

# Profile of pembrolizumab in the treatment of patients with unresectable or metastatic urothelial carcinoma

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**Abstract:** The prognosis of patients with unresectable or metastatic urothelial carcinoma (UC) is poor. Platinum-based chemotherapy has been the standard first-line treatment in these patients for the past decade; however, the 5-year overall survival (OS) rate is only 13–22%. Recent advances in cancer immunology research have highlighted the pivotal role of the immune system in cancer development and progression, and new immune checkpoint inhibitors (ICIs) have demonstrated efficacy in a large variety of tumors including UC. Currently, five ICIs, including two anti-PD-1 antibodies (pembrolizumab and nivolumab) and three anti-PD-L1 antibodies (atezolizumab, avelumab, and durvalumab), have been granted approval by the US Food and Drug Administration (FDA) for patients with unresectable or metastatic UC who recurred or progressed after platinum-based chemotherapy. Among these agents, only pembrolizumab is supported by strong evidence from a large randomized Phase III trial (KEYNOTE-045). This trial demonstrated statistically significant improvements in OS for patients assigned to the pembrolizumab arm compared with the chemotherapy arm, both in the total population (HR 0.73;  $P=0.002$ ) and in the population with high PD-L1 expression (HR 0.57;  $P=0.005$ ). For patients with cisplatin-ineligible UC, pembrolizumab and atezolizumab were approved based on Phase II studies, with limitations on the use of these agents in patients with high tumor PD-L1 expression later imposed by the FDA. In conclusion, pembrolizumab may be a potential first-choice second-line therapy for unresectable or metastatic UC patients following platinum-based chemotherapy. Several Phase III trials are ongoing to evaluate the efficacy and toxicity of combination therapies of ICIs with chemotherapy, and ICIs with other ICIs with or without chemotherapy as first-line therapy. The results of these trials might redirect treatment strategies for patients with unresectable or metastatic UC.

**Keywords:** urothelial carcinoma, pembrolizumab, PD-1, immune checkpoint inhibitor, PD-L1

## Introduction

Urothelial carcinoma (UC) can arise from the urothelium of the entire urinary tract, including upper urinary tract (renal pelvis and ureter) and urethra, but most commonly from bladder. Bladder cancer (BC) is the seventh most commonly diagnosed cancer in the male population worldwide, and the eleventh in both sexes.<sup>1</sup> Approximately 75% of patients are diagnosed with non-muscle invasive cancer, and are managed with transurethral resection and intravesical instillation of Bacillus Calmette-Guerin (BCG) or chemotherapeutic agents.<sup>2</sup> These patients show relatively favorable prognosis, while patients with muscle-invasive BC showed

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poor prognosis and the 5-year overall survival (OS) rate of less than 50%.<sup>3</sup> Ten to fifteen percent of patients show metastatic disease at initial diagnosis, and the prognosis of these patients is poor.<sup>4</sup>

Platinum-based chemotherapy has been the standard first-line treatment in patients with unresectable or metastatic UC for the past decade. The MVAC (methotrexate, vinblastine, doxorubicine, and cisplatin) regimen was introduced with good objective response rate of 69%.<sup>5</sup> Recently, a regimen of dose-dense MVAC was introduced, which showed more favorable toxicity profile compared with the original MVAC regimen, higher complete response (CR) rate (21% vs. 9%,  $P=0.009$ ), higher overall response rate (ORR) (64% vs. 50%,  $P=0.06$ ), and comparable median OS (15.1 vs. 14.9 months).<sup>6,7</sup> The other commonly used regimen is GC (gemcitabine and cisplatin), which showed comparable OS to the original MVAC (median 14.0 vs. 15.2 months) (hazard ratio [HR], 1.09;  $P=0.66$ ), and fewer toxicities.<sup>8</sup> Despite these improvements and modifications, the median OS in patients who received cisplatin-based chemotherapy was approximately 15 months, and the 5-year OS rate was 13–22%.<sup>4,7,8</sup>

Recent advances in the understanding of immunological mechanisms against malignant neoplasms have initiated a revolution in the treatment of various solid malignancies including UC. Immune checkpoint inhibitors (ICIs) have been the leading drugs in this field, and upregulate anti-tumor activity by inhibiting the immune escape mechanism in tumor cells and immune cells.<sup>9</sup> This review summarizes critical data from recent clinical trials of ICIs for unresectable or metastatic UC, and describes pembrolizumab, currently the only agent with strong evidence.

## Immune check point inhibitors (ICIs)

Recent advances in the cancer immunology field have highlighted the pivotal role of the immune system in cancer development and progression.<sup>10</sup> Under physiological conditions, the immune system eliminates tumor cells based on its recognition of tumor-specific antigens. Cytotoxic T cells and natural killer (NK) cells are the main effectors that attack tumor cells, either directly or indirectly, and activation of these cells is tightly regulated by multiple co-stimulatory and co-inhibitory receptor signals, so-called immune checkpoints, and inflammatory cytokines. However, tumor cells can evade the host anti-tumor response through activation of co-inhibitory receptors, such as programmed cell death 1

(PD-1) and cytotoxic T lymphocyte-associated protein 4 (CTLA-4). PD-1 has two main ligands, programmed death ligand 1 and 2 (PD-L1/PD-L2) which are expressed on antigen-presenting cells (APCs) and cancer cells, and interactions with PD-1 and PD-L1/PD-L2 inhibit T cell function. Therefore, targeting these immune checkpoints is expected to lead to enhanced anti-tumor responses in a large variety of tumors including UC (Figure 1).

Anti-CTLA-4 antibodies have been reported to have excellent therapeutic effects in advanced melanoma patients.<sup>11</sup> Anti-PD-1 or anti-PD-L1 antibodies, inhibitors of the PD-1/PD-L1 pathway, were subsequently developed and used to treat patients with kidney cancer, non-small cell lung cancer, and malignant melanoma, with favorable therapeutic effects.<sup>9</sup>

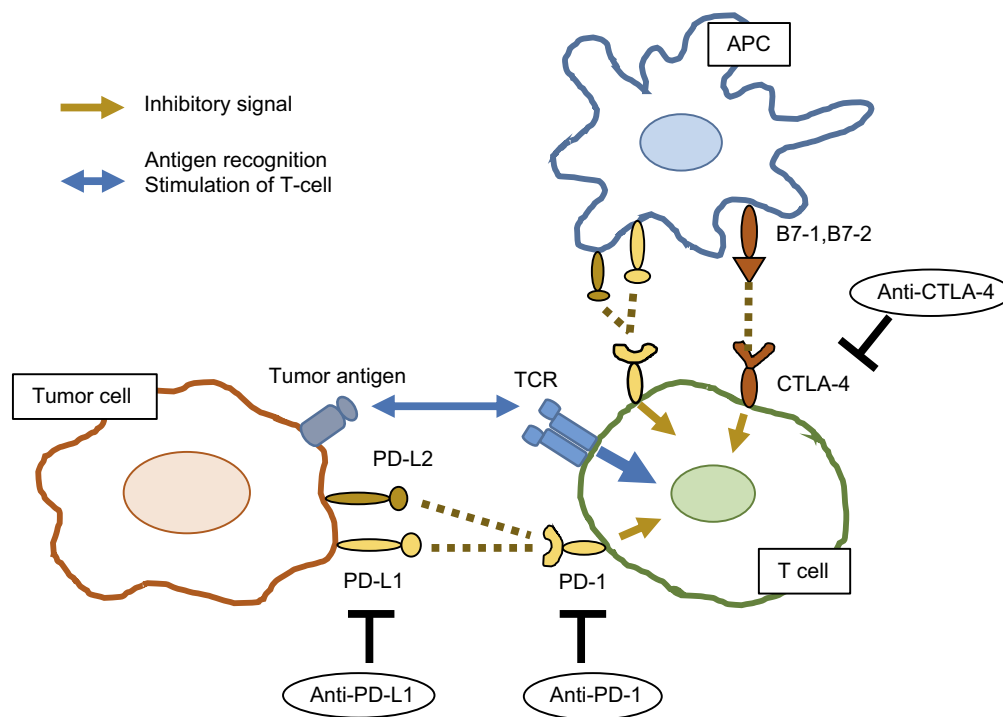
## ICIs for post-platinum-based chemotherapy setting

Since May 2006, five ICIs, including two anti-PD-1 antibodies (pembrolizumab and nivolumab) and three anti-PD-L1 antibodies (atezolizumab, avelumab, and durvalumab), have been granted approval by the US Food and Drug Administration (FDA) for patients with unresectable or metastatic US who exhibited disease progression during or following platinum-based chemotherapy (Table 1). Among these agents, only pembrolizumab is supported by strong evidence from a large randomized Phase III trial (KEYNOTE-045); therefore, the FDA granted regular approval for pembrolizumab in May 2017, while the others have received accelerated approval.

### Pembrolizumab

Pembrolizumab, a humanized monoclonal IgG4κ isotype antibody against PD-1, showed anti-tumor activity in patients with unresectable or metastatic UC in the Phase Ib KEYNOTE-012 study.<sup>12</sup> In this study, 33 patients with positive PD-L1 expression who were diagnosed with unresectable or metastatic UC were enrolled. The ORR at the median follow-up of 13 months was 26% with a CR rate of 11%, and the safety profile was acceptable. This study supported the rationale for a Phase II study (KEYNOTE-052) and a Phase III trial (KEYNOTE-045).<sup>13,14</sup>

KEYNOTE-045 was a Phase III open-label randomized trial that compared pembrolizumab with the investigator's choice of chemotherapy, including paclitaxel, docetaxel, and vinflunine, in patients with unresectable or metastatic UC that recurred or progressed after platinum-based chemotherapy.<sup>13</sup> A total of 542 patients were randomly assigned in a 1:1 ratio to



**Figure 1** Mechanisms of action of ICIs.

**Abbreviations:** APC, antigen-presenting cell; TCR, T cell receptor; PD-1, programmed cell death 1; PD-L, programmed death ligand; CTLA-4, cytotoxic T lymphocyte-associated protein 4.

**Table 1** Immune checkpoint inhibitors (ICIs) for patients with unresectable or metastatic urothelial carcinoma (UC)

	Target	Type	FDA approval	Trial phase based on approval	Assay for PD-L1 expression
Pembrolizumab	PD-1	IgG4	Post-platinum-based chemotherapy* First-line, cisplatin-ineligible	Phase III Phase II	Dako PD-L1 IHC 22C3 pharmDx assay
Nivolumab	PD-1	IgG4	Post-platinum-based chemotherapy	Phase II	Dako PD-L1 IHC 28-8 pharmDx assay
Atezolizumab	PD-L1	IgG1	Post-platinum-based chemotherapy First-line, cisplatin-ineligible	Phase II Phase II	VENTANA PD-L1 (SP142) assay
Durvalumab	PD-L1	IgG1	Post-platinum-based chemotherapy	Phase I/II	VENTANA PD-L1 (SP263) assay
Avelumab	PD-L1	IgG1	Post-platinum-based chemotherapy	Phase Ib	Dako PD-L1 IHC73-10 pharmDx assay

**Note:** \*Regular approval.

receive either pembrolizumab 200 mg every 3 weeks (n=270) or the investigator's choice of a chemotherapy regimen (paclitaxel [n=84], docetaxel [n=84], or vinflunine [n=87]) every 3 weeks (n=272). The co-primary endpoints in this trial were OS and progression-free survival (PFS), which were assessed in the total population and in the population with high tumor PD-L1 expression. In this trial, PD-L1 expression was assessed using the PD-L1 IHC 22C3 pharmDx assay (Dako North America, Inc., Carpinteria, CA), and high expression was defined as the PD-L1 combined positive score (CPS, the percentage of PD-L1-expressing tumor and infiltrating immune cells relative to the total number of tumor cells) of 10% or more.

This trial demonstrated statistically significant improvements in OS for patients assigned to the pembrolizumab arm compared with the chemotherapy arm, both in the total population and in the population with high PD-L1 expression. The median OS in the total population was 10.3 and 7.4 months in the pembrolizumab and chemotherapy arms, respectively (HR 0.73; 95% CI: 0.59–0.91;  $P=0.002$ ). The median OS in the population with high PD-L1 expression was 8.0 and 5.2 months, respectively (HR 0.57; 95% CI: 0.37–0.88;  $P=0.005$ ). However, no statistically significant difference in PFS between the two arms was observed. The median PFS in the total population was 2.1 and 3.3 months in the pembrolizumab and chemotherapy arms, respectively

(HR 0.98; 95% CI: 0.81–1.19;  $P=0.42$ ). The PFS in the population with high PD-L1 expression showed a similar tendency (HR 0.89; 95% CI: 0.61–1.28;  $P=0.24$ ). ORR was 21% for pembrolizumab and 11% for chemotherapy ( $P=0.001$ ) in the total population. The duration of response was longer in patients who responded to pembrolizumab than in those with a response to chemotherapy. The estimated percentage of patients with a response duration of at least 12 months was 68% and 35% in the pembrolizumab and chemotherapy arms, respectively. Adverse events (AEs) were reported at a lower rate in the pembrolizumab arm than in the chemotherapy arm (any grade: 61% vs. 90%; grade 3, 4, or 5: 15% vs. 49%). Based on the results of this trial, pembrolizumab was granted regular approval by the FDA for patients with unresectable or metastatic UC, regardless of PD-L1 status.

### Other ICIs (atezolizumab, nivolumab, avelumab, and durvalumab)

Atezolizumab, an anti-PD-L1 antibody, was initially investigated in patients with BC in a Phase I study. This study showed noteworthy anti-tumor activity, durable responses, and the favorable toxicity profile of atezolizumab.<sup>15,16</sup> Based on these positive results, single-arm, two cohort, Phase II study (IMVigor 210) was launched.<sup>17,18</sup> In one of the cohorts, patients with unresectable or metastatic UC whose disease had progressed after previous platinum-based chemotherapy were enrolled, showing durable anti-tumor activity and good tolerability; furthermore, there was an association between increased level of PD-L1 expression and increased responses.<sup>17</sup> The PD-L1 expression was assessed by immunohistochemistry with VENTANA SP142 assay (Ventana Medical Systems, Inc, Tucson, AZ), and the PD-L1 expression on tumor-infiltrating immune cell (IC) status was defined by the percentage of PD-L1-positive immune cells in the tumor microenvironment: IC0 (<1%), IC1 ( $\geq 1\%$ , <5%), and IC2/3 ( $\geq 5\%$ ).

To confirm the utility of atezolizumab in patients in a post-platinum-based chemotherapy setting, an open-label randomized Phase III trial (IMVigor 211) was launched, which compared atezolizumab with the investigator's choice of chemotherapy, including paclitaxel, docetaxel, and vinflunine.<sup>19</sup> A total of 931 patients were randomly assigned in a 1:1 ratio to receive either atezolizumab 1200 mg every 3 weeks ( $n=467$ ) or the investigator's choice of a chemotherapy regimen ( $n=464$ ). The primary endpoint of OS was assessed hierarchically in a population

with high PD-L1 expression (IC2/3) followed by low PD-L1 expression (IC1/2/3), and then by intention-to-treat populations. Unfortunately, in high PD-L1-expressing population, OS did not differ significantly between the atezolizumab and chemotherapy arms, and the median OS was 11.1 and 10.6 months, respectively (HR 0.87; 95% CI: 0.63–1.21;  $P=0.41$ ). However, the safety profile for atezolizumab was favorable compared with chemotherapy, and exploratory analysis of the intention-to-treat population showed longer OS in the atezolizumab arm than the chemotherapy arm (HR 0.85; 95% CI: 0.73–0.99). Taken together, these results suggest the benefit of atezolizumab in a post-platinum-based chemotherapy setting, despite the negative primary endpoint in the Phase III IMVigor 211 trial.

Nivolumab, an anti-PD-1 antibody, was investigated for its safety and anti-tumor activity in several solid tumors in an open-label, Phase I/II study (CheckMate 032).<sup>20,21</sup> In patients with unresectable or metastatic UC whose disease progressed after previous platinum-based chemotherapy, nivolumab monotherapy was associated with a substantial and durable response, as well as acceptable safety.<sup>21</sup> These results supported a single-arm Phase II study (CheckMate 275) in patients in post-platinum-based chemotherapy setting.<sup>22</sup> A total of 270 patients were enrolled and treated with nivolumab 3 mg/kg every 2 weeks. Among 265 evaluable patients, ORR was approximately 20% with 2% CR. Based on this study, the FDA granted accelerated approval to nivolumab, and recommended the dose and schedule for the above indication as 240 mg intravenously every 2 weeks.

Avelumab, an anti-PD-L1 antibody, was initially assessed in a Phase I, open-label, dose-expansion study in several solid malignancies (JAVELIN Solid Tumor study).<sup>23–25</sup> To assess the safety profile in patients treated with avelumab and the anti-tumor activity of this drug in unresectable or metastatic UC, a pooled analysis of two cohorts from the JAVELIN Solid Tumor study was performed.<sup>26</sup> A total of 249 patients were eligible and were treated with avelumab 10 mg/kg every 2 weeks. Among 161 evaluable patients, ORR was 17% with 6% CR. Avelumab showed a manageable safety profile, and the most frequent AEs were infusion-related reactions (29%) and fatigue (16%). Based on these data, the FDA granted accelerated approval to avelumab and recommended a dose of 10 mg/kg intravenously over 60 mins every 2 weeks. To avoid infusion-related reactions, pre-medication with an antihistamine and acetaminophen prior to the first four infusions of avelumab is recommended.

Durvalumab, an anti-PD-L1 antibody, was investigated for its safety and anti-tumor activity in a Phase I/II open-label dose-escalation and dose-expansion study.<sup>27,28</sup> Patients with unresectable or metastatic UC were enrolled and treated with durvalumab 10 mg/kg every 2 weeks. Among 182 evaluable patients with post-platinum-based chemotherapy, durvalumab demonstrated favorable anti-tumor activity, with an ORR of 18% and 3% CR, and a manageable safety profile. Based on these data, the FDA granted accelerated approval to durvalumab.

## First-line ICIs for cisplatin-ineligible patients

Up to 50% of patients with unresectable or metastatic UC who show impaired renal function are ineligible for cisplatin-based chemotherapy, which is the standard first-line treatment for these patients.<sup>29</sup> Treatment alternatives including carboplatin-based combinations and single-drug chemotherapy are associated with inferior outcomes compared with cisplatin-based chemotherapy in cisplatin-eligible patients; therefore, the development of alternative treatment approaches in cisplatin-ineligible patients was anticipated.<sup>8,30,31</sup> In 2017, the FDA granted accelerated approval to pembrolizumab and atezolizumab as first-line treatment for cisplatin-ineligible patients with unresectable or metastatic UC (Table 1).

### Pembrolizumab

Pembrolizumab for cisplatin-ineligible patients was assessed in a single-arm Phase II study (KEYNOTE-052).<sup>14</sup> Cisplatin-ineligible patients were defined as meeting at least one of the following criteria: Eastern Cooperative Oncology Group (ECOG) performance status 2, creatinine clearance 30–60 ml/min, grade  $\geq 2$  audiometric hearing loss, grade  $\geq 2$  peripheral neuropathy, or New York Heart Association Class III heart failure. A total of 370 patients received pembrolizumab 200 mg every 3 weeks. With a median follow-up of 5 months, the ORR was 24% with 5% CR, and 83% of responses were ongoing at the time of cutoff. High PD-L1 expression, defined as a CPS of at least 10%, was associated with high ORR of 38%. Pembrolizumab showed acceptable tolerability in this study population. Based on the updated data of this study, the FDA granted accelerated approval as a first-line indication in cisplatin-ineligible patients with unresectable or metastatic UC. However, the FDA limited the use of pembrolizumab in these patients in June 2018, based on the data of an ongoing Phase III trial, KEYNOTE-

361 (ClinicalTrials.gov Identifier: NCT02853305), in which patients were randomly assigned to receive pembrolizumab with or without chemotherapy, or chemotherapy alone. The Independent Data Monitoring Committee (DMC) found that patients with low PD-L1 expression, defined as CPS  $< 10\%$ , who received pembrolizumab alone had poorer survival compared with patients receiving platinum-based chemotherapy. Based on these results, the FDA revised the indications for pembrolizumab in cisplatin-ineligible patients. Pembrolizumab is now indicated for cisplatin-ineligible patients with high tumor PD-L1 expression (CPS at least 10%), and patients who are ineligible for any platinum-containing chemotherapy regardless of tumor PD-L1 expression.<sup>32</sup>

### Atezolizumab

Atezolizumab for cisplatin-ineligible patients was assessed in single-arm two-cohort Phase II study (IMvigor 210), as mentioned above.<sup>18</sup> One of the cohorts consisted of previously untreated cisplatin-ineligible patients, and was treated with atezolizumab 1200 mg every 3 weeks, in the same procedure as another cohort in a post-platinum-based chemotherapy setting. A total of 119 patients were enrolled and treated with atezolizumab, exhibiting an ORR of 23% and a CR of 9% with a median follow-up of 17.2 months. The FDA granted accelerated approval to atezolizumab as first-line indication in cisplatin-ineligible patients, but similarly to pembrolizumab, the FDA have limited the indication. Atezolizumab is now indicated for cisplatin-ineligible patients with high tumor PD-L1 expression (PD-L1 stained tumor-infiltrating immune cells covering  $\geq 5\%$  of the tumor area), and patients who are ineligible for any platinum-containing chemotherapy regardless of tumor PD-L1 expression.

## Adverse events associated with pembrolizumab

The KEYNOTE-045 trial showed that treatment-related AEs of any grade were seen in 61% of patients treated with pembrolizumab, the most common AEs being pruritus (20%), fatigue (14%), and nausea (11%).<sup>13</sup> Severe AEs, including grade 3, 4, and 5 events, were observed in 15% of patients, while the incidence of each AE was less than 5%. Wang et al reported the safety profile of pembrolizumab through a pooled analysis based on randomized controlled trials for solid cancers.<sup>33</sup> They analyzed a total of 3,922 patients, and reported the incidence of all-

grade AEs including rash (15%), pain (14%), pruritus (18%), vitiligo (11%), arthralgia (11%), and dry mouth (10.0%), while severe AE rates of rash, pruritus, and arthralgia were rare. The incidence rate of AEs is similar to those associated with other anti-PD-1/PD-L1 antibodies.<sup>9</sup>

Immune-related AEs are characteristic events among ICIs, and physicians must closely monitor them to enable their management. The following immune-related AEs associated with pembrolizumab have been reported: pneumonitis, colitis, hepatitis, nephritis, hyper- or hypothyroidism, thyroiditis, hypophysitis, type 1 diabetes mellitus, arthritis, myositis, Guillain-Barré syndrome, pancreatitis, and skin reactions.<sup>34</sup> In the KEYNOTE-045 trial, immune-related AEs of any grade were recorded in 17% of patients, and the incidence of grade 3, 4, or 5 events included pneumonitis (2%), colitis (1%), and nephritis (1%).<sup>13</sup>

## Ongoing Phase III clinical trials using pembrolizumab and other ICIs

Table 2 indicates the current ongoing Phase III trials of pembrolizumab in patients with unresectable or metastatic UC. Pembrolizumab monotherapy is the standard treatment with level 1 evidence for patients who failed first-line platinum-based chemotherapy. Therefore, it is necessary to design clinical trials with a control arm of pembrolizumab monotherapy for the development of new treatment in the post-platinum-based chemotherapy setting. Two Phase III trials of pembrolizumab in such patients are detailed in ClinicalTrials.gov.

Erdaftinib, a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, showed clinical efficacy in patients with FGFR-altered unresectable or metastatic UC in a Phase II study, BLC2001, which was presented at the 2018 Genitourinary Cancers Symposium. The FDA have granted Breakthrough Therapy Designation for erdaftinib in the treatment of FGFR-mutated UC. A Phase III trial investigating erdaftinib monotherapy in the second-line setting was launched in patients with unresectable or metastatic UC and *FGFR* genetic aberrations. In this trial, erdaftinib was compared with pembrolizumab (control arm) in patients with prior chemotherapy (cohort 2), or with chemotherapy in patients with prior chemotherapy and ICI (cohort 1). The primary endpoint of this trial was OS. Meanwhile, the development of combination therapy of

pembrolizumab with epacadostat had run into difficulties. Epacadostat is an inhibitor of indoleamine 2, 3-dioxygenase-1 (IDO1), which suppresses T-cell-mediated immune surveillance.<sup>35</sup> A Phase I/II trial (ECHO-202/KEYNOTE-037) showed that the combination of pembrolizumab and epacadostat was tolerated and that it exhibited encouraging antitumor activity in multiple advanced solid tumors.<sup>36</sup> A Phase III trial (KEYNOTE-698/ECHO-303) was launched in patients who had failed first-line platinum-based chemotherapy. However, another Phase III study investigating the same combination therapy in patients with unresectable or metastatic melanoma failed to meet its primary endpoint of PFS, and thus the enrollment of patients for KEYNOTE-698/ECHO-303 was halted.

Currently, the standard first-line therapy in cisplatin-eligible patients with unresectable or metastatic UC is cisplatin-based chemotherapy. Pembrolizumab is being investigated as a first-line therapy with or without chemotherapy in platinum-eligible patients with unresectable or metastatic UC. A Phase III three-armed randomized trial is currently ongoing that includes pembrolizumab with the gemcitabine plus cisplatin or carboplatin arm, the pembrolizumab monotherapy arm, and the placebo with gemcitabine and cisplatin/carboplatin arm (KEYNOTE-361). The total estimated enrollment is 990 patients, and the co-primary endpoints of this trial are PFS and OS. Atezolizumab is also being investigated in a Phase III trial with a similar design (IMvigor130) (ClinicalTrials.gov Identifier: NCT02807636).

Another strategy of combination therapy is to use anti-PD-1/PD-L1 antibodies with other ICIs such as those targeting the CTLA-4 pathway, including ipilimumab and tremelimumab. A Phase III trial evaluating nivolumab 1 mg/kg and ipilimumab 3 mg/kg combination with or without platinum-based chemotherapy in the first-line setting (CheckMate 901) (ClinicalTrials.gov Identifier: NCT03036098) is ongoing. Durvalumab monotherapy or combination therapy of durvalumab with tremelimumab are also being compared with platinum-based chemotherapy in an open-label Phase III trial (DANUBE trial) (ClinicalTrials.gov Identifier: NCT02261220). In addition to first- and second-line therapy for unresectable or metastatic UC, the role of avelumab in maintenance therapy is being evaluated in patients with advanced UC who have completed at least four cycles of platinum-based chemotherapy without evidence of disease progression (JAVELIN Bladder 100 study) (ClinicalTrials.gov Identifier: NCT02603432).

Table 2 Ongoing Phase III trials of pembrolizumab in patients with unresectable or metastatic urothelial carcinoma

Disease setting	Study title		ClinicalTrials.gov Identifier	Intervention	Study design* (Estimated/actual primary completion date)	Primary endpoint
1st-line	A Phase III Randomized, Controlled Clinical Trial of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy in Subjects With Advanced or Metastatic Urothelial Carcinoma	MK-3475-361 KEYNOTE-361	NCT02853305	Pembrolizumab vs pembrolizumab +chemotherapy vs chemotherapy	N=990 Active not recruiting (June, 2019)	PFS/OS
1st-line, cisplatin-ineligible	A Phase III Randomized, Double-Blind Trial of Pembrolizumab (MK-3475) in Combination With Epacadostat (INCB024360) or Placebo in Participants With Cisplatin-ineligible Urothelial Carcinoma (KEYNOTE-672/ECHO-307)	KEYNOTE-672 ECHO-307	NCT03361865	Pembrolizumab + epacadostat vs pembrolizumab + placebo	N=94 Active Enrollment was halted (August, 2018)	ORR
2nd-line	A Phase III Randomized, Double-Blind Clinical Study of Pembrolizumab + Epacadostat vs Pembrolizumab + Placebo as a Treatment for Recurrent or Progressive Metastatic Urothelial Carcinoma in Patients Who Have Failed a First-Line Platinum-containing Chemotherapy Regimen for Advanced/Metastatic Disease (KEYNOTE-698/ECHO-303)	KEYNOTE-698 ECHO-303	NCT03374488	Pembrolizumab + epacadostat vs pembrolizumab + placebo	N=84 Active Enrollment was halted (July, 2018)	ORR
2nd-line, with FGFR aberrations	A Phase III Study of Erdafitinib Compared With Vinflunine or Docetaxel or Pembrolizumab in Subjects With Advanced Urothelial Cancer and Selected FGFR Gene Aberrations	BLC3001	NCT03390504	Erdafitinib vs vinflunine or docetaxel (cohort 1) vs pembrolizumab (cohort 2)	N=631 Active Recruiting (November, 2020)	OS

Note: \*Recruitment status in March 2019.

The results of these trials of ICIs might influence treatment strategies in second-line or following setting of unresectable or metastatic UC patients. Recently, the FDA has granted Breakthrough Therapy Designations for enfortumab vedotin and erdafitinib for patients following platinum-based chemotherapy.<sup>37</sup> Several Phase III trials are ongoing to evaluate the efficacy of enfortumab vedotin and FGFR inhibitors including erdafitinib, in post-ICIs setting for unresectable or metastatic UC patients.

## Conclusions and future view

Pembrolizumab is a potential first-choice second-line therapy for unresectable or metastatic UC patients following platinum-based chemotherapy, because it is the only biologic to have strong evidence of efficacy in this setting. Several Phase III trials are ongoing to evaluate the efficacy and toxicity of ICIs with chemotherapy combination therapies, and ICIs with other ICIs with or without chemotherapy as first-line therapy. The results of these trials might influence the treatment strategies for unresectable or metastatic UC patients.

Another notable point is that the treatment using ICIs is currently investigating in non-metastatic patients. Multiple trials are ongoing which investigate ICI mono- or combination-therapy in muscle-invasive resectable BC, as neoadjuvant or adjuvant treatment, and also in non-muscle-invasive BC. In the near future, ICIs might be incorporated into the standard of care for these non-advanced disease, and it will be strongly required to develop the novel treatment in patients with post-ICI setting.

In addition, it is necessary to consider the cost-effectiveness of ICI-containing therapies because ICIs are priced high. Although considerable patients have long-term durable response, some patients do not benefit from these treatments. Therefore, the identification of patients who benefit or do not benefit from these treatments is the key for personalized medicine, which might improve the cost-effectiveness. Unfortunately, the current biomarker, PD-L1 staining, showed inconsistency results in the trials using ICIs, and is far from decision-making tool. Further research to find biomarkers for identifying potential treatment responders is required.

## Abbreviations

AE, adverse event; BC, bladder cancer; CR, complete response; CTLA-4, cytotoxic T lymphocyte-associated protein 4; FDA, the US Food and Drug Administration; FGFR,

fibroblast growth factor receptor; ICI, immune checkpoint inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PD-1, programmed cell death 1; PD-L1, programmed death ligand 1; UC, urothelial carcinoma.

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## Disclosure

ME reports honoraria for speaking from Ono, BMS, MSD, Chugai, Pfizer, AstraZeneca, Astellas, and Bayer. He also reports personal fees from MSD, outside the submitted work. The authors report no other conflicts of interest in this work.

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