Integration of Immunotherapy Into the Treatment of Advanced Urothelial Carcinoma

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ABSTRACT

Five new PD-1/PD-L1 checkpoint inhibitors have been approved for the treatment of metastatic urothelial carcinoma (UC): pembrolizumab, atezolizumab, durvalumab, nivolumab, and avelumab. Although cisplatin-based chemotherapy remains the recommended frontline option for cisplatin-eligible patients with metastatic UC, immunotherapy is now an available option in the second-line setting as well as the frontline setting for selected cisplatin-ineligible patients who are either unable to tolerate chemotherapy or PD-L1–positive. This review describes the updated clinical efficacy of these checkpoint inhibitors in the treatment of advanced UC and suggests how they can be sequenced in the context of available chemotherapeutic options.

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More than 80,000 new cases of urothelial cancer (UC) are diagnosed annually in the United States, with approximately 18,000 deaths occurring from the disease.¹ Although most UC arises from the bladder, approximately 10% originates in the upper urinary tract. Approximately 50% of patients with localized UC experience recurrence after cystectomy and approximately 4% present with metastatic UC (mUC) at diagnosis.²

Cisplatin-based chemotherapy remains the standard first-line treatment for mUC, with encouraging overall response rates (ORRs) of approximately 60% to 70%,³ and is historically associated with an overall survival (OS) of 14 to 15 months and a 5-year survival rate of 13% to 15%.⁴ After failure of first-line chemotherapy, mUC is a universally fatal malignancy, with a median survival of 6 to 7 months. Additionally, because UC is largely a disease of the elderly (aged >65 years),⁵ approximately 30% to 50% of patients are not cisplatin-eligible due to renal dysfunction, ECOG performance status (PS) ≥ 2 , or comorbidities, such as cardiac dysfunction, neuropathy, and hearing loss.^{6,7}

During the past 5 years, immune checkpoint blockade has become available as a new option for patients with mUC, and 5 immunotherapeutic agents have received FDA approval for this indication: the anti-PD-L1 therapies atezolizumab, durvalumab, and avelumab, and the anti-PD-1 therapies nivolumab and pembrolizumab, which are approved for patients who experience disease progression after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Two of these agents, atezolizumab and pembrolizumab, are also approved for frontline treatment of selected cisplatin-ineligible patients with locally advanced or metastatic UC. Additionally, early data from clinical trials combining chemotherapy with immunotherapy in the frontline setting are also now available. This article reviews the data that led to FDA approval of these agents for mUC in patients who are ineligible or refractory to platinum-containing chemotherapy. We also provide suggestions on how to integrate these therapies into clinical practice.

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Second-Line Therapy for mUC

Atezolizumab

Checkpoint blockade immunotherapy for UC was first investigated in the second-line setting among patients with platinum-refractory disease. Atezolizumab is an engineered anti-PD-L1 agent that received accelerated approval by the FDA in May 2016 for the treatment of patients with locally advanced or metastatic UC in the post-platinum setting. FDA approval was granted based on results from cohort 2 of IMvigor210, an international, multicohort, single-arm phase II study of atezolizumab (1,200 mg every 3 weeks) for the treatment of advanced UC.⁸ Cohort 2 consisted of patients with platinum-refractory mUC. The primary end point was ORR, and results were stratified by the degree of PD-L1 expression by immunohistochemistry on tumor-infiltrating immune cells (ICs). Patients treated with atezolizumab achieved an ORR of 13.4% (5% complete responses [CRs]). The IC2/3 subgroup (patients with tumor-infiltrating IC PD-L1 expression $\geq 5\%$) was enriched for responses (23% ORR, 11% CR). This proportion is higher than that seen with most standard systemic chemotherapies in this setting ($\sim 10\%$).^{9–11} OS was 7.9 months for the entire population and 11.4 months for patients with IC2/3. Updated efficacy data of the phase Ia trial using atezolizumab indicated that the median duration of response (DoR) with atezolizumab was 22.1 months.¹²

These encouraging results led to IMvigor211, a phase III study comparing atezolizumab versus physician's choice chemotherapy (docetaxel, paclitaxel, or vinflunine) for platinum-refractory UC.¹³ The primary endpoint of the study was OS among the PD-L1 IC2/3 subgroup. The trial accrued 931 patients, 25% of whom were PD-L1 IC2/3. In the PD-L1-high group, median OS was 11.1 months for atezolizumab versus 10.6 months for chemotherapy (hazard ratio [HR], 0.87; 95% CI, 0.63–1.21; $P=.41$) and thus the trial did not meet its primary endpoint.¹³ However, in the overall cohort, post hoc survival analysis demonstrated a statistically significant survival benefit (8.6 vs 8.0 months; HR, 0.85; 95% CI, 0.73–0.99; $P=.038$). One reason commonly cited for failure to meet the primary endpoint was the unexpected high response rate to chemotherapy in the IC2/3 group, underscoring the importance of biomarker development before it is used as a primary endpoint for randomized trials.

Pembrolizumab

Pembrolizumab is an anti-PD-1 monoclonal antibody that received full FDA approval in the second-line setting in May 2017 based on the phase III KEYNOTE-045 study in which 542 patients were randomized to pembrolizumab, 200 mg every 3 weeks versus chemotherapy.¹⁴ In contrast to IMvigor211, KEYNOTE-045 was designed to detect a

difference in OS and progression-free survival (PFS) across the entire cohort. Although the chemotherapy arm of the trial had a longer median PFS (3.3 vs 2.1 months) compared with pembrolizumab, the median OS was superior for pembrolizumab compared with chemotherapy (10.3 vs 7.4 months, respectively; $P<.01$). Unlike IMvigor211, PD-L1 status by immunohistochemistry was defined by the combined positive score (CPS), which was the sum of the percentage of PD-L1-expressing tumor cells (TCs) and ICs as a fraction of the number of TCs. As in IMvigor211, the ORR was 21.1% in the overall study population and 20.3% among PD-L1-positive patients. For patients with PD-L1 CPS scores $\geq 10\%$, the median OS was higher with pembrolizumab (8.0 vs 5.2 months; $P=.005$). Even for patients with a PD-L1 CPS score $<10\%$ the OS was higher with pembrolizumab, but it did not reach statistical significance.

Nivolumab

Nivolumab is an anti-PD-1 therapy that is also FDA approved in the platinum-refractory second-line setting. CheckMate 275, a phase II trial, evaluated nivolumab monotherapy in 265 patients with metastatic or non-resectable platinum-resistant bladder cancer.¹⁵ Updated results at 33.7-month follow-up were reported at the 2019 ASCO Annual Meeting and showed an ORR of 20.7%, with a 7% CR rate, OS of 8.6 months, and median DoR of 20.3 months.¹⁶ PD-L1 expression was determined in TCs as $\geq 5\%$ or $\leq 5\%$ (and as $\geq 1\%$ or $\leq 1\%$ after protocol amendment). Responses were observed across all PD-L1 subgroups.

Durvalumab

Durvalumab, an anti-PD-L1 monoclonal antibody, received accelerated approval in May 2017 in the platinum-refractory setting based on the results of one phase I/II trial of patients with mUC receiving durvalumab, 10 mg/kg every 2 weeks for up to 1 year. In this study, PD-L1 expression $\geq 25\%$ in either ICs or TCs was considered high. As part of protocol amendments enacted during the trial, the study population was enriched for PD-L1-high patients, limiting cross-trial comparisons. Updated results included 191 patients, of whom 103 were eligible for efficacy analysis. The ORR was 17.8% in the entire population, 27.6% in PD-L1-high patients, and 5.1% in PD-L1-low/negative patients. Median PFS was 1.5 months and OS was 18.2 months for the overall population.¹⁷

Avelumab

Avelumab, an anti-PD-L1 antibody, also received accelerated approval in May 2017 in the post-platinum setting based on results of the multicohort phase Ib JAVELIN study of 249 patients with mUC who either experienced disease progression after platinum-based therapy or

were cisplatin-ineligible.¹⁸ The primary endpoint of the study was ORR. In an updated analysis of 161 patients who had been followed for at least 6 months, the ORR was 17% (24% in the PD-L1-high subgroup vs 14% in the PD-L1-low subgroup), including 6% patients with CR.¹⁸

Nivolumab/Ipilimumab

CheckMate 032 is an open-label, multicohort phase I/II trial in previously treated patients with metastatic urothelial cancer studying nivolumab alone and in combination with the CTLA-4 inhibitor ipilimumab. The study included 3 cohorts with varying doses: nivolumab, 3 mg/kg (NIVO3) (n=78); nivolumab, 3 mg/kg + ipilimumab, 1 mg/kg (NIVO3+IPI1) (N=104); and nivolumab, 1 mg/kg + ipilimumab, 3 mg/kg (NIVO1+IPI3) (N=92). The primary endpoint of the study was investigator-assessed ORR, and the study was not designed to compare the 3 cohorts. ORRs were 25.6%, 26.9%, and 38.0% in the NIVO3, NIVO3+IPI1, and NIVO1+IPI3 arms, respectively.²⁰ A phase III trial is currently comparing NIVO1+IPI3 to chemotherapy combinations and a combination of nivolumab and chemotherapy is ongoing (ClinicalTrials.gov identifier: NCT03036098).

First-Line Therapy for mUC

Cisplatin-based chemotherapy remains the standard of care in the first-line treatment of mUC. However, cisplatin-based therapy is often not well-tolerated, and approximately 30% to 50% patients are not eligible for this therapy.⁶ In these patients, carboplatin-based alternative regimens can be considered, and are associated with an ORR of approximately 36% and an OS of <1 year.²¹ In patients who are not chemotherapy candidates, immunotherapy with pembrolizumab or atezolizumab is an available option.

Atezolizumab

Atezolizumab received accelerated approval for first-line treatment of advanced UC in cisplatin-ineligible patients based on the results of cohort 1 of the phase II IMvigor210 study.²² In this study, 119 patients with locally advanced or metastatic UC who were cisplatin-ineligible and treatment-naïve received atezolizumab. Patients were most commonly cisplatin-ineligible based on renal impairment (70%) and ECOG PS of 2 (20%). As in IMvigor210 cohort 2, the primary endpoint was ORR, which was 23.9%, with 9% of patients achieving a CR at a median follow-up of 17.2 months. Although the IC2/3 subgroup was slightly enriched for responses, 20% of the IC0 patients achieved a response. Importantly, the median DoR was not reached, with 70% of patients continuing to respond after a median follow-up of almost 1.5 years.²³ Median OS was 15.9 months for the entire population, 12.3 months for IC2/3 patients, and 19.1 months for IC0/1 patients, although not statistically different.²³ The 12-month landmark survival rate was 57% (95% CI, 48–66) in all patients.

Pembrolizumab

Based on results of the phase II KEYNOTE-052 study, pembrolizumab received accelerated approval for first-line treatment of cisplatin-ineligible locally advanced or metastatic UC.²³ Updated results presented at the 2019 ASCO Annual Meeting showed that among 370 patients, the ORR was 28.6%, with 9% of patients achieving CR at a median follow-up of 11.4 months. Patients with a PD-L1 CPS of ≥ 10 had a higher ORR than those with a CPS <10 (47.3% vs 20.3%, respectively). Median DoR was 30.1 months, with 67% and 52% of responders maintaining their response for ≥ 12 and ≥ 24 months, respectively. Median OS was 11.3 months for the overall population and 18.5 months for PD-L1-positive patients.²⁴

Checkpoint Inhibitor Combination With Enfortumab Vedotin

Enfortumab vedotin (EV) is composed of the Nectin-4 antibody enfortumab coupled to the microtubule-disrupting agent monomethyl auristatin E. A phase II trial using EV in heavily pretreated patients showed an encouraging ORR of approximately 44%, leading to EV-103, a phase Ib dose-escalation study combining pembrolizumab with EV. Based on data presented in cohort A (N=45), which consisted of cisplatin-ineligible patients who received EV + pembrolizumab as first-line therapy, an ORR of 71% with a 13% complete response rate was reported. Although this efficacy signal is very encouraging, larger trials may be needed to more completely characterize the efficacy of this combination.²⁵

Checkpoint Inhibitor Combination With Platinum-Based Chemotherapy

After atezolizumab and pembrolizumab were approved for treatment of cisplatin-ineligible patients in the second- and first-line settings, subsequent trials were initiated that tested combination chemotherapy and immunotherapy, including IMvigor130, for which data were presented at the ESMO Congress 2019.²⁶ The study was initially designed for cisplatin-ineligible patients but later also enrolled cisplatin-eligible patients. A total of 1,200 patients were randomized to either chemotherapy with atezolizumab, chemotherapy with placebo, or atezolizumab alone. Approximately 60% to 70% patients received carboplatin-based chemotherapy (gemcitabine/carboplatin), and the remaining patients received gemcitabine/cisplatin. The coprimary endpoints of the study were OS and PFS for the atezolizumab/chemotherapy versus placebo/chemotherapy comparison and OS for the atezolizumab versus placebo/chemotherapy comparison.

Median PFS was improved in the atezolizumab/chemotherapy versus placebo/chemotherapy arms (8.2 vs 6.3 months; HR, 0.82; 95% CI, 0.70–0.96; $P=.007$).

Median OS results are not mature, but median OS was higher in the atezolizumab/chemotherapy arm compared with the placebo/chemotherapy arm (16.0 vs 13.4 months; HR, 0.83; 95% CI, 0.69–1.00; $P=.027$). The atezolizumab-alone arm did not show significant benefit when compared with the placebo/chemotherapy arm. Furthermore, a steep decrement in survival was seen at 3 months in the atezolizumab-alone arm, with approximately 25% of patients deceased at 3 months compared with 10% in the chemotherapy arm. These early deaths seem limited to the PD-L1 IC0/1 group, given that such a decrement was not seen among the approximately 25% of the study patients who were PD-L1–high (IC2/3). These observations are likely what led the FDA to restrict the use of single-agent atezolizumab to PD-L1–positive patients. Combination therapy was well tolerated with a safety profile consistent with each individual agent, and no evidence was seen of synergistic immune-related toxicity. Several other similar trials combining checkpoint therapies with chemotherapy are ongoing (ClinicalTrials.gov identifiers: NCT03682068, NCT02989584, NCT02853305, NCT02516241).

Based on the interim safety analyses from IMvigor130 and KEYNOTE-361 (NCT02853305), in May 2018 the FDA issued a safety alert for atezolizumab and pembrolizumab, reporting decreased survival relative to chemotherapy among the PD-L1–low subgroups. The accelerated approvals for these agents in the first-line cisplatin-ineligible setting were subsequently amended to exclude patients with PD-L1–low tumors, although first-line PD-1/L1 blockade is still an option for patients unable to tolerate carboplatin due to poor performance status or comorbidities. Published data from these trials

will be highly informative regarding the importance of PD-L1 as a predictive biomarker in mUC.

Post-Platinum Maintenance Immunotherapy

Several trials are investigating the use of immunotherapy as maintenance therapy following platinum induction in patients achieving a response to first-line platinum-based chemotherapy. In the randomized, double-blind phase II HCRN GU14-182 study, 107 patients with mUC achieving at least stable disease after up to 8 cycles of first-line platinum-based chemotherapy were randomized to pembrolizumab or placebo for 24 months; crossover was allowed. The primary endpoint of the study was PFS. Preliminary results showed that at a median follow-up of 14.7 months, PFS was significantly longer for pembrolizumab (5.4 vs 3.2 months; HR, 0.64; $P=.038$).²⁷ Similarly, JAVELIN Bladder 100 is also underway, a randomized open-label phase III trial of maintenance avelumab in patients who achieved stable disease with 4 to 6 cycles of first-line platinum-based chemotherapy (ClinicalTrials.gov identifier: NCT02603432).

Integrating Immunotherapy in Clinic

In the first-line setting, patients present with metastatic disease and are either systemic therapy–naïve or develop metastatic disease beyond 12 months after adjuvant or neoadjuvant chemotherapy. Currently, cisplatin-based regimens are standard of care for first-line treatment of mUC, and use of checkpoint inhibitors in cisplatin-eligible patients is not recommended. Use of combination atezolizumab with chemotherapy may become an available option in the future in the frontline setting; however, OS results are not yet mature, and a clinician would need to weigh the risks of cumulative toxicity

Figure 1. Decision tree to determine first-line therapy for metastatic urothelial carcinoma. PD-L1 positivity is defined as a combined positive score of ≥ 10 for patients receiving pembrolizumab and immune cell 2/3 for patients receiving atezolizumab.

Figure 2. Overall response rates of immunotherapies compared with chemotherapy in first- and second-line settings regardless of PD-L1 status. Abbreviations: EV, enfortumab vedotin; NIVO1+IPI3, nivolumab, 1 mg/kg + ipilimumab, 3 mg/kg.

^aThe study enriched its population by amending the protocol to limit enrollment to PD-L1-high patients.

against the small benefit of combination therapy. It may be that combining chemotherapy and immunotherapy would not have a significant survival benefit compared with standard sequencing of these therapies.

In patients who are cisplatin-ineligible, PD-L1 testing is recommended. In PD-L1-positive patients, immunotherapy with either atezolizumab or pembrolizumab can be considered (Figure 1). There are no data directly comparing pembrolizumab to atezolizumab in the frontline treatment of mUC. However, based on the negative results of the phase III IMvigor211 study comparing atezolizumab with physician's choice chemotherapy in the platinum-refractory setting, there may be less enthusiasm for using atezolizumab in the first-line setting.¹³ In contrast, results of the phase III KEYNOTE-045 study comparing pembrolizumab versus chemotherapy were positive, showing superiority of pembrolizumab over

chemotherapy and a higher ORR compared with atezolizumab in this setting in cross-trial comparison.¹⁴ In patients who can tolerate chemotherapy, combination therapy with gemcitabine/carboplatin can also be considered, given the relatively high ORR of 36% and OS of 9.3 months in an EORTC phase II/II trial.^{21,28}

In cisplatin-ineligible patients who are PD-L1-negative, chemotherapy with gemcitabine/carboplatin is recommended as a first-line option. However, if patients are not eligible to receive chemotherapy, then single-agent immunotherapy with pembrolizumab or atezolizumab can be considered after careful discussion with patients, given the early deaths seen in the PD-L1-low group in IMvigor130 and the approximately 75% chance of being PD-L1-low.²⁶ Single-agent chemotherapy with gemcitabine can also be used in these patients, with an ORR of approximately 20%, similar to the ORR seen in

Table 1. Cross-Trial Comparison of Carboplatin-Based Chemotherapy and Immunotherapy in the First-Line Setting in Cisplatin-Ineligible Patients

Endpoint	P/A ^{14,22} (Overall Study Population)	P/A ^{14,22} (PD-L1-Positive)	P/A ^{14,22} (PD-L1-Negative)	C + G (HCRN Phase II Trial) ²⁷ N=60	C + G (EORTC Phase II/III Trial) ²¹ N=238
ORR, %	P: 28.6 A: 23.9	P: 47.3 A: 28.0	P: 20.3 A: 21.0	38.3	36.1
DCR, %	P: 46.7 A: 30.0	P: 67.3 A: 34.0	P: N/A A: 28.0	63.3	74.0
TTP/PFS, mo	~2-3	~2-3	~2-3	7.6	5.8
DoR, mo	P: 30.1 A: NR	P: NR A: NR	P: 18.2 A: NR	5.0	NR
OS, mo	P: 11.3 A: 15.9	P: 18.5 A: 12.3	P: 9.7 A: 19.1	16.3	9.3

Abbreviations: A, atezolizumab; C, carboplatin; DCR, disease control rate; DoR, duration of response; G, gemcitabine; HCRN, Hoosier Cancer Research Network; NR, not reported; ORR, overall response rate; OS, overall survival; P, pembrolizumab; PFS, progression-free survival; TTP, time to progression.

PD-L1–negative patients receiving immunotherapy (Figure 2, Table 1).²⁹

In the post-platinum setting, there is NCCN Category 1–level evidence supporting the use of pembrolizumab as a subsequent treatment option based on randomized phase III trial data.³⁰ Atezolizumab is also an option, and although the randomized phase III IMvigor211 study of atezolizumab versus chemotherapy failed to meet its primary endpoint,¹³ this may be related to the design of the trial rather than the activity of atezolizumab. The efficacy and toxicity of atezolizumab in the biomarker-unselected group was similar to what was seen in the nonrandomized trials. Durvalumab, nivolumab, and avelumab have similar efficacy and are reasonable options but have lower level of evidence compared with pembrolizumab. In cross-study comparison, response rates are superior to historical controls with second-line single-agent chemotherapy (Figure 2). Other drugs, such as the antibody-drug conjugate EV and anti-fibroblast growth factor receptor therapies, are beyond the scope of this review, but are also promising second- or third-line agents.

Conclusions

In the future, choice of drug will likely depend on several biomarkers, such as PD-L1, neoantigen and mutational

burden, molecular subtypes, and interferon- γ signatures that are being studied.^{8,31,32} Other factors, such as dosing, schedule, and cost, will also influence drug selection. Although cisplatin-based chemotherapy remains the standard of care in the first-line setting for patients who are cisplatin-eligible, several similarly efficacious drugs are available in the post-platinum setting. There are currently no level 1 data available to compare efficacy or toxicity between these agents, nor are there data to support any role for switching PD-1 pathway therapies at progression. Whether to give these drugs intermittently and the total length of treatment are also unclear at this time. Use of maintenance immunotherapy in patients experiencing response to cisplatin-based chemotherapy also remains undetermined.

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