Friedlaender A. The Changing Landscape of Urothelial Carcinoma Therapy: Updates from ASCO GU 2023. *healthbook TIMES Onco Hema.* 2023;16(2):38.
doi:10.36000/hbT.OH.2023.16.109

VIEWPOINTS

The Changing Landscape of Urothelial Carcinoma Therapy: Updates from ASCO GU 2023

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Keywords: urothelial carcinoma, asco gu 2023, therapies, KEYNOTE-057, CheckMate 274, IMvigor130, TROPHY-U-01

https://doi.org/10.36000/hbT.OH.2023.16.109

healthbook TIMES Oncology Hematology

Vol. 16, Issue 2, 2023

KEYNOTE-057: Pembrolizumab shows clinical benefit in patients with high-risk non-muscle invasive bladder cancer

Previous findings from the phase II KEYNOTE-057 trial showed that pembrolizumab is tolerable and invokes a promising anti-tumor activity in patients with high-risk (HR) non-muscle invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette–Guérin (BCG), with carcinoma *in situ* (CIS) (cohort A).[1] In this ongoing study, pembrolizumab monotherapy was also assessed in 132 BCG-unresponsive patients with papillary tumors (high-grade Ta or any T1) without CIS (cohort B).[2] After 12 weeks of therapy, patients who did not achieve complete response (CR) discontinued the treatment. At 24 weeks, patients showing no recurrence or progression of the disease continued to receive pembrolizumab for up to 2 years; otherwise, treatment was discontinued. The overall median follow-up was 45.4 months.

The primary endpoint of the 12-month disease-free survival (DFS) rate was 43.5%.[2] At 24- and 36-month landmark analyses, the DFS rate was sustained at 34.9%. This DFS benefit was uniform across nearly all prespecified subgroups based on demographic characteristics and tumor patterns. These also included patients with persistent and recurrent disease status at baseline, but not for the subset of patients with progressive disease.[2] Overall, these results support the use of pembrolizumab in patients with papillary HR NMIBC unresponsive to BCG.

CheckMate 274: Adjuvant nivolumab improves disease-free survival in patients with high-risk MIUC

Results from the phase III, placebo-controlled CheckMate 274 trial, investigating adjuvant nivolumab in patients with HR muscle-invasive urothelial carcinoma (MIUC),[3] ultimately led to the regulatory approval of nivolumab for use in this clinical setting. Updated results with a minimum follow-up of 31.6 months presented at this year's ASCO GU 2023 corroborated the clinical benefit of nivolumab in MIUC patients.[4]

Briefly, the trial enrolled patients with ypT2-ypT4a or ypN+ MIUC who have had neoadjuvant cisplatin chemotherapy and patients with pT3-pT4a or pN+ MIUC who did not have prior neoadjuvant cisplatin chemotherapy and were not eligible for or refused cisplatin chemotherapy.[4] Patients were randomized 1:1 to receive either nivolumab (240 mg) (n=353) or placebo (n=356) every 2 weeks for up to a year. At a median follow-up of 36.1 months, the primary endpoint of DFS was doubled with nivolumab in the intent-to-treat (ITT) population (22.0 months vs 10.9 months with placebo; HR: 0.71 [95% CI: 0.58–0.86]), with considerably pronounced DFS improvement in the programmed death-ligand 1 (PD-L1) ≥1% population (52.6 months vs 8.4 months; HR: 0.52 [95% CI: 0.37–0.72]). DFS results with nivolumab were consistent across all pre-specified subgroups, except for two very small subsets of patients with renal pelvis and ureter carcinoma. The subgroup analysis further showed that PD-L1 expression ≥1% and previous neoadjuvant cisplatin treatment were the main drivers for DFS benefit. Progression-free survival 2 (PFS2) was also improved with nivolumab versus placebo in both the ITT and PD-L1 ≥1% populations. Together with previous data from CheckMate 274, these results showed robust and durable clinical outcomes with adjuvant nivolumab in patients with HR MIUC, particularly in those with PD-L1 expression ≥1%.

Metastatic urothelial carcinoma: Updates from IMvigor130 and TROPHY-U-01

Atezolizumab is currently indicated in Switzerland for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) after prior platinum-based chemotherapy.[5] In the IMvigor130 study, atezolizumab was further examined in combination with platinum/gemcitabine-based chemotherapy in patients with locally advanced or metastatic UC with no prior systemic therapy in a metastatic setting.[6] A total of 1,214 patients underwent 1:1:1 randomization to receive either atezolizumab plus platinum/gemcitabine (Arm A), atezolizumab monotherapy (Arm B) or placebo plus platinum/gemcitabine chemotherapy (Arm C). At data cut-off, no significant overall survival (OS) difference was reported between Arms A and C (16.1 months vs 13.4 months; HR: 0.85 [95% CI: 0.73–1.00]; p=0.023 [final efficacy boundary: p=0.021]), with 24-months OS rates of 38% versus 32% and 36-month OS rates of 26% versus 22%.[6] Notably, however, patients given cisplatin-based chemotherapy appeared to achieve improved OS compared with those given carboplatin-based chemotherapy. Similar results were reported for the atezolizumab monotherapy arm, with a median OS of 15.2 months in the ITT population (vs 13.3 months in the placebo-containing arm; HR: 0.98 [95% CI: 0.82–1.16]). In the high PD-L1 expression subgroup, there was a difference of 8.6 months in the median OS between Arms B and C (18.6 months vs 10.0 months; HR: 0.56 [95% CI: 0.34–0.91]).

Another potential therapy for patients with metastatic UC is the antibody-drug conjugate (ADC), sacituzumab govitecan which consists of a topoisomerase I inhibitor coupled to an antibody targeting Trop-2, a glycoprotein heavily expressed in UC.[7] The phase II TROPHY-U-01 trial evaluated the use of sacituzumab govitecan in platinum-ineligible patients with metastatic UC whose disease progressed after a checkpoint inhibitor (CPI). In Cohort 2 of the study, 38 patients received sacituzumab govitecan (10 mg/kg on day 1 and 8 on a 21-day cycle); treatment was continued in the absence of unacceptable toxicity or disease progression.[8] The primary endpoint of objective response rate (ORR) was 32% (partial response: 32%), with a clinical benefit rate of 42%. Of note, among patients who were not treated with prior platinum chemotherapy or enfortumab vedotin (n=13), the ORR was 53.8%. In the overall cohort, the median time to response was 1.4 months whilst the median duration of response was 5.6 months. In addition, the median PFS was 5.6 months and the median OS was 13.5 months. Comparable results were reported in Cohort 1 of this trial, assessing sacituzumab govitecan in metastatic UC patients whose disease progressed after prior platinum-based chemotherapy and a CPI. More specifically, the ORR was 28%, with a time to response of 1.6 months. The median PFS and OS were 5.4 months and 10.9 months, respectively. Altogether, these data showed that sacituzumab govitecan might represent an additional treatment option in this patient population.

Conflict of interest

The author received payments from Amgen, AstraZeneca, Roche, Astellas, Takeda, Bristol-Myers Squibb, Merck Sharpe Dohme, Pfizer, Merck, Novartis and Janssen. These funding entities did not play a role in the development of the manuscript and did not influence its content in any way.

Funding

The author has declared that no financial support was received from any organization for the submitted work.

Author Contributions

The author created and approved the final manuscript.

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