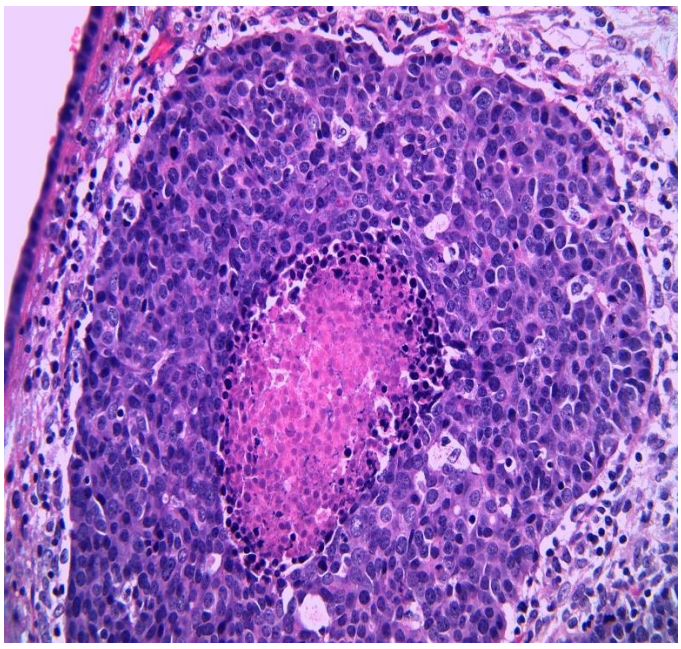
A Review of Antibody-Drug Conjugates for the Treatment of Urothelial Carcinoma: The Rise of Enfortumab Vedotin

Key Takeaways

- Enfortumab vedotin-ejfv (EV) targets nectin-4, showing efficacy in urothelial carcinoma (UC) and gaining approval as a first-line treatment.
- Combination of EV with pembrolizumab enhances outcomes, establishing a new standard of care for locally advanced or metastatic UC.
- EV's adverse events, including skin toxicity and peripheral neuropathy, require vigilant monitoring and management by healthcare professionals.
- Ongoing trials explore EV's potential in perioperative settings and other solid tumors, indicating its expanding therapeutic role.

Enfortumab vedotin-ejfv has transformed treatment in locally advanced and metastatic urothelial carcinoma from decades-long platinum-based chemotherapy to the new standard of care combination of antibody-drug conjugate and PD-1/PD-L1 inhibitor.

Abstract



The recognition of enfortumab vedotin-ejfv (EV) as an effective therapeutic in urothelial carcinoma (UC) is supported by clinical trials such as EV-201, EV-301, EV-103/KEYNOTE-869, and EV-302/KEYNOTE-A39. EV is an antibody-drug conjugate (ADC) that targets nectin-4, a transmembrane protein highly expressed in UC. EV's rise in locally advanced and metastatic UC took approximately 4 years from its initial accelerated approval in 2019 to its full approval as a first-line treatment in 2023. ADCs continue to represent a frontier for all cancers, with few having the impact that EV has had for UC. In addition to EC's use in the treatment of UC, future clinical trial results may show that EC is effective in the perioperative setting and potentially other solid tumors. As with many anticancer therapeutics, caution should be taken, as EV can lead to unique adverse events while also having overlapping toxicities with PD-1/PD-L1 inhibitors. Pharmacists in the clinic or infusion center reviewing laboratory tests and assessing patients may provide a key link for patient monitoring, early detection, and toxicity management.

Introduction

Antibody-drug conjugates (ADCs) represent a promising frontier in targeted cancer therapy, combining the specificity of monoclonal antibodies with the cytotoxic efficacy of chemotherapy. Unlike traditional chemotherapy, which can damage cancerous and healthy cells, ADCs selectively target tumor cells, thereby reducing systemic toxicity and enhancing therapeutic precision.1 The ADC structure typically includes a monoclonal antibody specific to an antigen highly expressed on cancer cells, a cytotoxic drug (payload), and a linker that attaches the drug to the antibody. Upon binding to the target antigen, the ADC-antigen complex is internalized and the linker is cleaved, releasing the cytotoxic payload directly into the tumor cell to induce cell death and sparing the healthy tissue.[2,3]

Advances in ADC technology help addressed challenges that manifested with first-generation ADCs, such as off-target effects and instability. Second- and third-generation ADCs incorporate several improvements to allow higher drug-to-antibody ratios, employ stable linkers that reduce premature release, and maintain a lower presence of unconjugated antibodies to limit adverse effects (AEs).2,4 These modifications enhance the safety and efficacy of ADCs, improving their therapeutic potential across a broad range of malignancies.2,4 By focusing on tumor-specific markers, ADCs such as enfortumab vedotin-ejfv (EV; Padcev; Astellas Pharma US and Seagen) for urothelial carcinoma (UC) have achieved remarkable clinical success, broadening the horizons of cancer treatment. Continued research and advancements in ADC technology are anticipated to further refine their therapeutic profile, providing new and more effective treatment options for patients with difficult-to-treat cancers such as UC.

The prognosis for UC varies considerably based on the cancer's stage at diagnosis and the patient's response to treatment. For patients with early-stage, non–muscle-invasive cancer that remains within the bladder lining, the 5-year survival rate is approximately 90% due to effective localized treatments such as surgery and intravesical therapy with agents such as Bacillus Calmette-Guérin.1 However, in cases of locally advanced or metastatic UC (la/mUC) where cancer has spread to distant organs, survival rates decline sharply, with 5-year survival dropping to approximately 8% to 10%.5Historically, for metastatic cases, the treatment mainstay is platinum-based chemotherapy and then immunotherapy agents, specifically immune checkpoint inhibitors. In cases where patients are ineligible for chemotherapy or have specific genetic alterations, targeted treatments such as the FGFR inhibitor erdafitinib (Balversa; Janssen Biotech, Inc) are considered.[6,7]

Recent advancements in ADCs such as EV have expanded options for patients with advanced disease. The development of these ADCs underscores the shift toward targeted therapy in UC, providing new options for patients with limited alternatives. Ongoing research focuses on optimizing ADC delivery, exploring combination regimens, and identifying novel targets to further improve outcomes in UC.

Nectin-4 and Biomarker Use in Urothelial Carcinoma

Nectin-4 is a transmembrane protein highly expressed in UC that plays roles in cellular adhesion, cell differentiation, and cell proliferation.8 Nectin-4, also known as PVRL4, is a protein encoded by NECTIN4 and belongs to a family of 4 immunoglobulin-like proteins, nectin-1 through nectin-4.9 Through its role in cell adhesion, nectin-4 expression may promote cellular proliferation, tumor growth, motility, and immune modulation.8,10Nectin-4 has been found to be highly expressed in not only UC but several other solid tumors, such as breast, lung, and head and neck cancers. Nectin-4 is also moderately expressed in human skin, likely resulting in the variety of observed cutaneous toxicities.10 Nectin-4 expression may result in increased sensitivity to certain molecular subtypes. In one retrospective study of more than 1900 specimens, nectin-4 expression was critical for EV-induced cell death, and luminal subtypes exhibited the highest expression of the 6 subtypes (luminal papillary, luminal nonspecified, luminal unstable, basal/squamous, stroma-rich, and neuroendocrine-like).[11]

Because nectin-4 expression is anticipated to be widespread in mUC, preselection for nectin-4 as a biomarker was only done for the phase 1 EV-101 trial (NCT02091999).12 When a majority of patients were found to have high nectin-4 expression (H-score > 150; Table 1), the protocol was amended to remove nectin-4 expression as an enrollment requirement. It subsequently has not been required in any other EV trial and is not tested for in clinical practice.[9,13]

TABLE 1. Clinical Trial Data of Enfortumab Vedotin

	EV-101 (NCT02091999)	EV-201 (NCT03219333)	EV-301 (NCT03474107)	EV-103 cohort K (NCT03288545)	EV-302 (NCT04223856)
Phase	Phase 1	Phase 2	Phase 3	Phase 1/2	Phase 3
Treatment	EV	EV	EV vs CT[a]	EV/pembro vs EV[b]	EV/pembro vs platinum CT
Place in therapy	Patients with mUC who progressed on 1 or more prior regimens with either CT and/or an anti–PD-1/PD-L1	Patients with la/mUC previously treated with platinum CT and anti-PD-1/PD-L1 inhibitor	Patients with la/mUC previously treated with platinum CT and anti–PD-1/PD-L1 inhibitor	Cisplatin-ineligible patients with previously untreated la/mUC	la/mUC previously untreated
H-score	290 (range, 0-300)	290 (range, 14-300)	Protocol amended; nectin-4 expression removed	262.5 (range, 0-300)	Combo arm: 280 (range, 0-300) CT arm: 270 (range, 0-300)
N	155	125	608	149	886
ORR	43%	44%	40.6% vs 17.9%	64.5% vs 45.2%	67.7% vs 44.4%
DOR (mo)	7.4	7.6	7.4 vs 8.1	NR vs 13.2	NR vs 7.0
Median follow-up (mo)	16.4	10.2	11.1	14.8 vs 15.0	17.2
Median PFS (mo)	5.4	5.8	5.6 vs 3.7	N/A	12.5 vs 6.3
HR for PFS (95% CI); *P* value	N/A	N/A	0.62 (0.51-0.75); *P* < .001	N/A	0.45 (0.38-0.54); *P* < .001)
Median OS (mo)	12.3	11.7	12.9 vs 9.0	22.3	31.5 vs 16.1
HR for OS (95% CI); *P* value	N/A	N/A	0.70 (0.56-0.89); *P* = .001	N/A	0.47 (0.38-0.58); *P* < .001

CT , chemotherapy; DOR, duration of response; EV, enfortumab vedotin; la/mUC , locally advanced or metastatic urothelial carcinoma; mUC , metastatic urothelial carcinoma; N/A, not available; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; pembro , pembrolizumab.

Pharmacokinetics and Pharmacodynamics

No significant differences in the pharmacokinetics of the ADC and unconjugated cytotoxic payload monomethyl auristatin E (MMAE) were noted following administration of EV as monotherapy or in combination with pembrolizumab (Keytruda; Merck & Co).14 EV is administered as a 30-minute intravenous infusion, with peak concentrations observed near the end of the infusion session. Peak concentration of the unconjugated MMAE was seen 2 days following EV infusion, and steady state concentrations were achieved after 1 treatment cycle. The volume of distribution of EV was 12.8 L at the estimated mean steady state.[14]

The ADC undergoes enzymatic catabolism, which leads to the production of small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. MMAE is released via proteolytic cleavage, whereas unconjugated MMAE is primarily metabolized via CYP3A4.14 ADC elimination displayed a half-life of approximately 3.6 days (87.2 hours).14 Elimination of MMAE appeared to be limited by its rate of release from EV and had a half-life of approximately 2.6 days (61.2 hours).15Although results were not reported in the EV package labeling, studies with brentuximab vedotin (Adcetris; Pfizer), another MMAE-containing ADC, demonstrated that the primary excretion route of MMAE cytotoxic payload was via feces.[15]

Regarding immunogenicity, the incidence of antitherapeutic antibodies was low (<3%) in clinical studies.15No significant pharmacokinetic differences in the components of EV were identified based on age, sex, race, renal impairment, or mild hepatic impairment (defined as total bilirubin of 1 to 1.5 times the upper limit of normal, or elevated aspartate aminotransferase and bilirubin within normal limits).[14]

Clinical Efficacy

EV has demonstrated significant clinical efficacy in the treatment of patients with mUC. EV's success story in locally advanced and mUC (la/mUC) spans multiple treatment lines, initially as a third-line single agent until eventually replacing cisplatin as first-line treatment for all patients with locally advanced or metastatic disease. This journey of EV's clinical efficacy in clinical trials spans EV-101, EV-201 (NCT03219333),16 EV-301 (NCT03474107),17EV-103/KEYNOTE-869 (NCT03288545)18 and EV-302/KEYNOTE-A39 (NCT04223856).19, 10, 20-23

EV-101 and EV-201

EV-101 was a phase 1 dose-escalation and expansion study that explored the safety, tolerability, and preliminary efficacy of EV in patients with advanced solid tumors, including UC. EV-101 established a recommended dose and provided early evidence of efficacy, particularly in patients with advanced UC who had prior treatment with immune checkpoint inhibitors.[10]

EV-201 was a phase 2, single-arm, multicenter trial. Cohort 1 included 125 patients previously treated with platinum chemotherapy and immunotherapy, and cohort 2 included 89 patients who were ineligible for platinum-based chemotherapy and had received immunotherapy only.20 This

cohort addressed a significant gap in treatment, as patients who are ineligible for platinum-based chemotherapy and have progressed on immune checkpoint inhibitors typically have limited therapeutic options.

EV was administered intravenously at a dose of 1.25 mg/kg (up to a maximum dose of 125 mg) on days 1, 8, and 15 of every 28-day cycle. Patients were treated until disease progression, development of unacceptable toxicity, investigator decision, consent withdrawal, start of a subsequent anticancer therapy, pregnancy, or study termination by the sponsor. The primary end point was objective response rate (ORR) assessed by blinded independent central review, and secondary end points included duration of response (DOR), disease control rate at week 14, progression-free survival (PFS), and overall survival (OS).7,13,20 The trial reported an ORR of 44% (95% CI, 35.1-53.2), with complete responses in 12% of patients and partial responses in 32%. The median DOR was reported at 7.6 months (95% CI, 6.3-not estimable), with a median treatment duration of 4.6 months. Furthermore, the median PFS was 5.8 months, and the median OS was 11.7 months, suggesting significant clinical benefit in patients.[20]

Overall, EV showed clinical efficacy and a manageable safety profile in patients with la/mUC who did not succeed with standard therapies, making it a significant advancement in the treatment landscape for this malignancy. Supported by these data, the FDA granted accelerated approval on December 18, 2019, to EV for adult patients with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or a PD-L1 inhibitor and a platinum-containing chemotherapy in the neoadjuvant/adjuvant, locally advanced, or metastatic setting.[24]

EV-301

The phase 3, open-label, randomized, multicenter trial EV-301 compared EV with standard chemotherapy (docetaxel, paclitaxel, or vinflunine) in patients with advanced UC previously treated with chemotherapy and a checkpoint inhibitor. The investigators reported a median OS of 12.88 months (95% CI, 10.6-15.2) for EV compared with 8.97 months (95% CI, 8.1-10.7) for chemotherapy (HR, 0.70; 95% CI, 0.56-0.89, P = .0014).21 This confirmed the survival benefit and supported the use of EV as a new standard of care in the second line and later for patients with advanced UC.21 Based on this study, on July 9, 2021, the FDA granted regular approval to EV for adult patients with la/mUC who have previously received a PD-1 or PD-L1 inhibitor and a platinum-containing chemotherapy, or who are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more lines of therapy.[25]

EV-103/KEYNOTE-869 and EV-302/KEYNOTE-A39

Both EV and pembrolizumab have shown clinical activity as single agents in late-line settings. In addition, preclinical data have shown that EV in combination with PD-1/PD-L1 inhibitors may enhance antitumor activity. Investigators have moved their attention to the potential combination in the first-line setting.22

Cohort K of the phase 1/2 EV-103/KEYNOTE-869 trial included patients who had not received prior systemic therapy and were ineligible for cisplatin-containing regimen. They were randomly

assigned to either the combination of EV and pembrolizumab (n=76) or EV alone (n=73). Approximately half of all patients with la/mUC are ineligible for cisplatin-based chemotherapy due to concomitant comorbidities such as impaired renal function, poor performance status, hearing loss, neuropathy, or heart failure.22 After a median follow-up of 14.8 months (95% CI, 12.9-17.3) in the combination arm and 15.0 months (95% CI, 12.7-17.4) in the monotherapy arm, the primary end point of ORR was 64.5% (95% CI, 52.7%-75.1%) in the combination group and 45.2% (95% CI, 33.5%-57.3%) in the enfortumab monotherapy group.22 The results of EV-103 represented a new therapeutic option as a first-line regimen for cisplatin-ineligible patients with la/mUC. On April 3, 2023, the FDA granted accelerated approval to EV with pembrolizumab for patients with la/mUC who are ineligible for regimens containing cisplatin.[26]

For platinum-eligible patients, platinum-based chemotherapy has been the standard of care for decades.23 EV-302/KEYNOTE-A39 was a phase 3, global, open-label, randomized trial of 886 patients with la/mUC who had had no prior systemic therapy. In the trial, patients received either combination EV plus pembrolizumab or platinum-based chemotherapy with gemcitabine and either cisplatin or carboplatin. The primary end points were PFS and OS.[23]

At a median follow-up of 17.2 months, the median PFS was 12.5 months (95% CI,10.4-16.6) in the combination arm vs 6.3 months (95% CI, 6.2-6.5) in the chemotherapy arm (HR, 0.45; 95% CI, 0.38-0.58; $P < .001$).23 The median OS was 31.5 months (95% CI, 25.4-not reached) in the combination arm vs 16.1 months (95% CI, 13.9-18.3) in the chemotherapy arm (HR, 0.47; 95% CI, 0.38-0.58; $P < .001$).23 An impressive 55% and 53% lower risk of disease progression or death in the combination arm compared with the chemotherapy arms, respectively, led to the FDA's regular approval of EV and pembrolizumab for the first-line treatment of patients with la/mUC on December 15, 2023.[27]

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