insufficiency, which can impact treatment were common.^{32,33} Though some studies provide breakdown between bladder and UTUC sites in subgroup analyses, these comparisons are hypothesis-generating, and no studies to date have been powered to compare response rate based on tumors in the upper or lower tract location, including these EV trials.

Table I Summary of Enfortumab Vedotin (EV) Trials in Urothelial Cancer (UC)

Study	N	Therapy	Population	% Bladder/ UTUC	ORR %	OS Months
EV-101 ²¹ Phase I	112	EV with dose escalation up to 1.25 mg/kg on D1, D8, D15 of 28 day cycle	Metastatic (m) Nectin-4 + solid tumors or mUC PD post ≥1 therapy	Bladder 71% UTUC 24.5% Other 4.5%	43*	12.3
Japan ²² Phase I	17	EV Arm A: 1.0 mg/kg or Arm B: 1.25 mg/kg Both on days 1, 8, 15 of 28 day cycle	Japanese pts with mUC PD post platinum or platinum ineligible	Bladder 70.6% UTUC 19.6%	A: 44.4 B: 25 All: 35.3	-
EV-201 ²³ Cisplatin eligible Phase II	125	EV 1.25 mg/kg D1, D8, D15 of 28 day cycle	mUC – post prior platinum and ICI	Bladder 65% UTUC 35%	44	11.7
EV-201 ⁴¹ Cisplatin ineligible Phase II	89	EV 1.25 mg/kg D1, D8, D15 of 28 day cycle	mUC post prior ICI platinum ineligible	Bladder 57% UTUC 43%	52	14.7
EV 301 ²⁵ Phase III	608	EV 1.25 mg/kg D1, D8, D15 of 28 day cycle vs docetaxel or vinflunine or paclitaxel D1 of 21 day cycle	mUC post prior platinum and ICI	EV: bladder 67.4% UTUC 32.6% CT: bladder 65.1% UTUC: 34.9%	EV: 40.6 CT: 17.9	EV: 12.88 CT: 8.97
EV+PB ²⁶ Phase Ib/II	45	EV 1.25 mg/kg D1 and D8 and pembrolizumab 200 mg D1 of 21 day cycle	Treatment-naïve mUC cisplatin ineligible	Bladder 66% UTUC 33%	73.3	26.1

Note: *Reported on patients with UC treated at 1.25 mg/kg level.

Abbreviations: EV, enfortumab vedotin; PD, disease progression; CT, chemotherapy; PB, pembrolizumab; D, day; UTUC, upper tract urothelial cancer.

The ORRs reported in the real-world multi-institution UNITE study analyzing outcomes from 260 patients treated with single-agent EV in bladder and upper tract cancers were not significantly different at 50% and 61%, respectively.

Tomiya et al utilized primary antibodies against nectin-4 (1:3000; EPR15613-68; Abcam, Cambridge, UK) to investigate expression in high- and low-grade UTUC specimens, noting expression level of 65.7% in these heterogeneous UTUC specimens.³⁴ Of interest in this retrospective cohort, strong nectin-4 expression was associated with worse clinical outcomes, though it was unclear if any patients had enfortumab exposure. Similarly, Calandrella et al evaluated nectin-4 IHC expression in 27 subjects with UTUC from biopsy and nephrectomy specimens using the rabbit polyclonal antibody ab155692, noting expression in 44% of cases with this antibody.²⁶ Furthermore, these authors found nectin-4 expression correlated with DNA mismatch repair (MMR) protein loss in this small hypothesis-generating retrospective report. Heterogeneity of anti nectin-4 antibodies used for biomarker analysis in these small studies, and in the prospective enfortumab vedotin trials, makes cross-study interpretations challenging.

EV in Variant Histology

Little is known about expression of nectin-4 in rare bladder cancer subtypes such as pure squamous cell or adenocarcinoma variants, or activity of EV in these variant individual subgroups. Variant histology was allowed in all EV trials with the caveat that conventional urothelial cancer constitute >50% of specimens. Some variant histology was present in >77% of patients in the enfortumab and pembrolizumab Cohort A dataset, but outcome by the variant group, or of the individual variant subtypes, was not reported.²⁶ Thirty percent of subjects treated with EV in the second-line setting post checkpoint had variant histology, but again outcomes were not separately reported.²⁴ The same was true of the 15% with variant histology in the phase III second-line study of enfortumab compared to chemotherapy, the 33% in the definitive

EV-201 study, and of those with variant histology in the phase I trial.^{21,23,25} In the real-world UNITE dataset, patients with pure urothelial histology had ORR of 58% compared to those with any variant component with ORR of 42%.³⁰ By subtype, squamous variant subtype was the most common and had ORR of 50% to single-agent enfortumab. The other variants were less common with reported ORR between 33% and 50% in micropapillary ($n=19$), sarcomatoid ($n=4$), plasmacytoid ($n=4$), adenocarcinoma ($n=3$), mixed ($n=4$), and unknown ($n=9$). In one patient with reported mixed neuroendocrine cancer, best response was stable disease.

Utilizing the rabbit monoclonal human nectin-4 antibody (EPR 15613–68, Abcam), nectin-4 expression was analyzed in a cohort of 83 non-muscle-invasive and 86 muscle-invasive bladder cancer samples, with focus on those with variant histologic subtype.³⁵ In the conventional urothelial cancer subgroup in this study, nectin-4 was expressed in 87% of non-muscle-invasive samples (72/83) and 68.2% (15/22) muscle-invasive specimens. In the ten samples with squamous cell variant histology, 7/10 expressed nectin-4 in both the urothelial and squamous portions of the samples. The three that did not have nectin-4 expression were similarly negative in both the urothelial and squamous portions. Of 8 samples of plasmacytoid variant, 62.5% (5/8) had any nectin-4 expression. Twenty-eight percent of the 11 micropapillary samples had weak nectin-4 staining, and 66% of the 6 glandular tumors had mostly strong nectin-4 expression. Of note, all 15 samples of pure or mixed small cell cancer had no nectin-4 expression with the tested antibody. Furthermore in a dataset of over 1900 samples analyzed for nectin-4 expression using the anti-NECTIN4 PE antibody (Miltenyi Biotec #130–116–027), nectin-4 IHC expression was similarly low in their reported neuroendocrine subgroup.³⁶

EV Response and Resistance

Studies to date outlined above that have reported findings on nectin-4 IHC expression show there is no clear correlation between expression level and clinical response to enfortumab. There are insufficient numbers of subjects with no nectin-4 expression vs any expression in these trials for a comparison of these subgroups. Given nectin-4 expression when reported in prospective trials is so high, thought leaders have called into question why the ORR to EV does not match the reported rate of biomarker expression.³⁷ This indicates that presence of nectin-4 on cell surface alone does not guarantee response, and other mechanisms of resistance are at play.

In a study evaluating over 1900 tumor samples, some of which were from patients who had prior platinum therapy, Chu et al evaluated nectin-4 mRNA expression levels based on tumor molecular subtypes.³⁶ These subtypes have been previously defined in several bladder cancer cohorts and include the broad categories of luminal, basal/squamous, and neuroendocrine, categories which can help predict response to platinum chemotherapy.³⁸ These authors found the highest nectin-4 expression in the luminal subtype of tumors, lower expression in basal/squamous, and none or low in the neuroendocrine subgroup. Prior platinum therapy did not appear to impact these mRNA expression levels, which were confirmed on a smaller subset of samples evaluated also for nectin-4 expression by IHC. Using luminal and basal cell lines, the authors determined that luminal type cells were much more sensitive to cell death from enfortumab in culture than basal type cells, despite measurable levels of nectin-4 in all samples.

Taking the hypothesis one step further, the authors knocked down nectin-4 mRNA expression in these sensitive luminal cell lines, which led to enfortumab resistance. Similarly, upregulating nectin-4 expression in relatively resistant cell lines increased sensitivity to enfortumab, indicating that expression of nectin-4 in these cell lines was required for EV-related cytotoxicity. These hypothesis-generating data may help uncover mechanisms of primary resistance to enfortumab, particularly for basal/squamous and neuroendocrine subtypes.

Interestingly, using mouse models of nectin-4 expressing tumors, investigators developed models of enfortumab resistance, indicating that upregulation of a multi-drug resistance transporter protein contributed to primary enfortumab resistance after several months of exposure.³⁹ Finally, nectin-4 expression by IHC was analyzed in three male patients with initial clinical benefit, followed by disease progression on enfortumab (exposure 4–8 EV cycles).⁴⁰ Utilizing fresh biopsy samples from sites of disease progression on enfortumab, nectin-4 expression by IHC was measured using the ABCAM ab192033 clone EPR15613-68 antibody. These patients were heavily pretreated with platinum, checkpoint inhibitor therapy, and FGFR2/3 targeted therapy. Nectin-4 levels were uniformly high in these 3 enfortumab-refractory specimens (300/300), indicating that loss of nectin-4 expression was not the driver of clinical resistance in this small hypothesis-generative dataset.

Future Directions

The encouraging response and manageable toxicity profile support the ongoing global randomized phase III trials of enfortumab in various settings. In the neoadjuvant setting, several large-scale trials are evaluating use of enfortumab with and without checkpoint inhibitors, including one where patients are randomized to an enfortumab versus a platinum regimen (Table 2). In the frontline setting, enfortumab and pembrolizumab versus gemcitabine and cis- or carboplatin are

Table 2 Ongoing Enfortumab Trials in Urothelial and Other Cancers

NCTN	N	Title	Setting
Non-Muscle Invasive Bladder Cancer			
NCT05014139	58	A Study of Intravesical Enfortumab Vedotin For Treatment of Patients With Non-muscle Invasive Bladder Cancer (NMIBC)	High-risk Bacillus Calmette–Guerin (BCG) unresponsive disease
Neoadjuvant Prior to Cystectomy for Invasive Bladder Cancer			
NCT05239624	23	Enfortumab Vedotin in Combination With Pembrolizumab for Locally Advanced and/or Node Positive Urothelial Carcinoma Prior to Surgery (EV-ECLIPSE)	Clinical Stage T2–T4, N1–N3, M0 OR cT1, N2–N3, M0
NCT03924895	857	A Randomized Phase 3 Study Evaluating Cystectomy With Perioperative Pembrolizumab and Cystectomy With Perioperative Enfortumab Vedotin and Pembrolizumab Versus Cystectomy Alone (KEYNOTE-905/EV-303)	Cisplatin-ineligible or decline cisplatin with muscle-invasive bladder cancer (cT2–T4aN0M0 or T1–T4aN1M0) with predominant (≥50%) urothelial histology
NCT04960709	830	A Phase III Randomized, Open-Label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab in Combination With Tremelimumab and Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin (VOLGA)	Cisplatin-ineligible or decline cisplatin
NCT03288545	457	A Study of Enfortumab Vedotin (ASG-22CE) as Monotherapy or in Combination With Other Anticancer Therapies for the Treatment of Urothelial Cancer (EV-103)	Cohort H: enfortumab vedotin in MIBC neoadjuvant setting Optional Cohort J: EV+pembrolizumab in MIBC neoadjuvant setting Cohort L: enfortumab vedotin in MIBC in perioperative setting
NCT04700124	784	A Phase 3, Randomized, Open-label Study to Evaluate Perioperative Enfortumab Vedotin Plus Pembrolizumab (MK-3475) Versus Neoadjuvant Gemcitabine and Cisplatin in Cisplatin-eligible Participants With Muscle-invasive Bladder Cancer (KEYNOTE-B15 / EV-304)	Cisplatin eligible (T2–T4aN0M0 or T1–T4aN1M0) with predominant (≥50%) urothelial histology
First Line – Unresectable or Metastatic Urothelial Cancer			
NCT04223856	990	An Open-label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination With Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer (EV-302)	First-line treatment-naïve Cisplatin-eligible and ineligible
NCT03288545	457	A Study of Enfortumab Vedotin (ASG-22CE) as Monotherapy or in Combination With Other Anticancer Therapies for the Treatment of Urothelial Cancer (EV-103)	Cohort A: EV + pembrolizumab in cisplatin-ineligible 1L Cohort D: enfortumab vedotin + cisplatin in 1L Cohort E: enfortumab vedotin + carboplatin in 1L Optional Cohort F: enfortumab vedotin+gemcitabine in 1L and 2L Cohort G: enfortumab vedotin + platinum + pembrolizumab in 1L Randomized Cohort K: enfortumab vedotin + pembrolizumab

(Continued)

Table 2 (Continued).

NCTN	N	Title	Setting
Late Line Post Progression Following >1 Line of Therapy			
NCT04963153	30	Phase Ib Trial of Erdafitinib Combined With Enfortumab Vedotin	Post platinum and CPI for metastatic urothelial carcinoma with FGFR2/3 genetic alterations
NCT05524545	30	A Phase I, Open-label, Multicenter, Safety, Pharmacokinetic, Pharmacodynamic Study of ALX148 in Combination with Enfortumab Vedotin and/or Other Anticancer Therapies in Subjects With Urothelial Carcinoma (ASPEN-07)	Post platinum and CPI
NCT04724018	24	Sacituzumab Govitecan Plus Enfortumab Vedotin for Metastatic Urothelial Carcinoma Progressing on Platinum-based Chemotherapy and PD1/L1 Inhibitors: the Double Antibody Drug Conjugate (DAD) Phase I Trial	Post platinum and CPI
NCT04878029	32	A Phase I/Ib Open Label, Single-Arm Study of Cabozantinib in Combination With Enfortumab Vedotin (EV) in the Treatment of Locally Advanced or Metastatic Urothelial Cancer	Post platinum (if eligible) and CPI
NCT03288545	457	A Study of Enfortumab Vedotin (ASG-22CE) as Monotherapy or in Combination With Other Anticancer Therapies for the Treatment of Urothelial Cancer (EV-103)	Cohort B: enfortumab vedotin + pembrolizumab in 2L Optional Cohort F: enfortumab vedotin+gemcitabine in 1L and 2L
NCT03606174	425	A Phase 2 Study of Sitravatinib in Combination With PD-(L)1 Checkpoint Inhibitor Regimens in Patients With Advanced or Metastatic Urothelial Carcinoma	Experimental: Cohort 9 Post CPI and platinum
NCT03869190	645	A Phase Ib/II, Open-Label, Multicenter, Randomized Umbrella Study Evaluating the Efficacy and Safety of Multiple Immunotherapy-Based Treatments and Combinations in Patients With Urothelial Carcinoma (MORPHEUS-UC)	Atezolizumab + enfortumab vedotin for mUC
Non-Urothelial Cancer Trials			
NCT04754191	34	A Phase 2 Umbrella Protocol of Enfortumab Vedotin as Monotherapy and Combined With Other Agents in Patients With Metastatic Castration-Resistant Prostate Cancer	Late line mCRPC
NCT04225117	208	An Open-label, Multicenter, Multicohort, Phase 2 Study to Evaluate Enfortumab Vedotin in Subjects With Previously Treated Locally Advanced or Metastatic Malignant Solid Tumors (EV-202)	Cohort 1: HR+/HER2- breast cancer Cohort 2: triple negative breast cancer (TNBC) Cohort 3: squamous non-small cell lung cancer Cohort 4: non-squamous non-small cell lung cancer Cohort 5: head and neck cancer Cohort 6: gastric or gastroesophageal junction (GEJ) or esophageal cancer Cohort 7: gastric adenocarcinoma or esophageal adenocarcinoma (EAC) or GEJ adenocarcinoma Cohort 8: esophageal squamous cell carcinoma (ESCC)

Abbreviations: NCTN, National Clinical Trials Network; FGFR, fibroblast growth factor receptors; mCRPC, metastatic castration-resistant prostate cancer.

being evaluated in a global phase III study. In the late line setting, smaller studies are testing novel combinations with enfortumab, including erdafitinib, sacituzumab, cabozantinib, gemcitabine, and sitravatinib. Enfortumab vedotin is also being investigated for intravesical use in a small cohort of patients with high-risk *Bacillus Calmette–Guerin* (BCG) unresponsive non-muscle-invasive bladder cancer. Finally, EV is being studied in a small prostate cancer trial, as well as in the late line setting in expanded cohorts of breast, lung, and GI cancers.

Conclusion

Enfortumab vedotin is a very active and fairly well tolerated antibody–drug conjugate with excellent activity in the second line and beyond in patients with urothelial cancer. Of particular clinical importance is its efficacy in visceral disease, notably in liver metastasis, a poor prognostic disease phenotype. Serious skin rash is an uncommon but potentially high-grade event that can occur early in treatment, so close follow-up in early cycles is advised. Peripheral neuropathy is common and can be dose-limiting in patients with excellent disease response. Unlike platinum chemotherapy, enfortumab appears less nephrotoxic and well tolerated in those with lower GFR, though specific studies in this space have not been done. This is of particular importance given the prevalence of renal insufficiency in urothelial cancer, particularly for those with UTUC, and the impact this comorbidity has on eligibility for and tolerance of current frontline platinum therapy. Though it is a targeted therapy, there is no role for biomarker testing as nectin-4 expression is not predictive of response to enfortumab. Understanding the mechanisms of response and resistance to EV remains a large unmet need. Combination enfortumab and pembrolizumab is a well-tolerated and an impressively active regimen in two reported studies in cisplatin-ineligible patients. It is the experimental comparator in a phase III frontline global trial compared to platinum-based therapy for cisplatin-eligible and ineligible candidates. How to best combine and sequence enfortumab with other chemo, targeted, immunotherapies as well as other ADCs remain unanswered questions. Other ADCs will continue to be developed, expanding a pillar of novel therapy for patients with urothelial cancer. This includes ongoing studies of sacituzumab govitecan including a phase III post chemo and checkpoint versus physicians' choice chemotherapy study, as well as development of novel ADCs with HER2 targets such as trastuzumab emtansine and disitamab vedotin.

Disclosure

J Hoffman-Censits reports participation on an advisory board for Seagen. L Maldonado has no disclosure to report in this work.

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