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The Overall Survival Benefit in EV-302: Is Enfortumab Vedotin plus Pembrolizumab the New Frontline Standard of Care for Metastatic Urothelial Carcinoma?

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On October 22, 2023, results from the phase 3 trials EV-302, comparing enfortumab vedotin plus pembrolizumab (EV + P) with chemotherapy, and CheckMate 901, comparing gemcitabine, cisplatin, and nivolumab with chemotherapy alone, in metastatic urothelial carcinoma (mUC) were presented at the European Society for Medical Oncology (ESMO) Congress in Madrid, Spain [1,2]. Both trials achieved their primary endpoints of better overall survival and progression-free survival, collectively generating excitement in the field.

The excitement is well deserved, as there had been no successful phase 3 trial in this disease setting in more than 30 years. Interestingly, although both trials are positive, the results from EV-302 received considerably greater praise and public attention. One business journal stated "doctors cheered as data [from EV-302 were] presented at ESMO medical conference" given that this combination therapy is "set to replace chemotherapy as a top choice for bladder cancer patients" [3], and online videos showed a standing ovation. By contrast, there was no standing ovation for CheckMate 901.

Although we share enthusiasm for better treatment options for mUC, four concerns with EV-302 appear to be underappreciated amid the exhilaration: post-protocol therapies, extending the duration of therapy, toxicity, and costs, all of which may raise doubt among physicians and patients regarding whether this is a de-facto standard of care.

First, in any trial in the frontline setting for a cancer for which there are many life-prolonging therapies used in sequence, the benefit of a new regimen must be assessed against the current best available care. This did not happen in EV-302. Notably, 30.4% of individuals in the chemotherapy control arm of EV-302 received maintenance avelumab. The proportion of patients who received maintenance avelumab is lower than expected given that typically 50% of patients have stable disease or a better treatment response with cisplatin-based chemotherapy [4]. The EV-302 starting date was March 30, 2020, and maintenance avelumab for individuals with mUC that had not progressed on first-line platinum-containing chemotherapy received US Food and Drug Administration approval shortly thereafter on June 30, 2020 (ClinicalTrials.gov NCT04223856).

Acknowledging the limitations of cross-trial comparison and the exclusion of patients whose tumors showed early progression, long-term follow-up for individuals who received maintenance avelumab in JAVELIN Bladder 100 revealed median overall survival of 29.7 mo; by comparison, had median overall survival was 16.1 mo for the chemotherapy arm in chemotherapy in EV-302 [5].

In the absence of maintenance avelumab, pembrolizumab is generally the first salvage therapy administered for mUC. The EV-302 authors reported that 26.4% of patients received immunotherapy following disease progression on chemotherapy, but we do not know the denominator of how many progressed without immunotherapy who might have received it. Finally, patients who experienced disease progression on immunotherapy should have received EV; yet again this data point is unreported. Ultimately, we do not know how much of the 15.4-mo survival

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benefit with EV + P would be abrogated by better subsequent care.

Second, treatment courses are longer with EV + P, with no treatment breaks. According to the EV-302 trial protocol, there was no maximum number of cycles of EV, while pembrolizumab was given for a maximum of 35 cycles. By contrast, chemotherapy was given for a maximum of six cycles in the control arm. Although EV + P has been deemed a "chemo-free regimen" as EV is an antibody-drug conjugate (ADC) [3], industry sponsors have publicly acknowledged that "ADCs are targeted medicines that deliver chemotherapy agents to cancer cells" [6]. To the best of our knowledge, this is the first instance of indefinite chemotherapy being administered to individuals with mUC. The trial design of indefinite treatment as opposed to a fixed duration of treatment not only conflicts with many patients' values related to the treatment experience but also further adds to the potential for treatment-related toxicities, time lost related to treatment infusions and follow-up, and financial costs [7].

Third, although EV + P might not be traditional cytotoxic chemotherapy, it is no less toxic. The largest study evaluating patient preferences for mUC treatment revealed that most patients place more value on how they experience treatment, including treatment-related adverse events, than on overall survival [8]. While 97% of patients who received EV + P experienced treatment-related adverse events, versus 95.6% of those who underwent chemotherapy, the frequency of serious treatment-related adverse events was greater with EV + P (27.7%) than with chemotherapy (19.6%). Moreover, 15.5% of those who received EV + P experienced grade $\geq$3 skin reactions and 6.8% had grade $\geq$3 treatment-related peripheral neuropathy. By contrast, 0.2% in the chemotherapy arm had grade $\geq$3 skin reactions and none had grade $\geq$3 chemotherapy-related peripheral neuropathy. According to the National Cancer Institute's Common Terminology Criteria for Adverse Events, v4.0, grade 3 peripheral neuropathy is defined as "severe symptoms" that limit an individual's ability for self-care. In other words, a subset of individuals who receive EV + P may endure significant symptoms associated with long-lasting physical and psychological consequences with far-reaching effects on caregivers and family members who assist with an individual's self-care and other activities of daily living. Therefore, the known effects of time and financial toxicity and other stress associated with caring for individuals who experience serious treatment-related side effects are not adequately captured in a statement such as "grade $\geq$3 peripheral neuropathy" [9].

Fourth, UC is already one of the most expensive cancers to treat and this is poised to get worse. It has been estimated that the cost of treating UC was as high as $6 billion dollars in the USA in 2020 alone [10]. According to publicly available data, it is estimated that EV + P will cost $37 879.78 per cycle, as opposed to $296.26 for each cycle of cisplatin + gemcitabine chemotherapy (https://www.-drugs.com/price-guide/). In other words, 127 individuals with mUC could be treated with one cycle chemotherapy, or one individual could receive one cycle of EV + P. The likely approval of EV + P in the USA and subsequently in other nations on the basis of historical precedent will contribute to growing costs associated with UC treatment, in addition to other unknown costs related but not limited to laboratory tests, imaging, clinical visits for monitoring, and hospitalizations for treatment-related effects.

While the enthusiasm for a new treatment option for patients with mUC must be acknowledged, pending relevant data—including details on post-protocol treatments for individuals in the chemotherapy control arm and quality-of-life data for participants treated with EV + P—may provide further clarity on the role of this combination therapy in treating mUC. We celebrate the improvement in overall survival, which is the first seen in more than three decades. At the same time, we worry that the net result is that individuals with mUC receive more treatment for longer, with significant toxicity and costs, and that they might have been better served with careful sequencing of agents.

Conflicts of interest: David J. Benjamin has a consulting or advisory role with Seagen, Astellas, and Eisai; serves on a speaker bureau for Merck; and has received travel and accommodation expenses from Merck. Arash Rezazadeh Kalebasty has stock and other ownership interests in ECOM Medical; has a consulting or advisory role for Exelixis, AstraZeneca, Bayer, Pfizer, Novartis, Genentech, Bristol-Myers Squibb, EMD Serono, Immunomedics, Gilead Sciences; serves on a speaker bureau for Janssen, Astellas Medivation, Pfizer, Novartis, Sanofi, Genentech/Roche, Eisai, AstraZeneca, Bristol-Myers Squibb, Amgen, Exelixis, EMD Serono, Merck, Seattle Genetics/Astellas, Myovant Sciences, Gilead Sciences, and AVEO; has received research funding from Genentech, Exelixis, Janssen, AstraZeneca, Bayer, Bristol-Myers Squibb, Eisai, Macrogenics, Astellas Pharma, BeyondSpring Pharmaceuticals, BioClin Therapeutics, Clovis Oncology, Bavarian Nordic, Seattle Genetics, Immunomedics, and Epizyme; and has received travel and accommodation expenses from Genentech, Prometheus, Astellas Medivation, Janssen, Eisai, Bayer, Pfizer, Novartis, Exelixis, and AstraZeneca. Vinay Prasad has received research funding from Arnold Ventures; has received royalties from Johns Hopkins Press, Medscape, and MedPage; has a consulting role for UnitedHealthcare; has received speaking fees from Evicore; and has Patreon backers for the New Century Health Plenary Session podcast.

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