

Profile of Enfortumab Vedotin in the Treatment of Urothelial Carcinoma: The Evidence to Date

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Abstract: Nowadays the therapeutic landscape for advanced and metastatic urothelial carcinoma continues to evolve. The recent regulatory approval of enfortumab vedotin (EV) for the treatment of advanced urothelial cancer confirms the evolving role of antibody-drug conjugates. EV demonstrates a favorable profile in heavily pretreated patients with locally advanced or metastatic urothelial carcinoma. Early survival reports demonstrate a significant antitumor effectiveness along with a rather acceptable safety profile in a difficult-to-treat population.

Keywords: enfortumab vedotin, bladder cancer, metastasis, urothelial cancer

Introduction

Bladder cancer (BC) is the 8th most commonly diagnosed cancer in males, dropping to 12th when both genders are considered,¹ with approximately 550,000 new cases and 200,000 BC-related deaths in 2018.² Southern Europe presents the highest age-standardized rates (ASRs) in BC incidence in both genders, with 26.5 per 100,000 for males and 5.5 per 100,000 for females, respectively. About 25% of cases present with muscle-invasive BC (MIBC) and approximately half of them relapse after radical cystectomy (RC), depending on the pathological stage of the primary tumour and the nodal status.³ Approximately 5% of patients have metastatic disease at the time of diagnosis.⁴ Before the development of effective chemotherapy, patients with metastatic BC (mBC) had a median survival rarely exceeding three to six months.⁵ Cisplatin-based chemotherapy has been the standard of care for more than 30 years as first-line treatment in cisplatin-eligible patients. The combination of methotrexate, vinblastine, adriamycin plus cisplatin (MVAC) was equivalent to gemcitabine plus cisplatin (GC) in terms of overall survival (OS) prolongation.⁶

The high-dose intensity MVAC in combination with G-CSF is proven better in terms of safety and efficacy compared with standard MVAC, although median survival is similar.⁷ Long-term survival seems to be significantly dependent on the metastatic sites: in LN-only disease, 5-year survival reaches 20.9% compared to only 6.8% for patients with visceral metastases.⁶

In patients unfit for cisplatin, checkpoint inhibitors (CPIs) suggest promising alternatives along with carboplatin combination chemotherapy. In case of disease progress, the only second-line treatment option with relatively good results is CPI pembrolizumab.³ Several novel agents are tested in Phase 1 and 2 trials for second-line therapy in order to further prolong OS and improve severe toxicity issues that

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characterize established treatment for metastatic disease. Enfortumab vedotin (EV) is a promising drug recently approved by the FDA for the treatment of adult patients with locally advanced or mBC who have previously received a programmed death receptor-1 (PD-1) or programmed death ligand 1 (PD-L1) inhibitor and a platinum-containing chemotherapy.⁸ Herein, we present recent evidence on the profile, effectiveness and safety of EV.

Enfortumab Vedotin

Enfortumab Vedotin Outline and Mechanism of Action

Enfortumab vedotin (EV) is a novel, intravenously (iv) administered, fully humanized, monoclonal antibody–drug conjugate (ADC) designed for the treatment of neoplasms with cells that express Nectin-4, also known as poliovirus receptor-related protein 4 (PVR4).⁹ Nectin-4 is an adhesion immunoglobulin-like transmembrane molecule, consisted of extra- and intracellular domains as well as a transmembrane helix¹⁰ that plays a role in several stages of cellular cycle. Nectin-4 is highly expressed in urothelial cancer (UC) cells, especially in BC cells but poorly in normal cells and is associated with poor prognosis.^{11,12} Of note there are two versions of EV, the hybridoma (AGS-22M6E) and the Chinese Hamster Ovary (CHO or AGS-22CE) version, both of which were proven to induce cell death in vitro.¹²

Enfortumab suggests the anti-Nectin-4 monoclonal antibody part attached via a cathepsin-cleavable linker to vedotin. Vedotin refers to the monomethyl auristatin E (MMAE), a microtubule-disrupting agent, that is delivered and selectively bound to Nectin-4 expressing BC cells.¹³ The resulting ADC-Nectin-4 complex is internalized into the BC cells and then the valine-citrulline (Val-Cit) dipeptide linker is recognized and cleaved by cathepsin-B in the cells of the neoplasm, where the conjugated cytotoxic MMAE is selectively released. As a result, the microtubule networks are disrupted leading to apoptotic death.¹²

EV was granted accelerated approval by the FDA on 18 December 2019.¹⁴ According to NCCN guidelines on mBC, EV is recommended as a preferred second or subsequent-line systemic therapy option in previously treated patients in the setting of a clinical trial,¹⁵ while the EAU Guidelines consider EV as a promising drug for second or later-line therapy.³

Clinical Trials

EV-101 (ASG-22CE-13-2) (NCT02091999)

EV was initially assessed for safety/tolerability and anti-tumor activity in EV-101 trial (ASG-22CE-13-2) (NCT02091999), a phase 1, open-label, North American multi-center, dose escalation/dose expansion study in patients with Nectin-4–positive tumors (including metastatic UC (mUC) and especially mBC) who were heavily pretreated with at least 1 prior chemotherapy regimen and/or PD-L1 inhibitor, including a cohort of patients with mUC who received prior anti-PD-L1 therapy.¹⁶ Twenty-five patients were enrolled in the dose escalation phase, most of them with primary tumors in the bladder, renal pelvis, or ureter (n = 21); 110 patients (71% of the 155 totally enrolled patients) had mBC and were treated with EV 1.25mg/kg iv. Patients received escalating doses of EV up to 1.25 mg/kg on days 1, 8, and 15 of every 28-day cycle. Primary objectives of the study were the evaluation of safety/tolerability and pharmacokinetics; antitumor activity was a secondary objective. Enrolled patients with mUC (n = 155) were heavily pretreated, with 96% of them with prior platinum-based chemotherapy and 29% receiving at least 3 lines of prior treatment. Maximum tolerated dose (MTD) of EV was not established; however, the recommended Phase 2 dose was 1.25 mg/kg. The most common treatment-related adverse events (TRAEs) were rash, peripheral neuropathy, fatigue, alopecia, and nausea, with most of them grade 1–2 in severity. Among the 112 patients with mUC treated with single-agent EV 1.25 mg/kg, the investigator-assessed confirmed objective response rate (ORR) was 43%, while the duration of response (DOR) was 7.4 months. Median OS reported was 12.3months. Similar ORR and estimated median OS were observed in patients older than 75 years of age with and without prior anti-PD-L1 treatment, liver metastases, or upper-tract urothelial cancer (UTUC). It was therefore concluded that EV was generally well tolerated and provided clinically meaningful and durable responses in patients with mUC with encouraging survival data.

EV-201 (NCT03219333)

Because of the strength of the aforementioned data, single-agent EV has been investigated in patients with locally advanced/mUC previously treated with platinum-based chemotherapy and CPI therapy in a pivotal phase 2 study (EV-201) (NCT03219333).¹⁷ EV-201 is a global two-cohort, single-arm, phase 2 study, designed to establish the efficacy and safety of EV in 125 eligible patients

from USA and Japan with locally advanced or mUC. In total, 90% of enrolled patients suffered from metastatic visceral disease, while liver metastases were present in 40% of patients. Cohort 1 enrolled patients who were previously treated with both platinum chemotherapy and an anti-PD-1/L1 therapy, whereas Cohort 2 continues to enroll patients who were previously treated only with CPI therapy. Similar to EV-101, the median number of previous therapies was 3 (range, 1–6). EV 1.25mg/kg was administered iv on days 1, 8, and 15 of every 28-day cycle. The primary end point was ORR per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessed by blinded independent central review. Key secondary end points were DOR, progression-free survival (PFS), OS, safety, and tolerability. The median follow-up was 10.2 months (range: 0.5 to 16.5 months). Confirmed ORR by blinded independent reviewers was 44% (range: 35.1% to 53.2%), including 12% complete remissions. Similar responses were observed in prespecified subgroups, such as in poor prognosis patients with liver metastases or non-responders to previously received anti-PD-1/L1 therapy. Median DOR was 7.6 months (range: 0.95 to 11.3 months). The most common TRAEs were fatigue (50%), any peripheral neuropathy (50%), alopecia (49%), any rash (48%), decreased appetite (44%), and dysgeusia (40%), with approximately 90% of TRAEs grade 1–2. It was concluded that EV demonstrated a clinically meaningful response rate with a manageable and tolerable safety profile in patients with locally advanced or mUC who were previously treated with platinum and anti-PD-1/L1 therapies.

EV-301 (NCT03474107)

It is an open-label, multi-center, randomized, Phase 3 study to compare the OS of 608 participants with locally advanced or mUC treated with EV to the OS of participants treated with investigator's choice of chemotherapy, who showed progression of disease on either platinum-based chemotherapy or immunotherapy. Participants receive iv EV on days 1, 8 and 15 of each 28-day cycle or either iv docetaxel, vinflunine or paclitaxel on day 1 of every 21-day cycle. OS is the primary outcome of the study, while the secondary outcomes are PFS, ORR, the DCR and DOR per RECIST V1.1 and the assessment of safety and tolerability, the quality of life (QOL) and patient-reported outcomes (PRO) parameters.

Recently, a press release reported that EV-301 met its primary endpoint of OS compared to chemotherapy and

was considered to be positive. The study results were carefully reviewed by an independent Data Monitoring Committee following a planned interim analysis. EV was proven to significantly improve OS and PFS ($p=0.001$ and $p<0.00001$, respectively). Reported TRAEs were rash, hyperglycemia, decreased neutrophil count, fatigue, anemia and decreased appetite (the most frequent Grade 3 or greater AEs occurring in more than 5% of patients).¹⁸

EV-103 (NCT03288545)

It is a Phase1/2 randomized, multi-cohort, open-label, multi-center dose-escalation/dose-expansion study of iv EV as monotherapy or in combination with anticancer therapies such as chemotherapy or CPI for the treatment of locally advanced or mUC with estimated enrollment of 407 patients. In the dose-escalation phase, the combination of EV plus pembrolizumab as first-line or second-line in cisplatin-ineligible patients was assessed, while in the dose-expansion phase there were several cohorts examining EV combined with pembrolizumab, cisplatin, carboplatin or gemcitabine. The primary goal of the study is to determine the safety, tolerability, and efficacy of EV alone or in the aforementioned combinations. Initial results in 45 cisplatin-ineligible patients with mUC received 1.25mg/kg EV on days 1 and 8 plus 200 mg pembrolizumab on day 1 every 3 weeks, showed a preliminary confirmed ORR per RECIST 1.1 of 62% (14% with complete and 48% with partial response, respectively), while 90% was the disease control rate (DCR). The most common TRAEs were fatigue (66%, with 14% of the cases at least Grade 3), decreased appetite (52%, 0% \geq Grade 3), peripheral neuropathy of any type in (52%, 3% \geq Grade 3), alopecia (45%), rash of any type (45%, 14% \geq Grade 3), diarrhea (41%, 3% \geq Grade 3) and immune-related events that needed steroids (17%, 10% \geq Grade 3). A total of 7% of patients discontinued treatment with EV + pembrolizumab due to AEs (lipase increase, multi-organ failure).¹⁹

NCT03606174

It is a phase 2, non-randomized, multi-cohort, open-label, multicenter study with estimated enrollment of 425 participants previously treated with CPI and platinum-based chemotherapy. This study examines the safety and anticancer activity of EV given iv as monotherapy and in combination with other anticancer therapies as first line (1L) and second line (2L) treatment for patients with UC. The primary objective is ORR. There are 2 portions in the study - a lead-in dose escalation portion and a dose

expansion portion. In the dose escalation portion, patients are treated with up to 4 dose levels of sitravatinib (orally once per day continuously in 21-day cycles at 35 mg, 50 mg, 70 mg or 100 mg) in combination with pembrolizumab (200 mg over 30 min iv infusion every 3 weeks) and up to 2 dose levels of EV (30 min iv infusion on day 1 and day 8 in 21-day cycles at 1 mg/kg or 1.25 mg/kg) combination in order to determine the recommended doses to be used. These doses will be further studied in the dose expansion portion. The primary goal of the study is to determine the safety, tolerability, and efficacy of EV alone and in combination with pembrolizumab and/or chemotherapy. The early efficacy results of the study have demonstrated encouraging activity with a safety profile that appears manageable and tolerable. The addition of sitravatinib to the EV-pembrolizumab combination might further augment clinical activity by selectively inhibiting key molecular and cellular pathways strongly implicated in CPI resistance. The trial is still recruiting patients and has no results yet.

EV-202 (NCT04225117)

It is an open-label, multicenter, multicohort, non-randomized phase 2 study to evaluate EV in subjects with previously treated locally advanced or metastatic malignant solid tumors, with estimated enrollment of 240 participants. The primary purpose of this study is to determine the antitumor activity of EV as measured by confirmed ORR.

The study will also assess other measures of antitumor activity such as OS, safety and tolerability of EV and will consist of 3 periods: screening/baseline, treatment and follow-up. Screening/baseline period will take place up to 28 days prior to the first dose of study treatment. In the treatment period, starting at cycle 1, participants will receive EV on days 1, 8, and 15 every 28-day cycle until one of the treatment discontinuation criteria are met. Disease assessment will be performed at screening/baseline and repeated every 8 weeks (56 days \pm 7 days) from the first dose of study treatment throughout the study until the participant has radiologically confirmed disease progression, initiates a new subsequent anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first.

Participants who discontinue study treatment for reasons other than radiologically confirmed disease progression by RECIST Version 1.1 will enter into a post-treatment follow-up period and continue to receive imaging scans every 8

weeks (56 days \pm 7 days) until the subject has radiologically confirmed disease progression, initiates a new anticancer therapy, dies, withdraws consent, is lost to follow-up or the study closes, whichever occurs first.

After 1 year on study treatment, the frequency of disease assessment will be reduced to every 12 weeks (84 days \pm 7 days).

After radiologically confirmed disease progression or initiation of subsequent anticancer therapy, whichever occurs first, participants will be contacted every 12 weeks in the long-term follow-up period for survival status until death, withdrawal of consent, lost to follow-up or study closure, whichever occurs first.

EV-302 (NCT04223856)

It is an open-label, randomized, controlled phase 3 study of EV plus pembrolizumab with (Arm C) or without chemotherapy (Arm A) versus standard of care gemcitabine plus platinum-containing chemotherapy (Arm B) in 760 patients with previously untreated locally advanced or mUC.

EV may be administered for an unlimited number of cycles and pembrolizumab for a maximum of 35 cycles or until a protocol defined reason for study discontinuation occurs, whichever is first. Cisplatin or carboplatin plus gemcitabine may be administered for a maximum of 6 cycles or a protocol-defined reason for study discontinuation occurs, whichever is first.

The primary outcomes are PFS per RECIST v1.1 and OS and secondary outcomes are ORR, DOR, DCR and TRAEs.

Recently, based on promising data on ORR from chemotherapy + PD-1/PD-L1 combinations with a manageable safety profile, the study was modified to remove Arm C. The updated 2-arm design randomizes patients to EV plus pembrolizumab or gemcitabine plus cisplatin/carboplatin in 1:1 ratio with the following stratification factors: cisplatin eligibility, PD-L1 expression and liver metastases.²⁰

MK-3475-905/KEYNOTE-905/EV-303 (NCT03924895)

This is a randomized phase 3 study evaluating RC with either perioperative pembrolizumab or EV plus pembrolizumab versus RC alone in cisplatin-ineligible participants with MIBC with estimated enrollment of 836 patients. Participants receive 3 preoperative cycles of EV (1.25 mg/kg iv, given on days 1 and 8 of each 21-day

Table I Clinical and Ongoing Trials on EV

Trial [Ref]	Phase	Patients	Inclusion Criteria	Endpoints	Outcomes
EV-101 NCT02091999 ¹⁶	1	155	Patients with at least 1 prior chemotherapy regimen and/or PD-L1 inhibitor.	Primary objectives: evaluation of safety/tolerability and pharmacokinetics. Secondary objective: antitumor activity.	ORR: 43%. DOR: 7.4 months. OS: 12.3 months.
EV-201 NCT03219333 ¹⁷	2	125	Patients previously treated with platinum-based chemotherapy and CPI therapy. 90% of enrolled patients suffered from metastatic visceral disease, while liver metastases were present in 40% of patients.	Primary end-point: ORR per RECIST version 1.1. Key secondary end-points: DOR, PFS, OS, safety, and tolerability.	ORR: 44%. Complete remissions: 12%. DOR: 7.6 months.
EV-301 NCT03474107	3	608	Patients showed progression of disease on either platinum-based chemotherapy or immunotherapy.	Primary outcome: OS. Secondary outcomes: PFS, ORR, DCR and DOR per RECIST v1.1, assessment of safety and tolerability, QoL and PRO parameters.	Significantly improves: OS (p=0.001). PFS (p<0.00001)
EV-103 NCT03288545 ¹⁹	1/2	407	Assessment of EV as monotherapy or in combination with anticancer therapies such as chemotherapy or CPI.	Primary goal: safety, tolerability, and efficacy of EV alone or in combination with anticancer therapies such as chemotherapy or CPI.	Initial results in 45 cisplatin-ineligible patients: ORR per RECIST 1.1: 62% (14% with complete and 48% with partial response, respectively). DCR: 90%.
NCT03606174	2	425	Participants previously treated with CPI and platinum-based chemotherapy.	Primary goal: safety, tolerability, and efficacy of EV alone and in combination with pembrolizumab and/or chemotherapy. The primary objective: ORR.	No results yet
EV-202 NCT04225117	2	240	Subjects with previously treated locally advanced or metastatic malignant solid tumors.	Primary purpose: ORR. The study will also assess other measures of antitumor activity such as OS, safety and tolerability of EV	No results yet
EV-302	3	760	Patients with previously untreated locally advanced or mUC.	Primary outcomes: PFS per RECIST v1.1, OS. Secondary outcomes: ORR, DOR, DCR and TRAEs.	No results yet
EV-303 NCT03924895	3	836	Cisplatin-ineligible participants.	Primary outcomes: pCRR (in all participants as well as in those whose tumors express PD-L1 CPS ≥10), EFS (in all participants and in those with EFS in tumors expressing PD-L1 CPS ≥10).	No results yet

(Continued)

Table 1 (Continued).

Trial [Ref]	Phase	Patients	Inclusion Criteria	Endpoints	Outcomes
NCT03869190	1b/2	385	Patients progressed during or following a platinum-containing regimen.	Primary outcome: ORR. Secondary outcomes: PFS, OS, OS at specific time-points, DOR, DCR and the percentage of participants with AEs.	No results yet
NCT03070990 ²¹	I	19	Japanese patients. Post-chemotherapy setting or ineligible for cisplatin.	Assess the safety, tolerability and pharmacokinetics, immunogenicity as defined by the incidence of ADA and anti-tumor activity.	ORR: 35.3%. DCR: 76.5%.

Abbreviations: ORR, objective response rate; DOR, duration of response; OS, overall survival; PD-L1, programmed-death ligand 1; TRAEs, treatment-related adverse events; CPI, check-point inhibitor; RECIST, response evaluation criteria in solid tumors; PFS, progression-free survival; DCR, disease control rate; QoL, quality of life; PRO, patient-reported outcomes; mUC, metastatic urothelial cancer; pCRR, pathologic complete response rate; CPS, combined positive score; EFS, event-free survival; ADA, anti-drug antibody.

cycle) plus pembrolizumab, followed by standard of care surgery, followed by 6 cycles of postoperative EV plus pembrolizumab, followed by 8 cycles of pembrolizumab alone. This combination was compared to surgery alone and 3 preoperative cycles of pembrolizumab, followed by standard of care surgery, followed by 14 cycles of postoperative pembrolizumab. Each cycle is 21 days. The study started enrolling patients about a year ago and its primary outcomes are pathologic complete response rate (pCRR) in all participants as well as in those whose tumors express PD-L1 combined positive score (CPS) ≥ 10 and event-free survival (EFS) in all participants and in those with EFS in tumors expressing PD-L1 CPS ≥ 10 .

MORPHEUS mUC (NCT03869190)

EV is one of the drugs assessed in a phase 1b/2, open-label, multicenter, randomized, umbrella study in patients with locally advanced or mUC who have progressed during or following a platinum-containing regimen, with estimated enrollment of 385 patients. The study is designed with the flexibility to open new treatment arms as new treatments become available, close existing treatment arms that demonstrate minimal clinical activity or unacceptable toxicity, or modify the participant population (eg, with regard to prior anti-cancer treatment or biomarker status).

In this study that still recruits patients, participants receive atezolizumab and EV (EV is administered at a dose of 1.25 mg/kg iv on days 1 and 8 of each 21-day cycle). In case of unacceptable toxicity or loss of clinical benefit, in terms of radiographic and biochemical data assessment, unfavorable local biopsy results or clinical status deterioration, the regimen administration is

withdrawn. The primary outcome of the study is ORR, whereas secondary outcomes are PFS, OS, OS at specific time-points, DOR, disease control rate (DCR) and the percentage of participants with AEs. No results of the study are posted yet.

NCT03070990

It is an open-label, randomized, phase 1 study, designed to objectively assess the safety, tolerability and pharmacokinetics of EV when administered iv to Japanese patients with locally advanced or mUC in the post-chemotherapy setting or ineligible for cisplatin, as well as the immunogenicity as defined by the incidence of anti-drug antibody (ADA) and anti-tumor activity of EV. The estimated enrollment of the study is 19 participants. Patients were randomized 1:1 to receive 1.0 mg/kg (Arm A) or 1.25 mg/kg (Arm B) EV on days 1, 8, and 15 of each 28-day cycle. According to initial results, EV was well tolerated across both doses, with dysgeusia and alopecia being the most common TRAEs, while the most common grade ≥ 3 TRAEs were anemia and hypertension (n = 2 each). ORR and DCR were 35.3% and 76.5%, respectively.²¹

Tables 1 and 2 present a detailed summary of the aforementioned studies.

Conclusions

The therapeutic landscape for advanced and mUC continues to evolve. The recent regulatory approval of EV for the treatment of advanced urothelial cancer suggests a new, modern era, of precision therapeutics and confirms the evolving role of antibody-drug conjugates in solid tumors. EV shows a favorable profile in heavily pretreated

Table 2 Adverse Events of Clinical and Ongoing Trials on EV

Trial [Ref]	Phase	Patients	Adverse Events
EV-101 NCT02091999 ¹⁶	I	155	<p>145 patients (94%): ≥ 1 AE considered at least possibly related to EV.</p> <p>53 patients (34%): ≥ 3 TRAEs (hyperglycemia (5%) was the only grade ≥ 3 TRAE that occurred in $\geq 5\%$ of patients).</p> <p>Most common TRAEs ($\geq 30\%$ of patients receiving 1.25 mg/kg EV): fatigue (53%), alopecia (46%), decreased appetite (42%), dysgeusia (38%), nausea (38%), peripheral sensory neuropathy (38%), pruritus (35%), diarrhea (33%).</p> <p>Treatment-emergent rash (of any form): [70 patients (45%): 10 patients grade 3 1 patient grade 4].</p> <p>maculopapular rash: 33 patients (21%).</p> <p>Peripheral neuropathy (of any form): [76 patients (49%): majority of events grade ≤ 2].</p> <p>Peripheral sensory neuropathy: [49 patients (32%): 1 patient grade 3].</p> <p>TRAEs led to discontinuation: [16 patients (10%): most common peripheral sensory neuropathy (n = 5, 3%)].</p> <p>Fatal TRAEs: 4 (respiratory failure, urinary tract obstruction, diabetic ketoacidosis, multiorgan failure).</p>
EV-201 NCT03219333 ¹⁷	2	125	<p>Most common TRAEs: fatigue (50% all grade, 6% grade ≥ 3), alopecia (49% all grade), decreased appetite (44% all grade, 1% grade ≥ 3), dysgeusia (40% all grade, none grade ≥ 3), peripheral sensory neuropathy (40% all grade, 2% grade ≥ 3).</p> <p>Most common grade 3 or greater TRAEs: neutropenia (8%), anemia (7%), fatigue (6%).</p> <p>Most common serious TRAE: febrile neutropenia (4%).</p> <p>TRAEs led to dose reductions/discontinuation: 32%/12% of patients [peripheral sensory neuropathy was the most common TRAE led to dose reduction (9%) and discontinuation (6%)].</p> <p>TRAE peripheral neuropathy: [50% of patients, (94%) grade 2 or less].</p> <p>Peripheral sensory neuropathy: (44%), motor neuropathy (14%).</p> <p>TRAE rash: [48% of patients, (75%) grade ≤ 2].</p> <p>TRAE hyperglycemia: [11% of patients, (50%) grade 2 or less].</p> <p>No treatment-related deaths during the 30-day safety reporting period.</p>
EV-301 NCT03474107	3	608	Reported TRAEs were rash, hyperglycemia, decreased neutrophil count, fatigue, anemia and decreased appetite (the most frequent Grade 3 or greater AEs occurring in more than 5% of patients).
EV-103 NCT03288545 ¹⁹	I/2	407	<p>Most common TRAEs: fatigue (66%, 14% \geqGrade 3), decreased appetite (52%, 0% \geqGrade 3), alopecia (45%), diarrhea (41%, 3% \geqGrade 3).</p> <p>AEs of clinical interest: rash of any type [45% of patients (14% \geqGrade 3)], peripheral neuropathy of any type [52% (3% \geqGrade 3)], immune-mediated events that required systemic steroid treatment [17% (10% \geqGrade 3)].</p> <p>Treatment discontinuation: 2 patients [(7%) lipase increase, multi-organ failure].</p>
NCT03606174	2	425	No results yet
EV-202 NCT04225117	2	240	No results yet
EV-302	3	760	No results yet
EV-303 NCT03924895	3	836	No results yet
NCT03869190	Ib/2	385	No results yet

(Continued)

Table 2 (Continued).

Trial [Ref]	Phase	Patients	Adverse Events
NCT03070990 ²¹	I	19	<p>TRAEs were reported in 15 of the 17 patients (n = 9, Arm A; n = 6, Arm B).</p> <p>Most common TRAEs: dysgeusia and alopecia (52.9%, n = 9 each), dry skin and pruritus (47.1%, n = 8 each), anemia and decreased appetite (41.2%, n = 7 each), pyrexia (35.3%, n = 6).</p> <p>Grade ≥ 3 AEs: 10 of the 17 patients (n = 5, Arm A; n = 5, Arm B).</p> <p>Anemia (n = 3) and hypertension (n = 2) were the only grade ≥ 3 AEs reported in ≥ 2 patients.</p> <p>TRAE led to withdrawal: 2 patients in Arm A (peripheral sensory neuropathy, n = 1; abnormal hepatic function, n = 1); 1 patient in Arm B (one patient experienced two TRAEs (pneumonia and rash).</p> <p>Serious AEs: 7 of the 17 patients (n = 4, Arm A; n = 3, Arm B);</p> <p>Fatal AE: 1 patient (disease progression), unrelated to EV, 14 days after the last dose.</p> <p>No clinically meaningful mean changes from baseline were found in the ECG parameters.</p> <p>Significant ophthalmologic abnormalities: 1 patient [Arm A (dry eye and cataract)].</p> <p>2 patients (Arm B clinically significant cataracts).</p>

Abbreviations: ORR, objective response rate; DOR, duration of response; OS, overall survival; PD-L1, programmed-death ligand 1; TRAEs, treatment-related adverse events; CPI, check-point inhibitor; RECIST, response evaluation criteria in solid tumors; PFS, progression-free survival; DCR, disease control rate; QoL, quality of life; PRO, patient-reported outcomes; mUC, metastatic urothelial cancer; pCRR, pathologic complete response rate; CPS, combined positive score; EFS, event-free survival; ADA, anti-drug antibody.

patients with locally advanced or mUC. The available data is limited, however early survival reports demonstrate a significant antitumor effectiveness along with a rather acceptable safety profile in a difficult-to-treat population. Several clinical trials are ongoing in order to prove the possibly practice-changing role of EV advanced urothelial cancer.

Expert Opinion

In the recent years, the treatment paradigm of locally advanced and mUC has changed significantly, with the addition of CPIs and more recently with the FGFR-targeted therapies in our armamentarium. In 2019, EV achieved accelerated FDA approval in the post-platinum, post-CPI status of metastatic setting of disease as a result of its very encouraging and promising initial results in this special population of heavily pre-treated patients, even with unfavorable and poor prognostic factors, such as hepatic metastases.²²

EV is currently assessed in several ongoing trials in other clinical scenario (EV compared with second-line chemotherapy) as well as in combination with other agents (pembrolizumab, immunotherapeutic agents or chemotherapy). At the moment, targeted therapies are the preferred second-line treatment options in the post-platinum setting or first-line treatment option for platinum-ineligible patients.²³ According to NCCN guidelines, erdafitinib which is FDA-approved for the treatment of mUC patients with actionable FGFR3/FGFR2 alterations²⁴ is recommended as second-line therapy after CPI or third-line therapy after platinum-based

chemotherapy and CPI, with EV recommendation as a preferred subsequent-line systemic therapy option.^{15,25}

Both EV and erdafitinib are recommended treatment options in the post-platinum setting, however in everyday practice, the optimum sequencing protocol is still to be determined. FGFR alteration detection might be useful, in patients with progressive disease eligible for third-line therapy: for a patient with an *FGFR2/3* alteration the choice could be based on possible TRAEs and their impact on patients' life.

Special consideration is needed regarding EV's toxicity. EV-related neurotoxicity and neuropathy affects approximately half of the patients treated with EV. Given the fact that several degrees of residual neuropathy are associated with cytotoxic agents given as first-line therapy, possible overlapping or deteriorating toxicities may render the administration of EV as second-line treatment difficult.²⁶ Varying degrees of rash and severe eczematoid and lichenoid eruption are rather unusual, especially the cases with full-thickness epidermal necrosis or symmetrical drug-related intertriginous and flexural exanthema and are successfully treated with moisturizing agents and oral or topical corticosteroids.^{27,28}

In this changing treatment landscape, there is great opportunity to develop and validate predictive biomarkers that can identify patients who are most likely to benefit from a particular therapy.²⁹ Moreover, the optimal selection of best candidates for EV treatment remains a real challenge, while target expression and its biological factors such as selectivity, heterogeneity, internalization rate and functional role, are crucial in order to properly

ascertain the safety, effectiveness and treatment potential of EV.⁹ Despite the optimistic perspective, there is still lack of data regarding the best timing of EV administration or sequencing and there is yet no standard of care in patients with advanced UC.³⁰

Disclosure

The authors report no conflicts of interest in this work.

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