Outlook into the future of front-line immune checkpoint inhibition in metastatic urothelial carcinoma

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Abstract: Immune checkpoint inhibition has been approved for front-line treatment of metastatic bladder cancer in patients who are cisplatin-ineligible and demonstrate programmed death-ligand 1 (PD-L1) positivity. This approval followed the positive results of IMvigor210 and KEYNOTE-052 studies. Immunotherapy has also demonstrated efficacy as maintenance therapy patients for patients who initially respond to platinum-based chemotherapy. Other studies have investigated combinations of immunotherapy with chemotherapy, combinations between immunotherapies, and immunotherapy with novel agents. Although these combinations have demonstrated promise, further investigation is necessary to optimize the patients who would benefit from these approaches. Biomarkers beyond PD-L1 scoring can help predict response and resistance to immune checkpoint inhibition and will be integral to future studies.

Keywords: clinical trials, immunotherapy, metastatic urothelial cancer

Introduction
Urothelial cancer is the sixth-most diagnosed cancer in the United States (US), with 80,000 new cases projected this year. Prognosis is poor for metastatic disease with estimated 5% 5-year relative survival.1 Traditionally, front-line treatment for metastatic urothelial cancer has been platinum-based chemotherapy; however, most responses are not durable.2 Although cisplatin remains recommended front-line therapy for eligible patients, immunotherapy has recently emerged as an effective treatment for cisplatin-ineligible patients who exhibit PD-L1 positivity.3

Immunotherapy for front-line treatment of metastatic urothelial cancer
Initial studies of immune checkpoint inhibition in urothelial cancer evaluated efficacy in platinum refractory patients. Although all checkpoint inhibitors targeting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) pathway have demonstrated benefit in the platinum refractory setting, atezolizumab and pembrolizumab were the first two immunotherapies approved for the metastatic first-line setting after positive trials. IMvigor210, a single-arm phase II study testing the PD-L1 inhibitor atezolizumab contained one cohort of 119 cisplatin-ineligible patients with locally advanced or metastatic bladder cancer. In this cohort, objective response rate (ORR), the primary endpoint, was 27% [95% confidence interval (CI) 16–31%] with 57% (95% CI 48–66%) 12-month overall survival irrespective of PD-L1 expression.4 Responses appeared durable at greater than 2 years of follow up, and median OS was 16.3 months (95% CI 10.4–24.5).5 In IMvigor130, a randomized phase III study, median OS was significantly improved in the atezolizumab monotherapy arm compared with chemotherapy [18.6 months – 95% CI (13.1–NE) versus 10.0 months – 95% CI (7.4–19.1)] for cisplatin-ineligible patients with higher PD-L1 expression (IC 2/3), although this trend was not seen in PD-L1 low expression patients.6 The PD-1 inhibitor pembrolizumab demonstrated similar efficacy for cisplatin-ineligible advanced
urothelial cancer patients in the phase II KEYNOTE-052 study. The reported ORR, the primary endpoint, was 24% (95% CI 20–29), and response improved with PD-L1 score greater than 10%.7 In follow-up, reported median OS was 11.3 months (95% CI 9.7–13.1), which increased to 18.5 months (95% CI 12.2–18.5) in the population with PD-L1 combined positive score $\geq 10.8$

Potential immunotherapy combinations in front-line management of urothelial cancer

Immune checkpoint inhibitors combined with chemotherapy have great potential for front-line metastatic urothelial carcinoma, and large studies have reported positive results recently. In the phase III IMvigor 130 trial, one cohort was treated with atezolizumab plus platinum-based chemotherapy, which was compared with placebo plus platinum-containing chemotherapy. This trial had co-primary endpoints of progression free survival (PFS) and overall survival (OS). Median PFS was 8.2 months (95% CI 6.5–8.3) in the combination arm compared with 6.3 months (95% CI 6.2–7.0) in the standard of care arm [hazard ratio (HR) 0.82, $p=0.007$], meeting its progression-free survival endpoint. At interim analysis, median OS also improved from 13.4 months (95% CI 12.0–15.2) to 16.0 months (95% CI 13.9–18.9) in the chemoimmunotherapy arm (HR 0.83, $p=0.027$); however, this did not cross the interim OS efficacy boundary and therefore did not meet this co-primary endpoint. Final OS analysis has not yet been reported. There was no significant difference between response to atezolizumab monotherapy and chemotherapy.9 KEYNOTE-361 was another phase III trial that compared chemo-immunotherapy with chemotherapy. Patients with advanced urothelial carcinoma were randomized to treatment with pembrolizumab, gemcitabine, and platinum-based chemotherapy, pembrolizumab monotherapy, or chemotherapy alone. This was a negative trial that failed to meet its dual primary endpoints of PFS and OS. Median PFS was 8.3 months (95% CI 7.5–8.5) in the chemo-immunotherapy arm compared with 7.1 months in the chemotherapy arm (95% CI 6.4–7.9) (HR 0.78, $p=0.0033$); however, pre-specified PFS threshold for $p$ value was 0.0019. Median OS was similarly better with combined pembrolizumab and chemotherapy, 17.0 months (95% CI 14.5–19.5) versus 14.3 months (95% CI 12.3–16.7) with standard of care chemotherapy (HR 0.86, $p=0.0407$) but did not meet pre-specified $p$ value of 0.0142. ORR for the combination treatment was 54.7%.10

Avelumab in combination with gemcitabine and carboplatin did not show benefit compared with standard of care chemotherapy in a negative phase II study. The median OS (10.5 versus 13.2 months, $p=0.264$), PFS (6.9 versus 7.4 months, $p=0.712$), and ORR, the primary endpoint of the study (57.1% versus 53.5%, $p=0.78$), did not improve with chemoimmunotherapy.11 Other ongoing phase III trials combining immune checkpoint inhibitors and chemotherapy for first-line treatment of metastatic bladder cancer, including NILE and CheckMate901, are summarized in Table 1. Combinations between classes of immune checkpoint inhibitors are also under investigation in the first-line metastatic setting. Combination of durvalumab, an anti-PD-L1 antibody, and tremelimumab, an anti-CTLA4 antibody, was evaluated in the DANUBE phase III study. In the PD-L1 high population, median OS significantly improved from 12.1 months (95% CI 10.4–14.0) to 17.9 months (95% CI 14.8–24.2) between standard of care chemotherapy and combination immunotherapy, respectively, in an exploratory secondary endpoint (HR 0.74). In the intention-to-treat population, OS also trended toward improvement with combination immunotherapy (HR 0.85, $p=0.075$) but did not meet this primary endpoint.18,19 The combination of nivolumab and ipilimumab is being evaluated as front-line metastatic treatment in one arm of the ongoing phase III CheckMate 901 study (Table 1).

Many of these immunotherapy combination studies, including IMVIGOR130, KEYNOTE-361, and DANUBE demonstrated a benefit to the immunotherapy arm but did not meet at least one pre-specified endpoint. This contrasts with other cancers, including metastatic non-small cell lung cancer, head and neck cancer, and triple negative breast cancer for which chemoimmunotherapy has clearly demonstrated benefit and is used clinically. In the bladder cancer studies, patients who responded to immunotherapy often achieved a more durable response.5,10 This suggests there is a subset of patients who may derive benefit from this treatment; however, biomarkers beyond PD-L1 scoring to select these patients are necessary to ascertain maximal efficacy.
Immunotherapy as maintenance treatment

Immunotherapy can also be administered as maintenance therapy following response to chemotherapy. In the Javelin-100 trial, patients who exhibited initial response to first-line chemotherapy were randomized to maintenance avelumab or best supportive care. Median OS, the primary endpoint of this positive study, was 21.4 months (95% CI 18.9–26.1) in the avelumab group compared with 14.3 months (95% CI 12.9–17.1) in the control group (HR 0.69, \( p = 0.001 \)). Similarly, median PFS was significantly better with avelumab (3.7 months, 95% CI 3.5–5.5) compared with best supportive care (2.0 months, 95% CI 1.9–2.7) (HR 0.62). In the PD-L1 high subset, median OS \( (p < 0.001) \) and PFS were higher in avelumab treated patients.20 A phaseII study, HCRN GU 14–182, similarly investigated maintenance pembrolizumab following first-line chemotherapy. In this positive study, median PFS, the primary endpoint, was 5.4 months with pembrolizumab (95% CI 3.1–7.3 months) compared with 3.0 months with placebo (95% CI 2.7–5.5) (HR 0.65, \( p = 0.04 \)). There was no statistically significant difference in OS between the two trial arms, however. Median OS in the pembrolizumab arm was 22 months (95% CI 12.9–NE).21 In a discussion following presentation of the Javelin-100 data, avelumab and pembrolizumab maintenance were compared with previously published results of first-line checkpoint inhibition monotherapy or first-line chemoinmunotherapy. In this comparison, the maintenance strategy resulted in the longest OS, with the caveat of differences between clinical scenarios and further studies being necessary to support this conclusion.22 A single-arm phase II study evaluated combination of gemcitabine, cisplatin, and ipilimumab following two cycles of gemcitabine plus cisplatin. In this study, there was 69% ORR and 61% 12-month OS, which was the primary endpoint.23

Novel front-line immunotherapy combinations

Immune checkpoint inhibition combined with other novel therapies has also been explored in the first-line setting. Enfortumab vedotin is an antibody-drug conjugate with a monoclonal antibody binding to the nectin–4 protein linked to the payload chemotherapeutic monomethyl auristatin E (MMAE). Enfortumab vedotin was combined with pembrolizumab in the EV-103 trial. ORR, the primary endpoint, was 73.3% (95% CI 58.1–85.4) with 15.6% of patients demonstrating complete response, and response appeared durable.24,25 Based on these findings, this combination has been granted priority review by the US Food and Drug Administration (FDA), and the phase III trial EV-302 is an ongoing study randomizing treatment naïve advanced urothelial carcinoma patients to enfortumab vedotin and pembrolizumab or platinum-based chemotherapy.14 Additionally, the combination of tyrosine kinase inhibitors, such as lenvatinib and cabozantinib, with immune-checkpoint inhibitors are currently enrolling patients in the first line setting for cisplatin-ineligible advanced urothelial carcinoma (Table 1).

Table 1. Ongoing phase II and III studies of first-line immune checkpoint inhibition in metastatic urothelial carcinoma.

| Study                  | Phase | Experimental arm                              | Reference                      |
|------------------------|-------|----------------------------------------------|--------------------------------|
| NILE [ClinicalTrials.gov identifier: NCT03682068] | III   | Durvalumab + Tremelimumab + Chemotherapy     | Galsky et al.12                 |
| CheckMate901 [ClinicalTrials.gov identifier: NCT03036098] | III   | Nivolumab + Ipilimumab +/- Chemotherapy      | Galsky et al.13                 |
| EV-302 [ClinicalTrials.gov identifier: NCT04223856] | III   | Enfortumab + Pembrolizumab                   | van der Heijden et al.14        |
| LEAP-011 [ClinicalTrials.gov identifier: NCT03898180] | III   | Pembrolizumab + Lenvatinib                   | Loriot et al.15                 |
| PemCab [ClinicalTrials.gov identifier: NCT03534804] | II    | Pembrolizumab + Cabozantinib                 | ClinicalTrials.gov16            |
| KEYNOTE-672/ECHO-307 [ClinicalTrials.gov identifier: NCT03361865] | III   | Pembrolizumab + Epacadostat                 | Balar et al.17                  |
and epacadostat, an indoleamine-2,3 dioxygenase (IDO) inhibitor, demonstrated safety and efficacy in a phase I/II trial of advanced urothelial carcinoma,26 and is currently under investigation for front-line treatment of advanced urothelial carcinoma patients who are cisplatin-ineligible (Table 1). Additional combinations, including cabozantinib plus atezolizumab,27 sacituzumab govitecan plus pembrolizumab,28 and sitravatinib plus nivolumab,29 are currently under evaluation in refractory settings but will be explored as front-line therapy if they demonstrate activity.

Biomarkers of immunotherapy

With the emergence of several therapeutics with different mechanisms of action, predictive biomarkers are increasingly important to attain the optimal patient selection. PD-L1 expression studies in urothelial carcinoma have revealed many shortcomings amongst PD-L1 assays including disparate cellular populations and scores.30,31 Since PD-L1 scoring is unable to accurately select all responders to immunotherapy, further standardization is necessary to establish utility of PD-L1 scoring as a predictive biomarker.31 Other more promising biomarkers include tumor mutational burden (TMB), tumor infiltrating lymphocytes, and gene expression profiles. The KEYNOTE-158 trial demonstrated improved outcomes in solid tumor patients with high TMB, as defined by 10 or more mutations per megabase.32 Similar to approval for microsatellite instability-high tumors,33,34 pembrolizumab was recently granted accelerated approved by the FDA for high TMB tumors, including urothelial carcinoma.35,36 TMB is relatively high in urothelial carcinoma compared with other cancers, with a median of 7.2 versus 3.6 mutations per megabase, respectively.37,38 Furthermore, high TMB has been associated with improved response to immune checkpoint inhibition in urothelial carcinoma.5,30 Additionally, in studies including IMvigor210, the presence of tumor infiltrating lymphocytes also predicts favorable response to immune checkpoint inhibition in urothelial carcinoma.40-42 Gene expression analysis has also been used to predict markers of response and resistance to immune checkpoint inhibition. DNA damage repair mutations have been reported as a favorable predictive biomarker.23,43 An interferon gamma (IFN-γ) based immune genetic signature also correlated with improved response to Nivolumab in the CheckMate275 trial.44 In the future, a composite biomarker may optimize the predictive role of these and other biomarkers but would require prospective validation. Moreover, biomarkers of resistance to immune checkpoint inhibition have been reported, including peroxisome proliferator-activated receptor gamma (PPARγ)/retinoid X receptor alpha (RXRa) and transforming growth factor beta (TGF-β), that could provide future targets for patients who do not respond to immunotherapy.45,46

Conclusions

In summary, immunotherapy has shown great promise as front-line treatment in advanced urothelial carcinoma. Approved treatments include pembrolizumab and atezolizumab monotherapy as well as avelumab maintenance therapy. Combinations between immune checkpoint inhibitors as well as with chemotherapy are still under evaluation and have demonstrated varying efficacy in early phase clinical trials. There may also be synergy between immune checkpoint inhibitors and other novel therapies. Finally, further investigation in putative biomarkers is needed to unlock the full potential of immunotherapy in urothelial carcinoma.

Author contributions

J.B. and P.B. were involved in literature review and composition of the manuscript. S.K. and J.G. helped review the manuscript and offered suggestions for improvement.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Research ethics and patient consent

In this editorial work, there were no patients involved. Therefore, ethical board approval was not necessary.

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