Editorial Commentary

Avelumab first-line maintenance for advanced or metastatic urothelial carcinoma: analysis from JAVELIN Bladder 100 trial

Srigita Madiraju^, Firas G. Petros^

Department of Urology, College of Medicine and Life Sciences, The University of Toledo, Toledo, OH, USA

Correspondence to: Firas G. Petros, MD, FACS. Department of Urology, College of Medicine and Life Sciences, The University of Toledo, 3000 Arlington Ave. Mail Stop 1091, Toledo, OH 43614-2598, USA. Email: firas.petros@utoledo.edu.

Comment on: Sridhar SS, Powles T, Climent Durán MÁ, *et al.* Avelumab First-line Maintenance for Advanced Urothelial Carcinoma: Analysis from JAVELIN Bladder 100 by Duration of First-line Chemotherapy and Interval Before Maintenance. Eur Urol 2024;85:154-63.

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Since the phase 3 JAVELIN Bladder 100 trial, patients with advanced urothelial carcinoma (UC) were found to have significantly longer progression free survival (PFS) with avelumab first-line maintenance plus best supportive care (BSC) compared to BSC alone (1,2). Prior to JAVELIN trial, patients with locally advanced or metastatic UC underwent chemotherapy with studies only recommended up to six cycles but no further information on timing, or amount or duration based on individual factors (3,4). In addition, the optimal number of chemotherapy cycles preceding maintenance avelumab and its ideal timing of avelumab is not well known. A significant portion of patients are unable to tolerate that amount. No prior publications have focused on these subsets of patients with advanced UC without progression after 4–6 weeks of chemotherapy.

We applaud the contribution of Sridhar *et al.*, in their study: "Avelumab First-line Maintenance for Advanced Urothelial Carcinoma: Analysis from JAVELIN Bladder 100 by Duration of First-line Chemotherapy and Interval Before Maintenance" (5). This article further breaks down outcomes based on duration, number of chemotherapy cycles, and interval between chemotherapy and starting maintenance avelumab to provide a better clinical guidance and individualized treatment approach.

There was a good long-term follow-up with median ≥38 months. Group stratifications also benefited from being separated by complete or partial response and location of metastasis which could confound overall survival. Conversely, there are some considerations to interpreting the study. The study did not consider dose density or intensity for chemotherapy. There were some discrepancies with cycle timing which was <17 days being the same cycle and >17 days being a new cycle. The number of cycles was extrapolated from data records so the actual number may be different. There is limited information on how this 17-day timeline was decided on, however, this could model troubleshooting timing in real life as mentioned, such as patient or provider preference, room capacity, logistics etc. The study does mention that they did not include patients with intervals shorter than 4 weeks or longer than 10 weeks. While their decision regarding greater than 10 weeks unlikely to provide potential survival benefit, it could have been beneficial to include those with less than 4 weeks for resolution of chemotherapy related toxicity and what their baseline characteristic stratification was.

Some other important factors to consider when interpreting the study findings. There also was no formal statistical analysis of baseline characteristics which may have elucidated why certain individuals tolerated BSC better than others or why some had longer interval times to reach symptom free status after chemotherapy. However, baseline characteristics were at least well broken down and it was

^ ORCID: Srigita Madiraju, 0009-0002-2570-3610; Firas G. Petros, 0000-0003-3062-0780.

even noted that the 4- to less than 6-week interval between chemotherapy and start of maintenance subgroup included higher proportions of patients with Eastern Cooperative Oncology Group (ECOG) performance status 1 and visceral metastases which could enriched the study population with reduced length of survival. While this trial did not study those who received chemotherapy less than four cycles or greater than six cycles, there have already been previous reports showing no significant difference in overall survival with more (3). Lastly while quality of life (QoL) assessment was not within the primary outcome of this trial and is being studied in the DISCUS phase 2 trial, it will be interesting to see the impact of three versus six cycles of chemotherapy on QoL in these subgroups.

In conclusion, this well-formulated post hoc analysis substantiates utilization of avelumab first-line maintenance plus BSC compared to BSC alone and better elucidates duration, number of chemotherapy cycles and interval between chemotherapy and start of maintenance immunotherapy. As such, both first-line chemotherapy and first-line avelumab can be tailored according to individual patient factors. Further attention should be focused on assessing secondary outcomes such as QoL and analyzing baselines patient characteristics and how to interpret those to make decisions on duration or timing of treatments.

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Footnote

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