

Approved checkpoint inhibitors in bladder cancer: which drug should be used when?

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Abstract: The treatment of advanced metastatic urothelial carcinoma has recently evolved with the approval of five checkpoint inhibitors. In the second-line setting, in patients who have progressed on cisplatin-based chemotherapy, pembrolizumab, atezolizumab, durvalumab, nivolumab and avelumab are United States Food and Drug Administration (FDA) approved. In cisplatin-ineligible patients, atezolizumab and pembrolizumab are the FDA-approved checkpoint inhibitors. Here we describe the updated clinical efficacy of these checkpoint inhibitors in the treatment of advanced urothelial carcinoma and then suggest how they can be sequenced in the context of available chemotherapeutic options. For cisplatin-eligible patients, platinum-based chemotherapy remains the standard first-line treatment. For patients progressing on platinum-based therapy, phase III trials have been performed comparing pembrolizumab and atezolizumab separately with standard chemotherapy, and results favor the use of pembrolizumab.

Keywords: checkpoint inhibitor, chemotherapy, immunotherapy, predictive biomarker, urothelial carcinoma

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Urothelial carcinoma (UC) of the bladder is categorized into three main disease states based on clinical staging: nonmuscle invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC) and metastatic UC. At diagnosis, about 70% of patients with UC present with NMIBC.¹ These patients are treated with localized therapies including transurethral resection of the bladder tumor (TURBT) and adjuvant intravesical agents like *Bacillus Calmette–Guérin* (BCG) or chemotherapy. MIBC, which accounts for about 20% of initially diagnosed UC,¹ is treated with neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy. Bladder-sparing approaches using trimodal therapy with TURBT and chemoradiation are also used. Despite aggressive therapy, MIBC has about 50% chance of progressing to generally incurable metastatic disease, particularly in patients with advanced T-stage and lymph-node-positive disease at surgery. About 10% of patients with UC present with metastatic disease.

Cisplatin-based chemotherapy remains the standard for treatment in patients with metastatic UC.

The overall response rates (ORRs) are 60–70% with cisplatin-based chemotherapy² and are associated with an overall survival (OS) of 14–15 months and a 5-year survival of 13–15%.³ In patients who relapse after platinum-based chemotherapy, the ORR is about 15% and the median OS is about 7 months based on a meta-analysis of trials of second-line, single-drug taxane or vinflunine.^{4–7} Cisplatin-ineligible patients have a median OS of 8–9 months with first-line carboplatin-based combination chemotherapy.⁸

More recently, immune-checkpoint blockade has become available as a new option for patients with metastatic UC. Programmed cell-death 1 (PD-1) is a receptor expressed on activated T cells that binds to the programmed cell-death ligand 1 (PD-L1), found on the surface of normal cells and limits the immune response, thus acts as a checkpoint.⁹ Some cancer cells express PD-L1 as a mechanism to prevent T-cell activation, thereby evading an immune system attack. PD-L1 expression appears to increase in higher-grade and more advanced disease,^{10,11} and may also be

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associated with an increased chance of response to treatment including with either chemotherapy or immunotherapy, although phase III trials have not shown PD-L1 to be a reliable predictive marker.^{12–14} In the past year, five immunotherapeutic agents have received approval in the treatment of metastatic UC. These include anti-PD-L1 therapies, atezolizumab, durvalumab and avelumab, and anti-PD-1 therapies, nivolumab and pembrolizumab.

Immunotherapeutic agents have obtained United States Food and Drug Administration approval (FDA) in two settings in patients with advanced UC (Table 1). The first setting is in patients with locally advanced or metastatic UC who have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. Atezolizumab, pembrolizumab, nivolumab, durvalumab and avelumab are all approved in this space, as of 1 December 2017. Two of these agents, atezolizumab and pembrolizumab, are also approved for frontline treatment for cisplatin-ineligible patients with locally advanced or metastatic UC. Reasons for cisplatin-ineligibility include patients with renal dysfunction, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥ 2 , or comorbidities such as cardiac dysfunction, neuropathy and hearing loss.¹⁵

Here, we review the data that led to FDA approval of these agents in treatment of metastatic UC in platinum-refractory and platinum-ineligible patients. We also provide an opinion about how best to sequence therapy, especially given the availability of several treatment options.

Approved agents in the platinum-refractory setting

Atezolizumab

Atezolizumab is an engineered human monoclonal immunoglobulin G1 (IgG1) antibody against PD-L1 that received accelerated approval by the FDA in May 2016 for treatment of patients with locally advanced or metastatic UC in the postplatinum setting. FDA approval was granted on the basis of results from cohort 2 of a phase II trial (IMvigor 210) which included 310 patients with locally advanced or metastatic bladder cancer refractory to platinum-based chemotherapy.¹⁴

Patients received atezolizumab 1200 mg every 3 weeks, and the ORR was 16%, including a complete response (CR) rate of 6% at a median follow-up period of 11.7 months. Immunohistochemistry (IHC) on archival tumor tissue was performed on both tumor cells (TCs) and immune-infiltrating immune cells (ICs; macrophages, dendritic cells and lymphocytes). Tumors were classified as IHC 0, 1, 2 or 3 if $<1\%$, $\geq 1\%$ but $<5\%$, $\geq 5\%$ but $<10\%$ or $\geq 10\%$ of cells were positive for PD-L1 expression, respectively, both for TCs and ICs. For patients with IC IHC 2/3 the ORR was even higher (27%). This proportion is higher than that seen with most standard systemic chemotherapies in this setting ($\sim 10\%$).^{4,16,17}

The median progression-free survival (PFS) was 2.1 months by central review and 2.7 months by investigator assessment for the entire population. The OS was 7.9 months for the entire population and 11.4 months for patients with IC 2/3. Updated efficacy data of the phase Ia trial presented at ASCO 2017 indicated median duration of response (DOR) with atezolizumab was 22.1 months and 1-year OS rate was 29%.¹⁸

An analysis of outcomes by the number of prior lines of therapy conducted after a median follow up of 21.1 months showed that response was observed regardless of the number of prior regimens and responses appearing durable across the subgroups.¹⁹

Despite these promising results, recent findings from the phase III IMvigor 211 study comparing atezolizumab with physician's choice chemotherapy (docetaxel, paclitaxel or vinflunine) failed to show an improvement in OS for those with high PD-L1 expression, the primary endpoint of the study.²⁰ The trial accrued 931 patients, total, and 25% of patients were found to have high PD-L1 expression of IHC 2/3 as defined above. In the PD-L1-high group, median OS was 11.1 months with atezolizumab *versus* 10.6 months for chemotherapy [hazard ratio (HR): 0.87; 95% confidence interval (CI), 0.63–1.21, $p = 0.41$] and thus the trial did not meet its primary endpoint. In the overall study population of the IMvigor 211 study there was a small improvement in OS with atezolizumab *versus* chemotherapy (8.6 *versus* 8.0 months; HR, 0.85; 95% CI, 0.73–0.99, $p = 0.038$). Consistent with the phase II findings, however, there was a significant prolongation in the median DOR with atezolizumab *versus* chemotherapy (21.7 *versus* 7.4 months).

Table 1. Trials with approved checkpoint inhibitors in advanced urothelial carcinoma.

Drug/trial name	Phase	Patients, <i>n</i>	ORR	Median PFS	Median OS	Duration of response	Grade 3/4 AE (treatment-related deaths)	Maximal duration of treatment
Cisplatin refractory								
Atezolizumab IMvigor 210 cohort 2	II	310	16% (6% CR)	2.1 months	7.9 months (1 year 29%)	22.1 months	18% (0 deaths)	NR
Atezolizumab IMvigor 211	III	931	13%	NR	8.6 months	21.7 months	20%	NR
Pembrolizumab KEYNOTE-045	III	542	21%	2.1 months	10.3 months	NR	14% (4 deaths)	2 years
Nivolumab CheckMate 275	II	265	19.6% (2% CR)	2 months	8.7 months	NR	18% (3 deaths)	NR
Avelumab JAVELIN	Ib	242*	17% (6% CR)	6.6 weeks	6.5 months	NR	10% (1 death)	NR
Durvalumab	I/II	191	17.8% (4% CR)	1.5 months	18.2 months	NR	7% (2 deaths)	1 year
Cisplatin ineligible								
Atezolizumab IMvigor210 cohort 1	II	119	23% (9% CR)	2.7 months	15.9 months [1 year OS 57%]	NR	16% (1 death)	NR
Pembrolizumab KEYNOTE-052	II	370	29% (7% CR)	[6 month PFS: 30%]	[6 month OS: 67%]	NR	19% (1 death)	2 years

* 161 patients with follow up of at least 6 months.

CR, complete response; AE, adverse event; NR, not reported; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Pembrolizumab

Pembrolizumab is an IgG4k 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 for 2 years *versus* chemotherapy.²¹ PD-L1 status by IHC was defined by the combined positive score (CPS), which was the sum of the percentage of PD-L1 expressing TCs and ICs as a fraction of the number of TCs.

The trial met its primary endpoint showing superiority of pembrolizumab over chemotherapy at interim analysis, leading the independent data monitoring committee to recommend early termination of the trial. Although the chemotherapy arm of the trial had a longer median PFS (3.3 *versus* 2.1 months) compared with pembrolizumab, the median OS was superior with pembrolizumab compared with chemotherapy at 10.3 *versus* 7.4 months for ($p < 0.01$). For PD-L1 CPS score $\geq 10\%$, there was a median OS advantage with pembrolizumab (8.0 *versus* 5.2 months, $p = 0.005$). For patients with PD-L1 CPS score $< 10\%$, there was numerically greater OS with pembrolizumab but it did not reach statistical significance. Additionally, the ORR in the pembrolizumab cohort was nearly double that for chemotherapy (21.1% *versus* 11.4%). Updated efficacy data of the phase Ia trial using pembrolizumab showed that at a median follow up of 13 months, the ORR was 26%, with 11% having CR and 15% with partial responses.²² The DOR was longer with pembrolizumab (median not reached *versus* 4.3 months). The median PFS was not different in the two groups (2.1 *versus* 3.3, $p = 0.98$).

Nivolumab

Nivolumab is a humanized IgG4 monoclonal antibody targeting PD-1 that is also FDA approved in the platinum-refractory second-line setting. A phase II trial (CheckMate 275) evaluated nivolumab monotherapy in 265 patients with metastatic or nonresectable platinum-resistant bladder cancer and reported a ORR in 19.6% patients.²³ PD-L1 expression was determined in TC as $\geq 5\%$ or $\leq 5\%$ (and after protocol amendment as $\geq 1\%$ or $\leq 1\%$). ORR in PD-L1 TC $\geq 1\%$ was 23.8% and for PD-L1 $\geq 5\%$ was 28.4%. Median PFS was 2 months and median OS was 8.7 months in the overall population. The researchers also investigated whether a relationship existed between molecular subtype of

bladder cancer and response to immune-checkpoint inhibition as described below.

Durvalumab

Durvalumab, an IgG1k anti-PD-L1 monoclonal antibody, received accelerated approval in May 2017 in the platinum-refractory setting based on one single-arm phase I/II trial of patients with locally advanced or metastatic UC receiving durvalumab 10 mg/kg every 2 weeks for up to 1 year. Tumor testing was required and PD-L1 expression $\geq 25\%$ in either ICs or TCs were considered high. The study population was enriched for PD-L1-high patients as part of protocol amendments enacted during the trial. Updated results published recently report 191 patients, of whom 103 were eligible for efficacy analysis. The ORR was 17.8% in the entire population with seven complete responses, with an ORR of 27.6% in PD-L1 high and 5.1% in PD-L1 low/negative. Median PFS and OS were 1.5 months and 18.2 months, respectively, for the overall population.²⁴

Avelumab

Avelumab is a humanized IgG1 anti-PD-L1 antibody which also received accelerated approval in May 2017 in the postplatinum setting based on the results of a large phase Ib study (JAVELIN) that included a pooled cohort analysis of 249 patients with metastatic UC who had either progressed after platinum-based therapy or were cisplatin-ineligible.²⁵ In an updated analysis of 161 patients who had been followed for at least 6 months, ORR was 17%, including 6% patients with CR. Median DOR was not reached.²⁶ The median PFS was 6.6 weeks and median OS was 6.5 months.

Approved agents in the platinum-ineligible setting

Atezolizumab

Atezolizumab also received first-line accelerated approval for cisplatin-ineligible patients based on the results of cohort 1 of the phase II IMvigor 210 study. This study included 119 patients with locally advanced or metastatic UC who were cisplatin-eligible and treatment naïve. In these patients, ORR was 23%, including 9% of patients with CR at a median follow up of 17.2 months. The ORR for IC 2/3 was 28% and 21% for IC 0. Median DOR was not reached, with 70% of

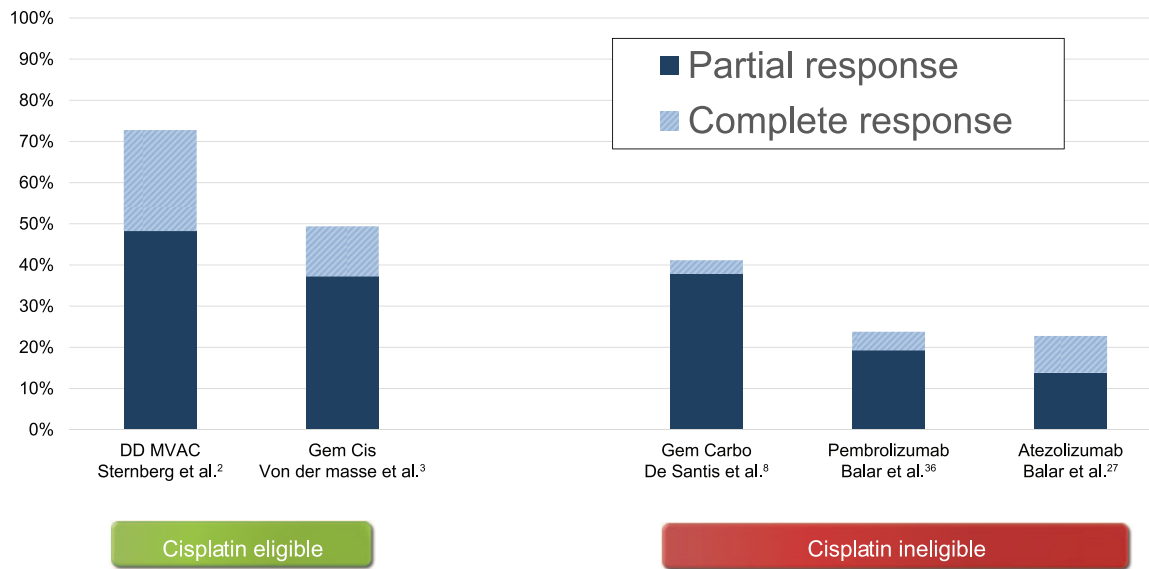


Figure 1. Response rates to first-line therapy for metastatic urothelial carcinoma.

DD, dose dense; MVAC, methotrexate, vinblastine, doxorubicin, and cisplatin; Cis, cisplatin; Gem, gemcitabine; Carbo, carboplatin.

patients continuing to respond after a median follow up of almost 1.5 years. The median PFS was 2.7 months for the entire population, 4.1 months for IC 2/3 and 2.6 months for IC 0. The median OS for the entire population was 15.9 months, 12.3 months for IC 2/3 and 19.1 months for IC 0/1 (not statistically different).²⁷

Pembrolizumab

Pembrolizumab received first-line accelerated approval for cisplatin-ineligible locally advanced or metastatic UC based on the results of the phase II KEYNOTE-052 study.²⁸ Among 370 patients, ORR was 29%, with 7% of patients achieving CR at a median follow up of 9.5 months. PD-L1 CPS of $\geq 10\%$ had a higher ORR of 51%. Median DOR was not reached, with 82% of responders maintaining their response for ≥ 6 months. At a median follow up of 5 months, estimated PFS and OS rates were 30% and 67% at 6 months, respectively.²⁹

Determining sequence of therapy

The first-line setting is defined as patients who present with metastatic disease who are either systemic therapy naïve or who develop metastatic disease beyond 12 months after adjuvant or neo-adjuvant chemotherapy. At this time, frontline cisplatin-based regimens have higher ORR and median OS compared with the approved

checkpoint inhibitors in the settings in which they have been tested to date (Figure 1), although the first-line PD1/PDL1 trials were phase II nonrandomized trials and cross-trial comparison should be performed with caution. However, no data are yet available on the use of checkpoint inhibitors in the cisplatin-eligible population. The ongoing DANUBE trial investigating durvalumab alone or in combination with tremelimumab in the frontline setting will provide the first checkpoint inhibitor data in a platinum-eligible frontline cohort. Until further trial results emerge, we recommend cisplatin-based chemotherapy with dose-dense MVAC (methotrexate, vinblastine, adriamycin, cisplatin) for eligible patients.² For patients truly ineligible for cisplatin, the use of atezolizumab or pembrolizumab is reasonable, based on patient tolerability and a higher likelihood of a durable response. We await randomized data to determine if this is the case. It is noted that based on response rate alone, the checkpoint inhibitors have not yet yielded superior results in cross-study comparison (Figure 1).

In the postplatinum setting, randomized phase III trial data clearly support the use of pembrolizumab, leading to a ‘level 1’ National Comprehensive Cancer Network guideline recommendation in this setting.¹ While it is noted that IMvigor 211, the randomized phase III study of atezolizumab *versus* chemotherapy, failed to meet its primary endpoint, the explanation for this

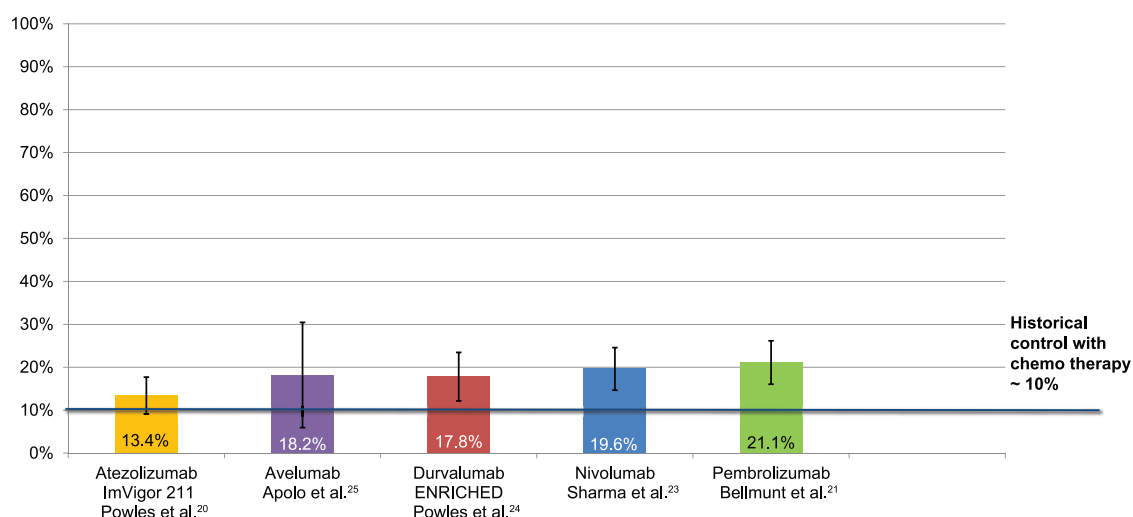


Figure 2. Overall response to programmed cell-death ligand 1 checkpoint inhibitors in urothelial cancer postplatinum in biomarker unselected patients. Enriched for PDL1+: the study enriched its population by amending to limit enrollment to PD-L1 high.

failure may lie more in the design of the trial than the activity of the atezolizumab. Specifically, the complex biomarker-based nested primary endpoint design coupled with the ultimately low predictive power of the biomarker seems to have doomed the study, precluding evaluation of the other predetermined endpoints. It is noted that the efficacy and toxicity of atezolizumab in the biomarker unselected group was similar to what was seen in the nonrandomized trials. The other three agents, durvalumab, nivolumab and avelumab, all show similar characteristics, and all four agents are reasonable options, based on lower-level evidence as compared with the evidence supporting pembrolizumab. In cross-study comparison of response rates, all are similar and superior to historical controls with chemotherapy (Figure 2).

Biomarkers may help identify patients who would most benefit from approved immunotherapy. Several clinical trials in the postplatinum setting showed that increased PD-L1 expression was associated with a higher ORR,^{14,19,23,24} but due to variability of PD-L1 testing methods (some consider expression only on ICs or TCs) and dynamic expression of the PD-L1 ligand, PD-L1 testing has not been an ideal predictive marker. Additionally, patients with lower PD-L1 expression also may attain a clinically relevant and durable response, thus using PD-L1 expression to deny patients access is not recommended at this time. For example, in the phase I trial using atezolizumab, ORR correlated with higher PD-L1 by tumor-infiltrating IC IHC ($p = 0.026$) but not

TC ($p = 0.93$). ORRs were higher for patients with immune cell IHC $> 5\%$ (43%) but were also observed in patients with $< 5\%$ PD-L1 expression (13%). Similarly in KEYNOTE-045, the benefit of pembrolizumab was independent of PD-L1 expression on TC and IC.²¹

More promising biomarkers have recently been described in the literature, including neoantigen and mutational burden, molecular subtypes and interferon gamma signature.^{14,30,31} Mutational burden is estimated by next-generation sequencing in tumor tissue and is associated with improved ORR and OS in single-arm trials, but further testing in prospective randomized studies is required to validate it as a reliable predictive marker. For instance, in IMvigor 210, mutation burden was assessed using an next generation sequencing (NGS) multi-gene panel performed by Foundation Medicine and the mutation burden was higher in responders versus nonresponders (12.4/Mb versus 6.4/Mb, $p < 0.0001$), but validation of this association in the IMvigor 211 study is ongoing. A recent study reported that DNA damage repair alterations, which are independently associated with increased mutation load, are associated with response to PD-1/PD-L1 blockade in metastatic UC.³²

Molecular subtypes have been described based on The Cancer Genome Atlas (TCGA) clusters, but their predictive role is not clear yet due to variation in the molecular categorizations. In the IMvigor 210 study, patients with IC 2/3 were present in 15% of luminal cluster I, 34% of luminal

cluster II, 68% of basal cluster III and 50% of basal cluster IV. Response to atezolizumab occurred in all subtypes but was most common in the luminal II group (34%) as compared with 10% in luminal cluster I, 16% in basal cluster III and 20% in basal cluster IV. Thus, although the basal cluster correlates with high PD-L1 immune-cell expression by IHC, the luminal II cluster was best associated with response to atezolizumab.¹⁴ These results also differ from the phase II nivolumab study in which patients with basal cluster III had higher ORR compared with other subtypes. Again, prospective testing as part of the two completed randomized trials, KEYNOTE-045 and IMvigor 21, will be extremely valuable.

Finally, the interferon gamma gene expression signature has been studied in four clinical trials using atezolizumab, nivolumab, durvalumab and pembrolizumab and is shown to be associated with higher ORR, PFS and OS,^{14,23,28,33} but validation in prospective studies is needed before clinical application.

In the future, choice of drug will likely depend on molecular subtype and other emerging biomarkers, dosing, schedule, and cost. While cisplatin-based chemotherapy remains the standard of care in first-line setting for patients who are cisplatin eligible, in the postplatinum setting, several similarly efficacious drugs are available. At this time, there are no level I data 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 or not to give these drugs intermittently, and total length of treatment, is unclear at this time.

Determining duration of therapy

Another area of uncertainty in the use of immunotherapy for UC is the optimal duration of therapy in the responders. In a *post hoc* analysis of the IMvigor 210 study assessing disease response in patients receiving atezolizumab beyond progression (per RECIST v1.1), 2 of 137 patients were found to have partial response and 3 of 137 patients had CR.³⁴ Similarly, analysis of these data suggests that in some patients, delayed responses may occur and treatment beyond progression can be considered. However, pseudoprogression is not very common in UC, and only patients with no clinical progression and mild radiographic progression should be considered for treatment beyond progression. Additionally,

in responders, the question of continuing treatment beyond CR is debated. KEYNOTE-045 and KEYNOTE-052 allowed pembrolizumab to be used for a maximum of 2 years and patients who had CR were allowed to discontinue treatment if they received at least eight doses of which at least two doses were administered after CR. The durvalumab phase II study allowed 1 year of treatment. Further molecular characterization of responders and following them prospectively may deepen our understanding of mechanisms leading to delayed (or continued) response. Finally, it's unclear if responders who discontinue treatment derive benefit from restarting immunotherapy. Analysis of the UC cohort in a phase Ia atezolizumab study reported that 11 of 25 responders discontinued treatment at cycle 16, per an earlier version of the protocol. Among them, two restarted treatment after disease progression and four restarted treatment while their disease was still in response.¹⁸

Elderly patients

Elderly patients comprise a large pool of patients with metastatic UC and treatment decisions should be guided by their comorbidities and functional status. More than 50% of patients are not eligible for cisplatin due to age or renal comorbidities.³⁵ Prior to available data with anti-PD1/PDL1 therapy, in frail elderly patients, recommended options include carboplatin or gemcitabine monotherapy or combination of gemcitabine and carboplatin, if tolerated. Subgroup analysis in randomized trials comparing chemotherapy with immunotherapy in elderly patients has shown similar efficacy in the older population. In the KEYNOTE-052 study with pembrolizumab in cisplatin-ineligible patients, about 80% patients were age 65+ (82%) and about 42% patients had ECOG PS 2 and above. These patients tolerated pembrolizumab well, with comparable response rates and adverse effect profile, suggesting that first-line pembrolizumab may be considered in these patients.³⁶

Rare bladder cancer subtypes

Clinical trials in metastatic rare bladder cancer subtypes have been limited due to the rarity and difficulty accruing in trials. However, the ongoing DART study by SWOG (dual anti-CTLA4 and anti-PD-1 blockade in rare tumors) is currently evaluating the combination of ipilimumab and

nivolumab in several rare tumors including bladder adenocarcinoma, as well as squamous cell carcinoma or the ureter and urethra [ClinicalTrials.gov identifier: NCT02834013], and the results are awaited.

Future clinical trials

Several ongoing trials comparing single-agent immunotherapy with combination immunotherapy and chemotherapy alone in first-line metastatic UC are pending. For example, there is a trial comparing durvalumab *versus* durvalumab/tremelimumab *versus* platinum/gemcitabine chemotherapy in the first-line setting for patients with metastatic UC [ClinicalTrials.gov identifier: NCT02516241], and there are other examples of such studies [ClinicalTrials.gov identifiers: NCT02807636, NCT02853305, NCT03036098]. Maintenance immunotherapy following first-line platinum-based chemotherapy is another interesting approach [ClinicalTrials.gov identifiers: NCT02500121 and NCT02603432], comparing maintenance pembrolizumab *versus* placebo and maintenance avelumab *versus* best supportive care, respectively. In the first-line setting for cisplatin-ineligible patients, clinical trials comparing immunotherapy alone or in combination with other agents are ongoing. A phase II trial comparing atezolizumab with or without bevacizumab [ClinicalTrials.gov identifier: NCT03133390], a phase II single-arm study of pembrolizumab with nab-paclitaxel [ClinicalTrials.gov identifier: NCT03240016] and a phase III trial comparing pembrolizumab with or without epacadostat (IDO1 inhibitor) [ClinicalTrials.gov identifier: NCT03361865] are examples of such ongoing trials.

Conclusion

The treatment paradigm of advanced UC has changed dramatically in recent years with the availability of checkpoint inhibitors, a new class of agents. With the approval of several agents in this class and lack of trials comparing them with one another, the optimal sequence of these agents and duration of treatment is currently not known. However, for cisplatin-eligible patients who are treatment naïve or have progressed >12 months since receiving platinum-based agents, cisplatin-based chemotherapy still remains the standard of care. For patients progressing on platinum-based therapy, phase III trials have been performed comparing pembrolizumab and atezolizumab with standard chemotherapy, and results favor

the use of pembrolizumab. In cisplatin-ineligible patients, pembrolizumab and atezolizumab have been studied but randomized trials are pending to determine their efficacy compared with noncisplatin-based chemotherapeutic agents. The ongoing immunotherapy combination trials and immunotherapy/chemotherapy combination trials are awaited and may provide better treatment options for metastatic UC patients. Additionally, these drugs are also studied in localized disease in the adjuvant and neoadjuvant setting in various trials. In the future, better biomarkers are needed to identify patients most likely to derive benefit from immunotherapy, to determine optimal sequence and duration of immunotherapy.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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