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Enfortumab vedotin and pembrolizumab as monotherapies and combination treatment in locally advanced or metastatic urothelial carcinoma: A narrative review

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Abstract

Background: Bladder cancer is the 10th most common cancer globally. The majority of bladder cancers are urothelial carcinomas (UCs), which, if locally advanced or metastatic, carry poor long-term prognosis. Cancer cells can evade the immune system by expressing the programmed cell death ligand 1 protein (PD-L1). Programmed cell death ligand 1 protein binds to programmed cell death protein 1 (PD-1) on T cells, inhibiting their antitumor action. Bladder tumor cells also overexpress nectin-4, a cell adhesion polypeptide that contributes to metastasis, worsening prognosis. Current platinum-based chemotherapy treatments are suboptimal. This review aimed to assess novel treatments for locally advanced or metastatic UC that specifically target PD-L1 or nectin-4, namely, the PD-1 inhibitor pembrolizumab and the anti–nectin-4 antibody-drug conjugate enfortumab vedotin (EV).

Materials and methods: Relevant English-language peer-reviewed articles and conference abstracts from the last 5 years were identified through MEDLINE and EMBASE database searches. A narrative review was performed, with key results outlined below.

Results: Pembrolizumab was demonstrated to be superior to chemotherapy as a second-line treatment for platinum-unresponsive participants in the KEYNOTE-045 trial, resulting in its Food and Drug Administration (FDA) approval. Enfortumab vedotin therapy resulted in superior outcomes compared with chemotherapy in the EV-301 trial, resulting in FDA approval for its use for patients with locally advanced or metastatic UC who had previously undergone treatment with platinum-based chemotherapy and PD-1/PD-L1 inhibitors. Positive preliminary results for pembrolizumab and EV combination therapy have led to FDA approval in patients with locally advanced or metastatic UC who are not eligible for platinum chemotherapy.

Conclusions: Pembrolizumab and EV represent novel treatment options for patients with locally advanced or metastatic UC with documented superior outcomes and tolerability as compared with standard chemotherapy.

Keywords: Urothelial carcinoma; Bladder; Review; Antibody-drug conjugate; Checkpoint inhibitor

1. Introduction

According to the World Health Organization, bladder cancer was the 10th most common cancer globally in 2020.[1] In the United Kingdom, approximately 5500 deaths are attributed annually to bladder cancer, making it the 10th most lethal cancer.[2]

Most bladder cancers are histologically defined as urothelial carcinomas (UCs).[3] Urothelial carcinoma is classified using the tumor-node-metastasis staging system. It can be further stratified as non–muscle-invasive, if the tumor invades the urothelium or the lamina propria, which applies to approximately 75% of patients at presentation, or muscle-invasive, accounting for the remaining 25% of patients.[4–6] Bladder cancer that has invaded the deep muscularis propria and extended to the perivesical fat or beyond qualifies as locally advanced. The presence of any pelvic nodal, visceral, or distant tumor metastases is defined as metastatic disease.[7]

Non–muscle-invasive bladder cancer treated with curative intent has a promising prognosis, with a 5-year overall survival (OS) of 90%. In contrast, OS for muscle-invasive bladder cancer is 60% to 70%, and locally advanced or metastatic disease confers an OS of only 5% to 30%.[8] Furthermore, bladder cancer has a high recurrence rate of more than 50% within 2 years of a radical cystectomy.[9] The current standard treatment for patients with muscle-invasive bladder cancer is neoadjuvant cisplatin-based chemotherapy before radical therapy, which may include cystectomy or radiotherapy.[10] However, between 20% and 50% of patients are ineligible for cisplatin chemotherapy treatment because of age and poor performance status, declining renal function, or preexisting comorbidities that would increase the risk of toxicity. In such patients, radical cystectomy remains the management of choice, with no alternative to neoadjuvant cisplatin-based chemotherapy yet identified.[11]

Treatment choices for UC become more limited and less successful as the cancer progresses, with locally advanced and metastatic UC considered incurable. Cisplatin-based chemotherapy is the first-line treatment option for these patients,[12] or carboplatin and gemcitabine combination therapy for cisplatin-ineligible patients.[8] Carboplatin-containing chemotherapy is not equivalent

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to cisplatin-based chemotherapy, however, as it achieves a lower complete response and OS.[12] For advanced UC, the superior effectiveness of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) combination therapy is offset by its severe adverse effects and mortality risk. Alternative regimens have been developed, such as combination gemcitabine and cisplatin therapy and dose-dense fashion MVAC. Although both are better tolerated and noninferior to MVAC, combination treatment had OS of 12 to 14 months and 5-year survival rates of only 10% to 15%.[8,12] Therefore, new approaches for treating locally advanced and metastatic are still being sought.

We aimed to review the molecular basis, rationale, and clinical evidence for novel treatments targeting crucial mutations for tumorigenesis in unresectable locally advanced or metastatic UC. Specifically, we reviewed the evidence for the checkpoint inhibitor pembrolizumab, the antibody-drug conjugate (ADC) enfortumab vedotin (EV), and the combination of these 2 drugs.

2. Materials and methods

This literature review was conducted by searching EMBASE and MEDLINE/PubMed databases from January 11 to September 21, 2022, using the search terms shown in Appendix 1 (http://links.lww.com/CURRUROL/A35). Additional publications were identified via searches of the reference lists of examined articles. Published peer-reviewed articles and conference abstracts from the last 5 years written in English were assessed independently by 3 reviewers and selected for review according to content relevance. This review was conducted in accordance with guidance outlined in the Scale for the Assessment of Narrative Review Articles.[13]

3. Results

3.1. Immunotherapy: Pembrolizumab

3.1.1. Mechanism of action Immunotherapy has revolutionized cancer treatment, improving progression-free survival (PFS) and OS in cancer patients.[14] Immunotherapy relies on stimulating the immune system to identify and subsequently eliminate threats, including malignant cells. T cells play a major role in the success of immunotherapy, because of their ability to differentiate between healthy and malignant cells via tumor antigens expressed on the cell surface of malignant cells.[15]

T cells themselves express molecules on their surface called checkpoint proteins. These include programmed cell death protein 1 (PD-1),[15,16] which targets and eliminates "nonself" cells including cells of foreign origin, such as externally acquired microbes or virally transformed cells, in addition to cancerous cells identified via tumor antigens on their surface.[17] However, cancer cells have developed mechanisms that allow them to evade the immune system. They can express programmed cell death ligand 1 (PD-L1) protein, which binds to PD-1, inhibiting the cytotoxic activity of T cells and allowing cancer cells to multiply unchecked.[15] Blocking either PD-1 or PD-L1 will inhibit the interaction between T cells and tumor cells, allowing T cells to mount an immune response against cancer cells.[17] The mechanism of action of PD-1/PD-L1 interaction and inhibition is shown in Figure 1.

Therapies exploiting this mechanism include the monoclonal antibodies (mAbs) atezolizumab, nivolumab, avelumab, durvalumab, and pembrolizumab.[19] They are all approved by the US Food and Drug Administration (FDA) for the treatment of metastatic UC. Atezolizumab, an anti–PD-L1 mAb, demonstrated an objective response rate (ORR) of 14.8% and median OS of 7.9 months. Durvalumab, also an anti–PD-L1 antibody, had an overall response rate of 31%. Nivolumab, an anti–PD-1 antibody, had an ORR of 20%. Avelumab, an anti–PD-L1 antibody, had an ORR of 18.2% with a median OS of 13.7 months.[19] Finally, pembrolizumab, a mAb against PD-1,[20] currently licensed by the FDA and the European Medicines Agency,[12,21,22] demonstrated a median OS of 10.3 months and an ORR of 21.1%. Pembrolizumab was the first mAb to demonstrate a survival advantage compared with standard chemotherapy.[23]

3.1.2. Clinical trials Pembrolizumab, previously approved for metastatic melanoma, was investigated as a therapeutic intervention for UC in the phase 3 KEYNOTE-045 (NCT02256436) trial.[24,25] During the KEYNOTE-045 trial, pembrolizumab and chemotherapy were compared as second-line therapy for participants with metastatic or advanced UC that recurred or progressed following platinum-based chemotherapy. The 2 coprimary endpoints were OS and PFS. Overall survival was defined as the time from randomization of a participant until death, and PFS as the time from randomization until disease progression or death. A total of 542 participants were randomized to receive either intravenous pembrolizumab (n = 270) or chemotherapy (n = 272).

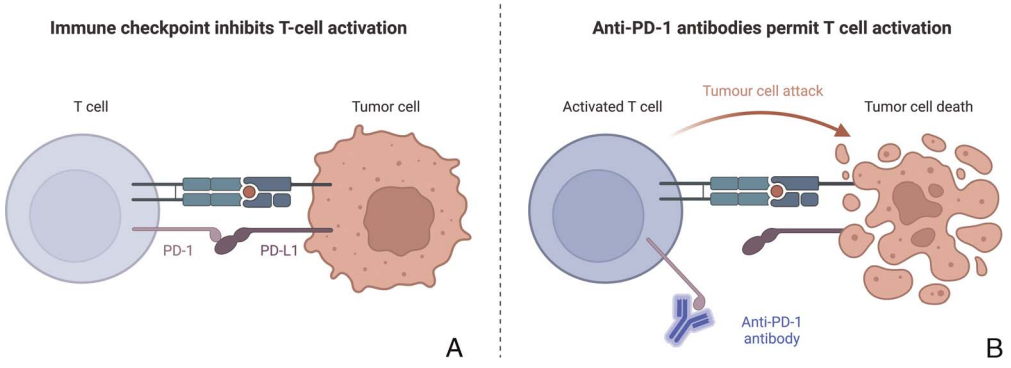

Figure 1. The mechanism of action of PD-1/PD-L1 interaction and PD-1/PD-L1 inhibition. (A) Checkpoint protein PD-1 on T cells, binding to PD-L1 on tumor cells, inhibiting cytotoxic action of T cells. (B) Binding of PD-1 to PD-L1 inhibited by immune checkpoint inhibitor, that is, monoclonal antibody against PD-1 such as pembrolizumab, enabling cytotoxic T cells to attack the tumor cells. Adapted from NIH.[18] Developed using Biorender. NIH = National Institutes of Health; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand protein 1.

Overall, 344 participants receiving pembrolizumab achieved longer OS as compared with those receiving chemotherapy ($p = 0.002$). Overall survival at 12 months was 43.9% and 30.7% for the pembrolizumab and chemotherapy groups, respectively. There was no significant difference in PFS between the 2 groups. Objective response rate, defined as the proportion of participants who had a complete or partial response to treatment according to the revised Response Evaluation Criteria in Solid Tumors (RECIST),[26] was significantly higher ($p = 0.001$) in the pembrolizumab (21.1%) than in the chemotherapy group (11.4%). Participants in the pembrolizumab group had fewer treatment-related adverse effects with a lower frequency of severe, life-threatening, and fatal adverse effects compared with those in the chemotherapy group (Table 1). Adverse effects were categorized according to the National Cancer Institute Common Terminology Criteria for Adverse Events. Notably, the most common adverse effects in patients taking pembrolizumab were pruritus (19.5%), fatigue (13.9%), and nausea (10.9%).

In summary, the pembrolizumab cohort had a statistically significant better ORR than the chemotherapy cohort while also experiencing fewer and less severe adverse events. Based on the results of the KEYNOTE-045 trial, pembrolizumab received FDA approval for the treatment of patients with locally advanced or metastatic UC with progression of their condition, while or after being treated with platinum-containing chemotherapy or within 1 year of platinum-containing neoadjuvant or adjuvant chemotherapy treatment.[32]

A subsequent article reporting the 2-year follow-up of the KEYNOTE-045 trial showed that OS remained higher in participants who received pembrolizumab.[24] In addition, after 24 months, PFS was 4 times higher (12.4%) among those who received pembrolizumab compared with those receiving chemotherapy (3.0%); however, the difference in PFS between the 2 groups was not statistically significant (Table 2).

KEYNOTE-045 was a randomized phase 3 trial that compared chemotherapy with pembrolizumab in participants with metastatic or locally advanced UC that recurred or progressed following platinum-based chemotherapy.[24,25] A subsequent phase 2 trial, KEYNOTE-052 (NCT02335424), investigated pembrolizumab as a first-line treatment in 370 cisplatin-ineligible patients with locally advanced, unresectable, or metastatic UC.[27,28] KEYNOTE-052 was a single-group assignment trial, with all participants receiving 200 mg of pembrolizumab every 3 weeks for up to 24 months. Objective response rate was the primary endpoint, and secondary endpoints were duration of response (DOR), PFS, OS, safety, and tolerability. Overall, ORR was 28.6%, and median DOR was 30.1 months (Table 2). Two hundred seventy-seven deaths (74.9%) occurred at a median of 11.3 months. One-year OS and 2-year OS were 46.9% and 31.2%, respectively. Lastly, median PFS was 2.2 months. Following the data cutoff, treatment was completed for 43 participants (11.6%), ongoing for 2 participants (0.6%), and discontinued for 325 participants (87.8%). Discontinuation predominantly occurred because of tumor progression (59.2%) or occurrence of adverse effects (16.2%). Two hundred forty-nine participants (67.3%) had treatment-related adverse effects, the most frequent being fatigue (18.1%), pruritus (17.8%), and rash (11.6%). Of all adverse effects, 77 (20.8%) were category ≥3, primarily fatigue (2.4%), colitis (1.9%), and muscle weakness (1.4%).

The study characteristics, outcomes, and adverse effect profiles of the KEYNOTE-045 and KEYNOTE-052 clinical trials are summarized in Tables 1, 2, and 3, respectively.

3.2. Antibody-drug conjugates: Enfortumab vedotin

3.2.1. Mechanism of action Another type of novel agent being explored for the treatment of locally advanced and metastatic UC is ADC. These comprised an antibody that binds to specific antigens expressed on tumor cells, an active cytotoxic drug, referred to as the "payload" and a linker molecule that conjugates the antibody to the payload.[35,36] These drugs allow targeting of cytotoxic drugs to specific tumor cells, minimizing the exposure of normal cells, preserving healthy tissue, and reducing adverse effects. The first ADC to gain FDA approval in 2019 for use in patients with UC was EV, which consists of a monoclonal antibody targeted against nectin-4.[37]

Nectin-4 is a transmembrane polypeptide, 1 of 4 members of the nectin family, which are Ca^{2+}-independent immunoglobulin-like cell adhesion molecules.[38] These molecules are expressed in healthy tissue and play a crucial role in creating and maintaining adherence junctions (in combination with cadherins), cell movement, proliferation, differentiation, and polarization.[35,38] Overexpression of nectin-4, however, is associated with cancers of the bladder, breast, lung, ovaries, and pancreas.[35] In addition to its role in cancer proliferation, angiogenesis, metastasis, and cell movement, nectin-4 is a biomarker for carcinogenesis and tumor relapse.[39]

The antibody part of EV is a fully humanized mAb that targets the extracellular domain of nectin-4 on cancer cells, and the payload is monomethyl auristatin E (MMAE), a potent antimitotic drug, which is conjugated to the anti–nectin-4 via a protease-cleavable linker. The detailed mechanism of action of EV is described in Figure 2.[35,36] Monomethyl auristatin E can also penetrate plasma membranes,

Table 1

Safety profile associated with clinical trials.

	Treatment-related AE		Grade ≥ 3 AE		Events leading to discontinuation of treatment		Events leading to death	
Clinical trial	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator	Intervention	Comparator
KEYNOTE-045[24] (NCT02256436)	162 (60.9)	230 (90.2)	40 (15.0)	126 (49.4)	15 (5.6)	28 (11.0)	4 (1.5)	4 (1.5)
KEYNOTE-052[27,28] (NCT02335424)	249 (67.3)		52 (20.8)		34 (9.2)		1 (0.3)	
EV-101[29] (NCT02091999)	145 (94.0)		53 (34.0)		16 (10.0)		4 (3)	
EV-201* (NCT03219333)								
Cohort 1	117 (93.6)		70 (56.0)		7 (5.6)		0 (0)	
Cohort 2	86 (96.6)		49 (55.1)		14 (15.7)		3 (3.4)	
EV-301[30] (NCT03474107)	278 (93.9)	267 (91.8)	152 (51.4)	145 (49.8)	51 (17.2)	51 (17.5)	21 (7.1)	16 (5.5)
EV-103[31] (NCT03288545)	7 (15.6)				11 (24.4)		1 (2.2)	

*Data extracted from the NCT03219333.

Events leading to either discontinuation of treatment or death are treatment related; numbers are represented as n (%).

AE = adverse effects; EV = enfortumab vedotin.

Table 2

Outcomes associated with clinical trials.

	OS, mo			PFS, mo			ORR, %			DOR, mo	
Clinical trial	**Intervention**	**Control**	***p***	**Intervention**	**Control**	***p***	**Intervention**	**Control**	***p***	**Intervention**	**Control**
KEYNOTE-045[24] (NCT02256436)	10.3	7.4	0.00224	21	3.3	0.41648	21.1 9.3 CR	11 2.9 CR	0.0007	N/A	4.4*
KEYNOTE-052† (NCT02335424)		11.3			2.2			28.6 8.9 CR			30.1
EV-101‡ (NCT02091999)		12.3			5.4			43 5 CR			7.4
EV-201[33,34] (NCT03219333)											
Cohort 1		12.4			5.8			44 12 CR			7.6
Cohort 2		14.7			5.8			51.7 20 CR			10.9
EV-301§ (NCT03474107)	12.88	8.97	0.00142	5.55	3.71	<0.00001	40.6 4.9 CR	17.9 2.7 CR	<0.001	7.39	8.11
EV-103[31] (NCT03288545)		26.1			12.3	73.3 15.6 CR					25.6

CR = complete response; DOR = duration of response; EV = enfortumab vedotin; N/A = not available; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.
*Intervention: pembrolizumab.
†Follow-ups: 6-month OS: 67%, PFS: 33.4%; 12-month OS: 46.9%, PFS: 22%.
‡Part A.
§Intervention: EV.

enabling it to diffuse out of the plasma membrane of targeted tumor cells and into neighboring tumor cells, regardless of whether nectin-4 is overexpressed, a phenomenon known as bystander killing.[35]

3.2.2. Clinical trials Enfortumab vedotin was first assessed in a phase 1 dose escalation/expansion trial, EV-101 (NCT02091999),[29] which evaluated safety and pharmacokinetics as primary outcomes, and antitumor activity, ORR, DOR, PFS, and OS as secondary outcomes. The trial enrolled 201 participants with nectin-4–positive tumors, of which 155 had histologically confirmed metastatic UC. Before the trial, all participants were treated with ≥1 chemotherapy agent and/or a PD-1/PD-L1 inhibitor. Specifically, 149 participants (96%) received platinum-based chemotherapy, 112 (72%) had anti–PD-L1 inhibitors, and 45 (29%) had ≥3 therapies. Among participants with metastatic UC, 112 received intravenous EV at a dose of 1.25 mg/kg, with the remaining metastatic UC participants treated with doses based on a dose escalation protocol as follows: 0.5 mg/kg (n = 2), 0.75 mg/kg (n = 14), and 1.0 mg/kg (n = 27).

Table 3

Comparison of trials assessing pembrolizumab, EV, and their combination for UC.

Clinical trial	**Population**	**Study characteristics**	**Intervention**	**Comparators**
KEYNOTE-045 (NCT02256436)	Locally advanced/unresectable or metastatic UC (recurred or progressed following platinum-based chemotherapy, n = 542)	Phase 3 Parallel assignment Randomized	Pembrolizumab 200 mg (n = 255) Day 1 of each Q3W	Paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) or vinflunine (320 mg/m^2) (n = 266) Day 1 of each Q3W
KEYNOTE-052 (NCT02335424)	Advanced/unresectable UC or metastatic UC, ineligible for cisplatin-based therapy, n = 374	Phase 2 Single assignment	Pembrolizumab 200 mg (n = 370) Day 1 of each Q3W	N/A
EV-101 (NCT02091999)	Histologically confirmed malignant solid tumors (excluding sarcomas), resistant or have recurred (n = 213)	Phase 1 parallel assignment Nonrandomized	EV increasing weight-based dose (0.5, 0.75, 1.0, 1.25 mg/kg; n = 155) 30-min infusion on days 1, 8, and 15 of a 28-d cycle	N/A
EV-201 (NCT03219333)	Locally advanced or metastatic UC cohort 1: previously received a checkpoint inhibitor and previously received platinum-containing chemotherapy, n = 128; cohort 2: previously received a checkpoint inhibitor and were platinum-naive and cisplatin-ineligible, n = 91	Phase 2 Single assignment	EV 1.25 mg/kg on days 1, 8, and 15 every 28 d (cohort 1: n = 125; cohort 2: n = 89)	N/A
EV-301 (NCT03474107)	Locally advanced or metastatic UC (received a platinum-containing chemotherapy and had experienced disease progression or relapse during or following treatment with PD-1 or PD-L1 inhibitors) (n = 608)	Phase 3 Parallel assignment Randomized	EV 1.25 mg/kg on days 1, 8 and 15 every 28 d (n = 296)	Paclitaxel (175 mg/m^2) or docetaxel (75 mg/m^2) or vinflunine (320 mg/m^2) (n = 285) Day 1 of each Q3W
EV-103 (NCT03288545)	Locally advanced or metastatic UC (cisplatin-ineligible) (n = 457)	Phase 1b/2 Sequential-assignment Multicohort Randomized	EV (1.25 mg/kg on days 1 and 8 every 21 d) and pembrolizumab (200 mg on day 1 every 21 d, given after EV) (n = 45)	N/A

EV = enfortumab vedotin; N/A = not available; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand protein 1; Q3W = every 3 weeks; UC = urothelial carcinoma.

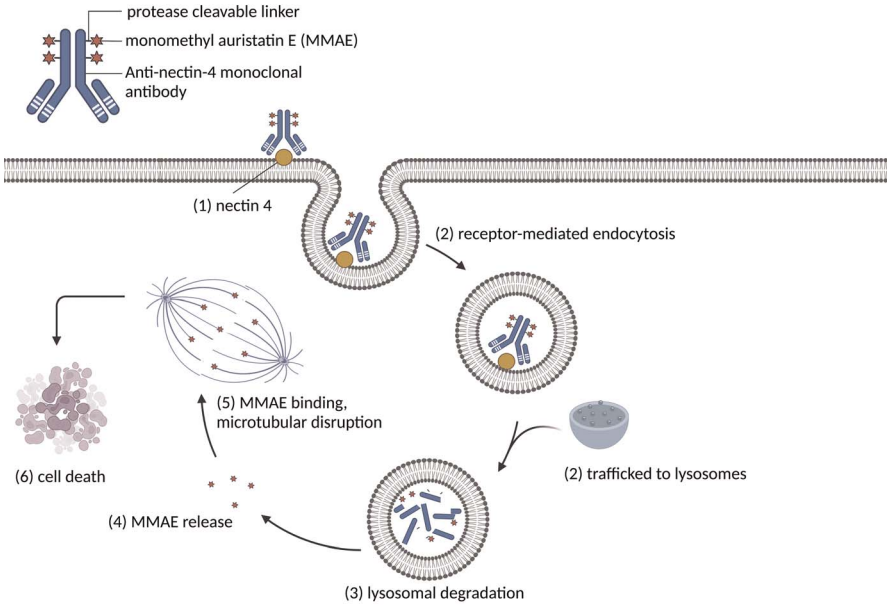

Figure 2. The mechanism of action of EV, an anti–nectin-4 monoclonal antibody. The antibody part of EV targets the extracellular domain of nectin-4, a transmembrane polypeptide overexpressed on cancer cells. The payload is MMAE, a potent antimitotic drug, which is conjugated to the anti–nectin-4 monoclonal antibody via a protease-cleavable linker. After administration, EV binds to the antigen nectin-4, and receptor-mediated endocytosis occurs (1). The complex gets trafficked intracellularly to the lysosomes (2), where the linker gets degraded (3). Following the degradation, MMAE gets released (4), which leads to microtubular disruption (5), ultimately ending with cell cycle arrest and apoptosis of the tumor cell (6). Adapted from Heath and Rosenberg.[35] Developed using Biorender. EV = enfortumab vedotin; mAb = monoclonal antibody; MMAE = monomethyl auristatin E.

Enfortumab vedotin showed linear pharmacokinetics for doses of 0.5 to 1.25 mg/kg; however, MMAE levels accounted for less than 0.1% of the EV serum concentration, suggesting that the ADC formulation is yet to be optimized. One hundred forty-five participants (94%) treated with EV experienced at least 1 adverse effect. Fatigue (53%), peripheral neuropathy (49%), alopecia (46%), rash (45%), and decreased appetite (42%) were most commonly reported. Fifty-three participants experienced grade ≥3 adverse effects, including 16 participants where the adverse event resulted in treatment discontinuation (Table 1). The recommended dose, developed according to tolerability and maintenance of antitumor activity, was 1.25 mg/kg on days 1, 8, and 15 of a 28-day cycle. Of the 112 participants with metastatic UC treated with EV 1.25 mg/kg dose, 48 responded to treatment (Table 2), with a median OS and PFS of 12.3 and 5.4 months, respectively.

A phase 2, international, single-arm trial (EV-201, NCT03219333) demonstrated the efficacy and antitumor activity of EV.[33,34] This trial included participants with metastatic UC who had previously received checkpoint inhibitor treatment who were then assigned into 2 cohorts, depending on their prior exposure to platinum-containing chemotherapy. The first cohort included 128 participants who had previously received platinum-containing chemotherapy, whereas the second cohort comprised 91 participants who were platinum-naive and cisplatin-ineligible. All participants were treated with EV, as summarized in Table 3.

Outcomes were consistent with those reported in the EV-101 trial.[29] Specifically, in cohort 1 (n = 125), the ORR was 44%, whereas the median OS and DOR were 11.7 and 7.6 months, respectively, and PFS was 5.8 months. Common adverse effects were fatigue (50%), peripheral neuropathy (50%), alopecia (49%), rash (48%), and decreased appetite (44%). No treatment-related deaths were reported during the 30-day safety reporting period; however, 1 death occurred outside of this period because of interstitial lung disease.[33] In cohort 2 (n = 89), the ORR was higher compared with cohort 1 (Table 2). Median OS and DOR were also longer at 14.7 and 10.9 months, respectively, whereas PFS was constant at 5.8 months. Commonly reported adverse effects were similar to those in cohort 1 (Table 1). Notably, 4 deaths related to treatment were reported: 3 within 30 days of the first dose and 1 more than 30 days after the last dose.[34] Because of the favorable results of EV-201, EV gained accelerated approval by the FDA in December 2019 for patients with metastatic or locally advanced UC who have had prior treatment with a PD-1/PD-L1 inhibitor and a platinum-based chemotherapy.[37] Nonetheless, the single-arm design of this trial limits the certainty of the outcomes reported, as no direct comparison was made with chemotherapy treatment.

Subsequently, a global, open-label, randomized, multicenter phase 3 trial (EV-301, NCT03474107) provided evidence that EV significantly improved survival compared with standard chemotherapy.[30] The primary endpoint of EV-301 was to assess OS, whereas the secondary endpoints were to explore PFS and response according to RECIST.[26] Participants were randomly assigned to receive EV (n = 296) or chemotherapy (n = 291), as presented in Table 3. In the EV group, the median OS was 12.9 and 9 months in the intervention and chemotherapy groups, respectively, with 51.5% of participants in the EV group remaining alive at 12 months compared with 39.2% in the chemotherapy group. After a median follow-up of 11.1 months, the EV group had superior OS ($p = 0.001$) compared with the chemotherapy group, with a 30% lower risk of death. In addition, median PFS was longer ($p < 0.001$) in the EV group (5.6 months) compared with the chemotherapy group (3.7 months). Objective response rate was also superior in the EV group; however, DOR was lower in the EV group compared with the chemotherapy group (Table 2). The rates of

treatment-related adverse effects and treatment-related adverse effects of grade ≥3 were similar for both groups, as detailed in Table 1. Nonetheless, when the adverse effects were adjusted for treatment exposure, the rate was lower in the EV group at 2.4 events per participant-year, compared with 4.3 events per participant-year in the chemotherapy group. The most reported EV-related adverse events were rash (43.9%), peripheral neuropathy (46.3%), and alopecia (45.3%). Seven deaths related to treatment were reported in the EV group and 3 in the chemotherapy group.

These findings confirmed the favorable outcomes of the EV-201 trial and resulted in EV gaining regular approval by the FDA in July 2021 for patients with locally advanced or metastatic UC who have been previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors or are unsuitable for platinum-based chemotherapy treatment but have received at least 1 other treatment.[40]

3.3. Combination therapy: Enfortumab vedotin and pembrolizumab

3.3.1. Mechanism of action Because of the efficacy of EV and pembrolizumab as monotherapies and their distinct mechanisms of action, combined with favorable preclinical evidence, these 2 drugs have also been investigated as a combination therapy. This combination is hypothesized to work sequentially rather than synergistically, as illustrated in Figure 3. Specifically, the payload of EV, MMAE, triggers 3 established hallmarks of immunogenic cell death: surface expression of heat shock protein 70 and calreticulin and stimulation of ATF6, a transcription factor. Immunogenic cell death is a distinctive type of cell death that activates the adaptive immune system against specific antigens and, in the context of tumor cells, results in the presentation of tumor antigens to T cells. T cells then target the cancer cells, a response that is magnified when PD-1/PD-L1 inhibitors are used concurrently, as these checkpoint inhibitors ensure that tumor cells expressing PD-L1 will not evade the immune system.[35,41]

3.3.2. Clinical trials EV-103 is a phase 1b multicohort study (NCT03288545), ongoing and estimated to be completed in December 2026, investigating the safety and efficacy of combined pembrolizumab and EV treatment.[31] Participants are randomly allocated to a treatment cohort, with all cohorts summarized in Appendix 2 (http://links.lww.com/CURROL/A35). The primary objective is to assess the safety of this combination, whereas the secondary objectives are to ascertain the optimum dose of EV, antitumor activity, disease control rate, DOR, PFS, and OS. Disease control rate is defined as the proportion of participants with a complete response, partial response, or stable disease as per RECIST.[26]

Preliminary results from cisplatin-ineligible participants with locally advanced or metastatic UC assigned to cohort A have been published as abstracts in 2019,[42] 2020,[43] and 2021[44] and as an article in 2022.[31] The positive 2019 interim results led to the FDA granting "breakthrough therapy" designation to this combination therapy in February 2020, as a first-line treatment for cisplatin-ineligible patients with inoperable, locally advanced, or metastatic UC.[45]

Overall, 45 participants were allocated to cohort A, receiving 1.25 mg/kg of EV plus 200 mg pembrolizumab (Table 3). A median of 9 treatment cycles were administered. At data cutoff, 21 patients were still enrolled in the study, 7 on treatment and 14 in follow-up. The efficacy of the combination treatment was particularly encouraging. The disease control rate and ORR were 93.3% and 73.3%, respectively, with swift responses to treatment demonstrated at a median of 2.1 months after treatment initiation. Crucially, the combination treatment provided a durable response of a median of 25.6 months, with median PFS and OS of 12.3 and 26.1 months, respectively.[31] Therefore, data from the combination of EV and pembrolizumab were promising, suggesting an effective platinum-free alternative for cisplatin-ineligible patients.

Moreover, the adverse effect profile of this combination treatment was manageable, with adverse effects observed similar to those of EV and pembrolizumab monotherapies. Nonetheless, 14 patients required a dose reduction, and 11 discontinued treatment because of treatment-related adverse effects, whereas 1 patient died because of multiple organ dysfunction system, classified as treatment-related. An overview of the safety profile of the combination therapy can be found in Table 1.

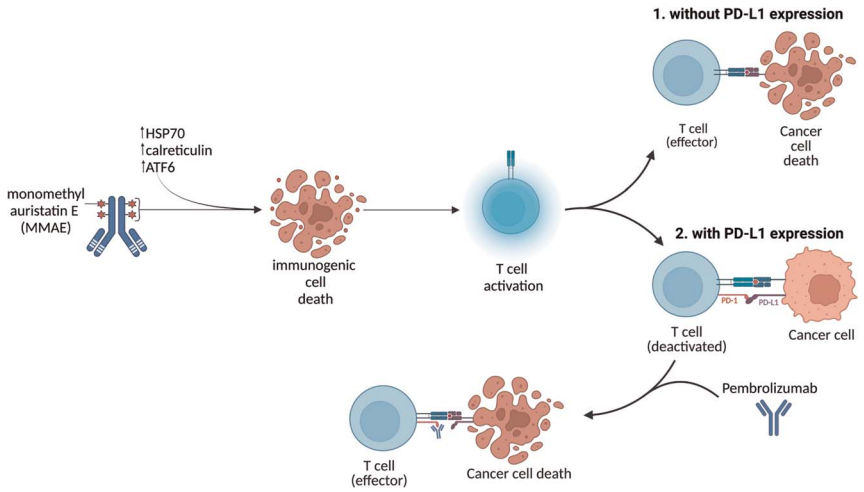

Figure 3. The hypothesized sequential mechanism of action of pembrolizumab and enfortumab vedotin. Monomethyl auristatin E triggers immunogenic cell death, a distinctive type of cell death that results in the presentation of tumor antigens to T cells, allowing T cells to target cancer cells. Cancer cells, however, could express PD-L1, which would bind to T-cell PD-1 and inhibit this immune-mediated cytotoxic action. PD-1 inhibitor pembrolizumab could prevent the PD-L1–mediated T-cell deactivation, securing the cytotoxic activity of T cells, despite tumor cell PD-L1 expression. Developed using Biorender. ATF = activating transcription factor; HSP = heat shock protein; PD-1 = programmed cell death protein 1; PD-L1 = programmed cell death ligand protein 1.

4. Discussion

Locally advanced or metastatic UC is an aggressive disease with poor long-term survival.[46] First-line treatment was defined as cisplatin-based combination chemotherapy over 20 years ago. However, OS and PFS after such therapy are disappointing, 15 months and 8 months, respectively, with a 5-year survival rate of only 14%.[47] Furthermore, patients are often elderly with multiple comorbidities and declining renal function, increasing the risk of toxicity from cisplatin-based chemotherapies. Given this context, the need for novel therapies for this fatal disease is evident. Currently, several new compounds have been recently approved for treatment of locally advanced or metastatic UC, namely, checkpoint inhibitors and ADCs. Here, we review up-to-date evidence of monotherapy with the checkpoint inhibitor pembrolizumab and monotherapy with the ADC EV, as well as the novel combination of the 2 drugs.

The phase 3 trial KEYNOTE-045 demonstrated pembrolizumab to have superior OS and a more manageable adverse effect profile compared with standard chemotherapy, as second-line treatment.[24] The phase 2 trial named KEYNOTE-052 showed that pembrolizumab is a suitable first-line treatment for patients who are cisplatin-ineligible. However, efficacy outcomes of this trial need to be interpreted carefully because of the open-label nature of the study and lack of a comparator group. In addition, participants in this cohort were elderly (49% were ≥75 years old) with poor prognostic factors and numerous comorbidities, resulting in unexceptional outcomes for ORR and PFS.[27,28] The phase 2 trial EV-201 investigated EV as a treatment option for participants with metastatic UC who had received checkpoint inhibitor treatment and were previously either platinum-treated or platinum-ineligible.[33,34] It showed that EV resulted in the highest response rate for participants who were cisplatin-ineligible compared with any other single agent, making EV an excellent treatment choice for such participants who have failed to respond to first-line PD-1/PD-L1 inhibitors. Nevertheless, because of the lack of a comparator group, efficacy results from EV-201 cannot be considered conclusive.[33,34] Consequently, a phase 3 open-label, randomized trial, EV-301, was undertaken, which validated EV-201 outcomes and indicated superiority of EV compared with chemotherapy in participants previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors, with similar treatment-related adverse effects.[30] Despite this, a key limitation of the EV-301 trial was the lack of participant and investigator blinding. As such, there is still a need for further phase 3 double-blind trials.

Both pembrolizumab and EV monotherapies resulted in superior outcomes compared with chemotherapy.[24,30] Nevertheless, the 2021 European Society for Medical Oncology clinical practice guidelines[48] still recommend cisplatin-containing combination chemotherapy as a first-line treatment for advanced or metastatic UC in cisplatin-eligible patients and carboplatin with gemcitabine for cisplatin-ineligible patients. Treatment with pembrolizumab is recommended as second-line therapy and treatment with EV as third-line therapy for advanced and metastatic UC. Interestingly, the National Institute for Health and Care Excellence acknowledges that pembrolizumab is a life-extending treatment for patients with locally advanced or metastatic UC but fails to meet cost-effectiveness considerations, and it is thus not recommended.[49]

The cost-effectiveness of pembrolizumab has been assessed using the incremental cost-effectiveness ratio (ICER), indicating the additional cost compared with chemotherapy as a second-line treatment for advanced UC. The ICER differs globally because of different drug acquisition costs and but was approximately $100,000 per quality-adjusted life-year (QALY) in the United States, United Kingdom, Canada, and Australia. However, only the United States considered pembrolizumab to be cost-effective.[50] Although the manufacturing company of pembrolizumab calculated an ICER of £37,000 per QALY compared with carboplatin plus gemcitabine for patients with advanced UC who were unsuitable for cisplatin-based therapy, an evidence review for a National Institute for Health and Care Excellence appraisal estimated the ICER to be approximately £65,000 per QALY gained. However, an ICER of double this figure per QALY gained was deemed plausible because of limited long-term survival outcome data.[51] Comparisons of pembrolizumab compared with taxanes or vinflunine monotherapies were between €50,000 and €80,000 for second-line treatment for advanced UC.[52] For EV, only one completed cost-effective analysis has been reported that compared EV to chemotherapy in advanced UC for patients who have already been treated with PD-1 or PD-L1 inhibitors. The ICER was considerably higher than for pembrolizumab, at more than $2 million, such that although EV may be efficacious, it is not cost-effective.[53] There have been no cost-effective analyses for the combination treatment of EV and pembrolizumab, but it seems likely that costs would be high.

Further phase 3 randomized double-blind trials may still be required for these novel agents to be provided in a first-line setting or, in some instances, to justify the cost implications for patients with advanced or metastatic UC.

Because of the superior outcomes of EV and pembrolizumab over chemotherapy alone, the need to investigate combination therapy with both drugs has become apparent. This is being explored by EV-103, a phase 1b/2 10-cohort trial.[31,42–44] Outcomes of cohort A surpass reported outcomes of either drug monotherapy, confirming that the combination of pembrolizumab and EV remains an optimistic first-line therapy in participants with locally advanced or metastatic UC ineligible for cisplatin chemotherapy.[31] The 2021 European Society for Medical Oncology clinical practice guidelines[48] acknowledged that the drug combination outcomes are encouraging, but did not provide a recommendation because of the small sample size (n = 45). Furthermore, the combination therapy is being investigated as a first-line treatment for cisplatin-eligible patients in a phase 3 randomized trial.[54] This trial (NCT04223856), with a target enrolment of 990 participants and with PFS and OS as primary outcomes, will compare combination treatment versus chemotherapy versus combination treatment plus chemotherapy and is estimated to be completed in November 2023.

Translating these results to clinical care, pembrolizumab and EV may represent a potentially novel treatment option for patients with locally advanced or metastatic UC, especially those who are cisplatin-ineligible. However, no true conclusions can be drawn until the EV-103 and EV-302 trials are completed.[44,54]

Because of the innovation and broader acceptance of genomic sequencing in a clinical setting, there is now a comprehensive understanding of the mutation types in tumors, allowing clinicians to subclassify UC depending on the mutation present, with the aim of delivering precision medicine.[55] This technology has allowed for the development and administration of the pioneering combination of EV and pembrolizumab for patients with nectin-4– and PD-L1–positive tumors, which has demonstrated outstanding outcomes so far and represents a step further toward provision of patient-centered medicine in cancer care. The advantage of this approach is that treatment is provided to patients who are more likely to respond to it, instead of patients who have a limited response but experience numerous adverse events. Nonetheless, long-term outcomes of combination therapy have yet to be explored, as well as those of triple-combination treatment outcomes (EV plus pembrolizumab plus chemotherapy), which could provide superior responses and prolong survival if tolerated. Furthermore, the exact

molecular pathway of interactions between EV and pembrolizumab still remains unclear and is an area of focus for future research. Finally, a vital issue that will require further investigation is the place of these treatments in clinical practice, highlighting the need for a review of current treatment guidelines, to ensure that they accurately reflect the most recent evidence.

5. Conclusions

The treatment landscape for locally advanced or metastatic UC is shifting after 20 years of first-line treatment with cisplatin-based chemotherapy. Over the last 5 years, new drug classes are slowly but steadily establishing their place in the treatment of locally advanced or metastatic UC, as reflected by the most recent update of the European Association of Urology guidelines.[12] Pembrolizumab and EV monotherapies have been approved by the FDA, whereas the combination therapy has been granted breakthrough therapy designation for UC, with the specific indications for each treatment summarized in Appendix 3 (http://links.lww.com/CURRUROL/A35). Early results have shown that the combination therapy is superior not only to standard chemotherapy but also to monotherapy with each drug, preparing the way for a new standard of care for locally advanced or metastatic UC. Early evidence suggests that combination therapy with pembrolizumab and EV may provide an additional treatment option in clinical settings for locally advanced or metastatic UC. Many more such novel therapies are still in clinical trials, the outcomes of which may be uncertain. Nevertheless, it is expected that with advances in biomarker-tumor profiling and genomic sequencing, future treatments for locally advanced or metastatic UC will become more targeted, personalized, and thus optimized.

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Statement of ethics

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Conflict of interest statement

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Author contributions

MAB: Conceptualization, methodology, writing—original draft, writing—review and editing;
JP: Conceptualization, visualization, writing—original draft, writing—review and editing;
LM, MCW, NOC: Conceptualization, writing—original draft;
HFG: Conceptualization, supervision, writing—review and editing.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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