

# Platinum-Free Systemic Therapy in First-Line Metastatic Urothelial Carcinoma: Mirage or Oasis in the Platinum Desert?

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*The Oncology Grand Rounds series is designed to place original reports published in the Journal into clinical context. A case presentation is followed by a description of diagnostic and management challenges, a review of the relevant literature, and a summary of the authors' suggested management approaches. The goal of this series was to help readers better understand how to apply the results of key studies, including those published in Journal of Clinical Oncology, to patients seen in their own clinical practice.*

The systemic treatment for metastatic urothelial carcinoma has evolved over the past decade; however, changes in the first-line setting have remained elusive and dependent on platinum-based chemotherapy regimens. Hoimes et al now present an update on the results of cohort A of the EV-103 phase Ib/II trial combining enfortumab vedotin and pembrolizumab in the first-line setting for patients with cisplatin-ineligible metastatic urothelial carcinoma. The efficacy results in this small, phase I cohort demonstrate an impressive response rate with the majority of patients deriving benefit in tumor control. In conjunction with the results from cohort K of EV-103, recently reported at the 2022 ESMO Congress, there is much anticipation regarding this combination as a future standard of care. However, despite this combination not including a traditional cytotoxic chemotherapeutic, it is still associated with potentially life-altering treatment-related toxicity, most notably rash and peripheral neuropathy, along with the risks of immune-related adverse events, which will need to be carefully calibrated for patients.

## PATIENT CASE

A 68-year-old man with significant medical history for type two diabetes mellitus with hemoglobin A1C of 6.9, mild diabetic nephropathy with a baseline estimated creatinine clearance (CrCl) of 44.2 mL/min, grade 1 diabetic peripheral neuropathy manifested mostly in the feet, a BMI of 32, and a 26 pack-year smoking history presented with 2 weeks of intermittent hematuria. Axial imaging using computed tomography (CT) with urogram revealed a mass in the urinary bladder and an enlarged right iliac lymph node measuring 2.5 cm in short axis. Cystoscopy with direct visualization and transurethral resection of bladder tumor confirmed muscle invasive urothelial carcinoma (mUC). Complete staging with CT of the chest revealed multiple bilateral lung nodules, with the largest in the left peripheral lower lobe measuring 2.1 cm in long axis and several enlarged mediastinal lymph nodes. Biopsy of the largest lung nodule confirmed metastatic mUC. The patient is referred to medical oncology for discussion of systemic therapy.

## CLINICAL CHALLENGES IN EVALUATION, TREATMENT, AND RELEVANT LITERATURE

Platinum-based systemic therapy for previously untreated or recurrent metastatic mUC has remained the standard of care for decades. The choice between cisplatin-based versus carboplatin-based regimens has

been rooted in clinical criteria and patient and physician preference.<sup>1-3</sup> Despite initial radiologic and clinical responses in a substantial proportion of patients, few patients achieve durable remissions. Despite notable advances in the systemic therapy landscape for mUC (including the approval of agents across four different therapeutic targets),<sup>4</sup> improvements in first-line therapy have proved elusive. The only exception has been the acceptance of programmed death 1 pathway (PD-1)-targeted therapies alone in patients unfit to receive any platinum-containing regimen, a cohort characterized by substantial comorbidities and poor prognosis.

Even as the systemic landscape for other tumors such as metastatic non-small-cell lung carcinoma, which has historically relied on platinum-based chemotherapy, has become more fertile, the initial treatment options for patients with mUC have remained a platinum desert. There have been two trials of first-line therapy combining anti-PD-1 pathway drugs with platinum-based chemotherapy and another evaluating combined checkpoint blockade that, to our knowledge, to date have demonstrated no survival benefit compared with chemotherapy alone.<sup>5-7</sup> In the three-arm KEYNOTE-361 trial, pembrolizumab was evaluated in combination with a platinum-gemcitabine combination (platinum as determined by investigator) versus chemotherapy alone or pembrolizumab alone. Neither median progression-free survival nor median overall survival (mOS) in the

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pembrolizumab/chemotherapy arm was improved compared with the chemotherapy alone group.<sup>5</sup> Similarly, the IMvigor130 trial used a three-arm design with the PD-L1 inhibitor atezolizumab replacing pembrolizumab. At final analysis, median progression-free survival was improved in the atezolizumab/chemotherapy arm as compared with chemotherapy alone; however, at initial and second interim analyses, mOS has not shown a statistically significant benefit in the intention-to-treat population.<sup>7,8</sup> Finally, the DANUBE trial took a different approach, testing combined immune checkpoint blockade with durvalumab and tremelimumab against durvalumab alone or platinum-gemcitabine. This trial did not meet either of its primary end points, neither in the PD-L1 high population where mOS in the durvalumab monotherapy arm was not significantly improved versus the chemotherapy arm nor when comparing mOS for the intention-to-treat population in the durvalumab/tremelimumab and chemotherapy-alone arms.<sup>6</sup> The lure of improved durable outcomes with up-front immune checkpoint blockade remained a distant mirage.

Benefit of targeting the PD-1 pathway in the first-line treatment of mUC was finally demonstrated using a switch maintenance strategy.<sup>9</sup> In the JAVELIN Bladder 100 trial, patients who had achieved at least stable disease after four cycles of chemotherapy with platinum-gemcitabine were randomly assigned to avelumab maintenance or best supportive care. The trial met its primary end point, improving mOS in the avelumab group versus the best supportive care group. Although acceptance and incorporation of this switch maintenance approach has changed the standard of care, it represents only an incremental change. The standard of care before JAVELIN Bladder 100 was to switch to pembrolizumab after first-line therapy at progression, either after a break or immediately in patients with primary progression. Since some patients did achieve durable remissions from platinum-based chemotherapy, the maintenance approach subjected those patients to immediate avelumab exposure they may not have needed for some time, along with the 7%-12% incidence of serious immune-related adverse events (AEs), in exchange for getting patients destined to have rapid progression after stopping chemotherapy immediately back on treatment. On the basis of the mOS, it may be a fair trade off for most patients. However, there is hope on the horizon, and in the companion to this article, Hoimes et al<sup>10</sup> provided an update on the first glimpse of a possible platinum-free oasis.

The report accompanying this article presents results from the 45 patients in cohort A of the EV-103 phase Ib/II study, in which patients received combination enfortumab vedotin (EV) and pembrolizumab. This trial included patients who were deemed cisplatin-ineligible by participating investigators and who either had no prior systemic therapy for mUC or had progressed after prior platinum-containing (neo)adjuvant therapy. Platinum eligibility was determined locally. However, like many phase I/II trial populations, this group appears relatively fit despite their cisplatin ineligibility, with the majority age younger than 75 years, HbA1c < 6.5, and

BMI < 30, which would describe a less comorbid population than might be expected in the real world. We do not know the median CrCl, but we do know that 17.8% were eligible because they were Eastern Cooperative Oncology Group 2. Nonetheless, the outcomes are quite striking, with an overall response rate (ORR) of 73.3%, a disease control rate of 93.3%, and no significant primary disease progression experienced by any patient. Responses were rapid, with nearly 90% demonstrating response by first tumor assessment and durable, with mOS and median duration of response both exceeding 2 years (26.1 and 25.6 months). Although efficacy in early-phase studies is rarely recapitulated in larger randomized trials,<sup>11</sup> the results are tantalizing and would represent a clear advancement in mUC if confirmed in the ongoing randomized trial (ClinicalTrials.gov identifier: [NCT04223856](https://clinicaltrials.gov/ct2/show/study/NCT04223856)) which randomly assigns unselected patients to the EV/pembrolizumab combination versus gemcitabine plus cisplatin or carboplatin. At the 2022 ESMO Congress, we saw initial results from cohort K of the EV-103 trial (ClinicalTrials.gov identifier: [NCT03288545](https://clinicaltrials.gov/ct2/show/study/NCT03288545)) which randomly assigned cisplatin-ineligible, previously untreated patients 1:1 to EV/pembrolizumab or EV alone.<sup>12</sup> Patients on the combination arm achieved a median ORR of 64.5%, and only 7.9% of evaluable patients had primary progressive disease. These are promising early efficacy signals supporting the excellent disease control achieved with EV/pembrolizumab.

Despite this unprecedented early efficacy signal, there are other factors to consider before we anoint this combination as a standard of care. First, the idea that this represents a chemotherapy-free regimen may be somewhat of a misnomer, at least when viewed from patient and care team perspectives. The scientific elegance of antibody-drug conjugates is certainly an achievement over traditional cytotoxic chemotherapeutics (in this case the microtubule inhibitor monomethyl auristatin E, also known as MMAE or with the linker as vedotin), but evidence that this mechanism minimizes damage to normal bystander tissues remains elusive. Peripheral neuropathy is the most common and potentially debilitating known side effect, and in this study, 62.2% developed treatment-related peripheral neuropathy, including 56.8% of patients who had no neuropathy at baseline. Although the majority were  $\leq$  grade 2 and two-thirds improved, this represents a potentially serious and significant cause for morbidity in these patients, especially if they may on average now live over 2 years with life-altering-associated symptoms. For patients who start with baseline neuropathy, the impact may be particularly acute as the incidence of treatment-related neuropathy was 87.5%. In cohort K of EV-103 presented at ESMO 2022, neuropathy incidence was similar but somewhat lower numerically, with 51.3% reporting any grade neuropathy and only 1.3% developing grade  $\geq$  3. This may be attributable to

evolution in clinicians' comfort in managing neuropathy with EV, as well as potentially greater willingness to dose reduce or stop EV in the setting of clinical responses. In comparison with current standard chemotherapy options such as gemcitabine/carboplatin, which is associated with a 16% incidence of any grade neuropathy, the EV/pembrolizumab regimen is distinct in this regard.<sup>13</sup> In the cisplatin-ineligible population, where comorbidities such as diabetes are likely to be more prevalent, an ability to alter treatment accordingly with dose reductions and/or treatment holds will prove paramount.

Cutaneous reactions make up another common and potentially serious class of AEs experienced by patients receiving EV (with or without pembrolizumab). Importantly, cutaneous reactions are an on-target, off-tumor effect of EV, as nectin-4 is expressed in keratinocytes in the skin and in sweat glands and hair follicles.<sup>14</sup> The numbers are difficult to parse, and it is nearly impossible to differentiate an EV-related rash from an immune-mediated cutaneous reaction, but two thirds of patients had some skin reaction, most of which were reported as  $\leq$  grade 3. Two patients had a grade 4 rash and 11.1% had a grade  $\geq$  3 maculopapular rash. In the cohort K results, a maculopapular rash was reported in 46.1% of patients at any grade, 17.1% at grade  $\geq$  3. Although many of these are treatable and reversible with dose reduction and/or topical or systemic treatment, it is notable that 26.7% of patients in cohort A had an ongoing cutaneous reaction at last follow-up, including one still at grade 4. Even grade 2 cutaneous reactions (defined in CTCAE as  $<$  50% of body surface area) can prove challenging for patients, caretakers, and treatment providers, increasing care time and decreasing quality of life. Additionally, management of both EV-related or immune-mediated cutaneous reactions may require systemic corticosteroids, which can affect another notable EV-associated AE—hyperglycemia. Although hyperglycemia was relatively uncommon, with only four grade 3 events on cohort A, all of which improved, fatal diabetic ketoacidosis has been reported with EV.<sup>15</sup> Other chemotherapy-like AEs reported in a significant subset of patients included fatigue, alopecia, and neutropenia. Thus, the promise of a chemotherapy-free regimen may be merely an academic distinction.

Additionally, it remains unknown whether there is true synergy between EV and pembrolizumab. One potential argument for synergy is the release of damage-associated molecular patterns by EV leading to increased immune cell recognition. Synergy is difficult to prove (impossible in a single-arm study) and may be rare when combining known active anticancer drugs with checkpoint inhibitors.<sup>16</sup> If we look for a historical perspective using ORR, we know from KEYNOTE-052 that the ORR of pembrolizumab alone in the first-line cisplatin-ineligible setting was 24%.<sup>17</sup> In the EV-201 study, in which patients with cisplatin-ineligible mUC and prior treatment with a checkpoint inhibitor were treated

with single-agent EV, the ORR was 52%.<sup>18</sup> Ultimately, the power of this combination may prove to be its high response rate and initial tolerability and toxicity rate, but not its inherent synergy. In the long-term though, most patients will need to stop EV owing to development of neuropathy, thus it is worth considering the optimal treatment duration for EV. The current paradigm calls for platinum-based chemotherapy for four to six cycles, followed by maintenance checkpoint inhibition. It is possible a similar benefit could be achieved with combination EV/pembrolizumab initially for six cycles, followed by pembrolizumab maintenance, minimizing EV toxicity and preserving rechallenge for some patients, analogous to strategies used in the metastatic colorectal cancer space with oxaliplatin as part of the FOLFOX regimen.<sup>19</sup>

## OUR APPROACH TO MANAGEMENT

For our patient, we recommended a platinum-based regimen, which given his CrCl was gemcitabine and carboplatin, followed by maintenance treatment with avelumab or pembrolizumab. Our patient was treated with gemcitabine/carboplatin for four cycles, with a decrease size in all disease by CT imaging consistent with a partial response. After four cycles, the patient was transitioned to maintenance pembrolizumab, which was well tolerated; however, the patient had evidence of disease progression after 6 months with growth in the known lung nodules and newly enlarged pelvic lymphadenopathy. Next, the patient was started on treatment with EV, with the first cycle complicated by a diffuse maculopapular rash over trunk and extremities, ultimately requiring a short course of oral corticosteroids and a dose reduction. After three cycles, restaging imaging again demonstrated a partial response. He continued on therapy for another 4 months; however, he experienced worsening of his peripheral neuropathy despite dose reduction and dose holds and thus needed to stop therapy. He currently remains on a break from systemic therapy with stable grade two peripheral neuropathy requiring treatment with gabapentin.

EV/pembrolizumab remains an exciting combination that is likely to become a standard of care in the first-line setting for patients with mUC. Right now, the evidence on the basis of EV-103 from cohorts A and K are insufficient to justify widespread use, given that these are small cohorts of patients and without comparison with the current standard of care. This combination is associated with significant morbidity that will have an impact on patients during and after completion of treatment and thus must be considered when recommending to patients. The flipside to the benefit of long-term disease control is that the length of time on treatment can be long, allowing for accumulation of toxicities which will eventually limit dose, particularly neuropathy in the case of this combination. We hope to see studies that seek to define the optimal duration of EV in responding patients. Data from on-going

and future randomized trials will determine the full benefit of EV/pembrolizumab, and decisions on treatment in the future will likely need to be based on multiple factors including disease control, long-term efficacy potential, and toxicity. Hopefully, future updates from EV-103,

EV-302, and other trials will also incorporate biomarkers that may help us choose the right treatment for the right patients. Although we await the results from EV-302, all the talk will be about a potential platinum-free future, but for now, the reality remains deserted in platinum.

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#### **AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

##### **Platinum-Free Systemic Therapy in First-Line Metastatic Urothelial Carcinoma: Mirage or Oasis in the Platinum Desert?**

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