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Pembrolizumab in the treatment of locally advanced or metastatic urothelial carcinoma: clinical trial evidence and experience

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Abstract: The treatment of advanced urothelial carcinoma (UC) has dramatically changed with the advent of immune checkpoint inhibitors that disrupt the T-cell inhibitory interaction between the programmed cell death (PD)-1 receptor and its ligand (PD-L1). Pembrolizumab, a highly specific, monoclonal antibody directed against PD-1, has demonstrated clinical efficacy as well as a favorable toxicity profile, and has emerged as a new standard of care in the treatment of advanced UC. This review will summarize clinical efficacy from recent trials that led to the approval of pembrolizumab in treating platinum-refractory advanced UC as well as treating patients who are ineligible for first-line cisplatin-containing chemotherapy. While immune checkpoint inhibition has reinvigorated the treatment landscape of advanced UC and generated a great deal of optimism, only a minority of patients benefit. Combination strategies with the goal of increasing response rates are desperately needed as are biomarkers predictive of response.

Keywords: advanced urothelial carcinoma, immunotherapy, PD-1, pembrolizumab

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Introduction

Urothelial carcinoma (UC), the most common histologic variant of cancer arising from the urothelial lining of the renal pelvis, ureter, bladder, or urethra, represents the sixth most common cancer overall and the fourth most common cancer in men in the United States (US).[1] UC encompasses a clinical spectrum that ranges from localized nonmuscle-invasive disease to advanced or metastatic disease. Nonmuscle-invasive bladder cancer (NMIBC) is managed with local therapy including transurethral resection of bladder tumor with or without intravesical chemotherapy or Bacillus Calmette–Guerin (BCG). Muscle-invasive UC is biologically more aggressive but potentially curable with perioperative cisplatin-based chemotherapy and radical cystectomy or bladder-sparing trimodal chemoradiotherapy. Advanced UC is generally considered incurable and treated primarily with palliative systemic therapy and is associated with high mortality rates and a median overall survival (OS) of approximately 14–15 months with cisplatin-based chemotherapy.[2] While most cases of UC are attributed to NMIBC, it is estimated that over 17,000 people will die of this disease in 2018 in the US alone.[1] UC generally afflicts the elderly and carcinogens from tobacco smoking represent the greatest risk factor.[3] Similar to other carcinogen-induced malignancies, UC is associated with high rates of DNA mutations and alterations, which can lead to the formation of novel peptides that are distinct from those formed by the normal genome.[4] These novel peptides are known as neoantigens and represent a target for the generation of an adaptive immune-mediated anti-tumor response. The interactions between cancer cells and the host immune system have become increasingly well characterized in recent years. The immune checkpoint programmed cell death-1 (PD-1), a transmembrane protein expressed on effector T-cells, and interaction

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with its ligand programmed death ligand-1 (PD-L1 and also known as B7-H1), expressed on suppressive immune cells as well as certain tumor cells, has been shown to downregulate T-cell effector response. Activation of the PD-1 receptor has been shown to decrease T-cell proliferation and cytokine production as well as impair T-cell migration, effectively dampening the extent and duration of the antigen-driven immune response.[5] The observation that certain tumors and tumor-infiltrating immune cells show upregulated expression of PD-1 and PD-L1, suggests that impaired T-cell immunity driven by the interaction between PD-1 and its ligand represents one mechanism through which tumors evade immune-mediated destruction.[6] Disruption of the PD-1/PD-L1 checkpoint has subsequently become the focus of intense research in an effort to develop effective therapies that reinvigorate innate anti-tumor immunity. Tumors such as UC with a high somatic mutation burden, and the resultant generation of high levels of neoantigens, are more likely to respond to therapies that target the PD-1/PD-L1 pathway.[7,8]

Pembrolizumab is a highly selective, humanized, monoclonal immunoglobulin (Ig)G4k isotype antibody with blocking properties against PD-1, which has demonstrated anti-tumor effects across a wide array of solid tumors.[9]

Management of advanced UC

Advanced UC, defined as inoperable/locally advanced or metastatic disease, has historically been considered as sensitive to chemotherapy, although the duration of response to cytotoxic chemotherapy has been shown to be brief and options for treatment upon recurrence are limited.[10] The reference standard treatment for advanced UC has centered on cisplatin-based combination chemotherapy, the only therapy shown to improve survival in the first-line setting. The most commonly employed regimens include MVAC (a four-drug regimen comprised of methotrexate, vinblastine, doxorubicin, and cisplatin) and GC (gemcitabine and cisplatin).[11] A phase III randomized trial demonstrated the non-inferiority of GC relative to MVAC, with similar progression-free survival (PFS; 7.7 *versus* 8.3 months; $p = 0.63$), objective response rate (ORR; 49% *versus* 46%; $p = 0.51$), and median OS (14 *versus* 15.2 months; $p = 0.44$).[2,11] GC was also associated with a favorable toxicity profile relative to standard MVAC, making it a preferred regimen, although dose-dense or accelerated MVAC with granulocyte colony-stimulating factor has helped to mitigate the toxicity profile of standard MVAC while also possibly improving response rates.[12] Only a minority of patients with advanced UC are eligible to receive cisplatin-based combination therapy due to toxicity concerns regarding the presence of significant medical comorbidities.[13] For those considered ineligible for cisplatin, a group comprising up to two-thirds of patients with advanced UC, carboplatin with gemcitabine has been the preferred regimen.[14] This is based on the European Organisation for Research and Treatment of Cancer (EORTC) 30986 phase II/III trial, the only level-I evidence in this setting, which found no difference in survival between gemcitabine with carboplatin and methotrexate, vinblastine, and carboplatin (M-CAVI). The median OS was 9.3 months with gemcitabine and carboplatin *versus* 8.1 months with M-CAVI ($p = 0.64$). Gemcitabine and carboplatin treatment was associated with a favorable toxicity profile relative to M-CAVI.[14]

Options for second-line treatment upon disease progression after platinum-based combination therapy have historically been associated with a limited benefit. Commonly used regimens in this setting include single-agent taxanes (docetaxel and paclitaxel) and pemetrexed, which have been associated with a modest benefit in PFS of 2–3 months but failed to demonstrate an OS benefit.[15,16] Vinflunine was approved in Europe based on a randomized study which initially failed to show a statistically significant survival benefit relative to best supportive care. However, imbalances in prognostic factors may have contributed to the negative results of the primary endpoint analysis. A statistically significant 2-month survival benefit was subsequently reported using a multivariate Cox analysis that adjusted for various prognostic factors.[17]

Efficacy of pembrolizumab as a second-line treatment for advanced UC among patients previously treated with platinum-based chemotherapy

The KEYNOTE-012 study was among the earliest to demonstrate the clinical efficacy of pembrolizumab in advanced UC in an open-label, multicohort, phase IB trial. A total of 33 patients with advanced UC were enrolled, and ORR was 27% with 11% achieving a complete response (CR).[18] The study also demonstrated a favorable safety

Table 1. Clinical outcomes data for pembrolizumab in advanced UC.

	Clinical trial	Phase	Overall survival	Objective response rate	Progression-free survival
First-line or subsequent therapy	KEYNOTE-012/ NCT01848834	Ib	N/A	27%	N/A
First-line, cisplatin-ineligible	KEYNOTE-052/ NCT023354224	II	mOS not reached; at the 6-month analysis, survival was estimated at 67% using the Kaplan–Meier method	29%	2 months
Second-line, platinum-refractory	KEYNOTE-045/ NCT02256436	III	10.3 months	21.1%	2.1 months

mOS, median overall survival; N/A, not applicable; NCT, ClinicalTrials.gov identifier; UC, urothelial carcinoma.

profile, enabling further investigation into the effectiveness and toxicity profile of pembrolizumab in advanced UC in phase II and III trials leading to new standards of care (Table 1). Building on the early evidence of activity and safety observed in KEYNOTE-012, pembrolizumab was compared with investigator's choice second-line chemotherapy in a randomized phase III trial of patients with advanced UC who had recurrent disease following or progressing on platinum-containing chemotherapy. In the KEYNOTE-045 study, 542 participants were randomized to pembrolizumab monotherapy or single-agent chemotherapy (docetaxel, paclitaxel, or vinflunine). The co-primary endpoints in the intention-to-treat analysis were median OS and PFS. With a median follow-up period of 14.1 months, the authors analyzed the results for both the study population as a whole, as well as among the subset of patients who had tumors with a PD-L1 combined positive score (CPS) $\geqslant$ 10%. For the entire study population, median OS in the pembrolizumab group was 10.3 months *versus* 7.4 months in the chemotherapy group [hazard ratio (HR) for death, 0.73; 95% confidence interval (CI), 0.59–0.91; $p = 0.002$]. Using the Kaplan–Meier method, the estimated OS at 12 months was 43.9% of patients in the pembrolizumab group *versus* 30.7% in the chemotherapy group. Pembrolizumab was also associated with a survival benefit relative to single-agent chemotherapy among patients who had tumors with a PD-L1 CPS $\geqslant$ 10% with a median OS of 8.0 months in the pembrolizumab group *versus* 5.2 months in the chemotherapy group (HR for death, 0.57; 95% CI, 0.37–0.88; $p = 0.005$). Furthermore, when pembrolizumab was compared with each chemotherapy agent individually, the survival advantage persisted.[19] The median PFS, reported as 2.1 months, however, did not differ between the pembrolizumab group and the chemotherapy group for either the population as a whole (HR, 0.98; 95% CI 0.81–1.19; $p = 0.42$) or those with a PD-L1 CPS $\geqslant$ 10% (HR, 0.89; 95% CI, 0.61–1.28; $p = 0.24$). However, the ORR was significantly higher in the pembrolizumab group relative to the chemotherapy group at 21.1% *versus* 11.4% ($p = 0.001$). Furthermore, among responders, the duration of response was significantly greater with pembrolizumab relative to chemotherapy. The median duration of response was not reached in the pembrolizumab group and was 4.3 months in the chemotherapy group.[19] With additional follow up, the survival benefit for pembrolizumab over chemotherapy was further improved with a HR of 0.70 (95% CI 0.57–0.85) at a median follow up of 2 years.[20]

This trial represents the most robust data for checkpoint inhibitor use in the second-line setting following platinum-based combination therapy for advanced UC. In a clinical space devoid of therapeutic advances for over two decades, there are now five United States Food and Drug Administration (US FDA) approved immune checkpoint inhibitors for the second-line treatment of platinum-refractory advanced UC, with similar efficacy and safety outcomes reported for each agent.[19,21–24] These include two anti-PD-1 antibodies, pembrolizumab and nivolumab, and three anti-PD-L1 antibodies, atezolizumab, durvalumab, and avelumab. The recent surge in approved checkpoint inhibitors used in the

second-line setting following platinum-based therapy reflects the previous lack of effective systemic treatments in this clinical setting. The observation that prior chemotherapy exposure can result in immunogenic cell death and a proinflammatory tumor microenvironment provides mechanistic justification for sequencing checkpoint inhibitors after progression on platinum-based chemotherapy in eligible patients and may be predictive of response.[25]

Pembrolizumab as front-line treatment for cisplatin-ineligible patients

While cisplatin-based combination chemotherapy has long been the standard of care and associated with a survival benefit for patients with advanced UC, a significant proportion of patients are ineligible for cisplatin for a variety of reasons, most commonly renal dysfunction or poor performance status; however, advanced age, peripheral sensory and auditory neuropathy as well as significant cardiovascular disease also pose risks. This heterogeneous population has done poorly with alternative chemotherapy regimens, most commonly carboplatin-based with median survival in the range of 9 months[15] Improving outcomes for this population is a significant unmet medical need and an important setting to test novel agents. An important initial step was generating a consensus definition of cisplatin-ineligibility for clinical trial purposes, which was first published in 2011.[25] To be ineligible for cisplatin, patients must meet at least one of the following criteria: renal insufficiency with a creatinine clearance less than 60 ml/min, an Eastern Cooperative Oncology Group performance status of 2, grade ⩾2 audiometric hearing loss, grade ⩾2 peripheral neuropathy, or New York Heart Association class III heart failure.[25] Building on prior studies that demonstrated anti-tumor activity and a favorable safety profile of pembrolizumab in patients with platinum-refractory advanced UC, researchers investigated the therapeutic efficacy of pembrolizumab among cisplatin-ineligible patients. The KEYNOTE-052 trial was a single-arm, multicenter, phase II study of pembrolizumab in cisplatin-ineligible patients with advanced UC defined by the consensus criteria. PD-L1 expression was assessed on archival tumor specimens using the Dako 22C3 assay and measured by scoring the proportion of tumor and immune cell expression over the total tumor cells present (CPS). PD-L1 expression was assessed in the first 100 patients to determine a diagnostic cut-off to define a positive level at which responses were most enriched, and then to validate that cut-off in the remaining study population. Data from the first 100 patients demonstrated an ORR of 24%, and a PD-L1 CPS expression level of 10% which optimally identified patients most likely to respond to treatment.[26] Ultimately, 370 patients were included in the primary outcome analysis, which measured the ORR to pembrolizumab therapy, defined as the proportion of patients who had a complete or partial response as per the centrally assessed Response Evaluation Criteria in Solid Tumors version 1.1 criteria. The ORR was reported to be 24% (n = 89/370) of treated patients with 5% having a CR.[27] An updated efficacy analysis with all patients having ⩾6 months of follow up demonstrated an ORR of 29% (95 CI, 24–34%) and a CR rate of 7%. The median time to response was 2 months.[28] At the preplanned data cut-off point, the median duration of response had not been reached (95% CI: 9 months to not reached). Using the Kaplan–Meier method, the authors estimated that 78% of responses lasted at least 6 months. The study also found that ORR increased with the PD-L1 CPS. In the most recent updated analysis presented at the 2018 ASCO annual meeting, among patients with a PD-L1 CPS ⩾10%, the ORR was 48%, with the majority of CRs occurring in this group.[29]

Based on these data, pembrolizumab was granted accelerated approval by the US FDA for the front-line treatment of advanced UC in cisplatin-ineligible patients.[30] Pembrolizumab and atezolizumab, a monoclonal antibody against PD-L1 which was similarly tested in the first-line cisplatin-ineligible population, are the only checkpoint inhibitors approved in this setting. The US FDA, however, later added a requirement for PD-L1 positivity to the label for both agents. For pembrolizumab, a CPS ⩾ 10% is now required. This change was based on interim survival analysis from the ongoing KEYNOTE-361 study (ClinicalTrials.gov identifier: NCT02853305), which is a phase III trial of pembrolizumab with or without chemotherapy compared with chemotherapy alone in advanced UC. Notably, all patients enrolled in this study were deemed to be eligible for platinum-containing chemotherapy, and therefore cisplatin-ineligible patients assigned to the chemotherapy arm received treatment with carboplatin and gemcitabine. An interim analysis performed by the Data Safety Monitoring Committee overseeing the trial reported that patients with PD-L1 low status tumors had decreased survival in the pembrolizumab monotherapy arm when compared with platinum-based combination therapy. As a result,

enrollment of PD-L1 low expressing patients to the single-agent pembrolizumab arm was halted. The US FDA's requirement for a PD-L1 tumor-infiltrating immune cells (IC)⩾ 5% (using the Ventana SP142 assay) for use of front-line atezolizumab is based on an interim analysis of the IMvigor130 study (ClinicalTrials.gov identifier: NCT02807636), which found similar results showing inferior survival with single-agent atezolizumab in PD-L1 low/negative patients relative to platinum-based chemotherapy.

Biomarkers predictive of response to PD-1/PD-L1 antibodies

Identifying biomarkers predictive of a clinical response to checkpoint therapy remains an area of active research and has obvious practical applications given the high cost of checkpoint inhibitor therapy and the potential adverse effects associated with their use. Overall, three emerging biomarkers represent important progress in this area and have been incorporated in recent clinical trials investigating the efficacy of various PD-1/PD-L1 antibodies. These include (1) tumor mutational burden (TMB), (2) PD-L1 expression (measured on tumor or immune cells in tumor tissue) and (3) gene expression profiling (GEP). The concept of TMB, defined as the number of somatic mutations per coding area of the tumor genome, emerged from quantitative genomics data that demonstrated heterogeneity both within and across types of solid tumors.[31] In an analysis of 27 different tumor types for which median TMB and response rates to immunotherapy were available, TMB was shown to correlate with ORR to treatment with checkpoint inhibitors with a correlation coefficient of 0.74, suggesting that 55% of the difference in ORR to checkpoint inhibitor therapy may be explained by TMB.[32] With respect to UC specifically, a relatively high mutation burden has been reported, with a median of 5.8 mutations per megabase in a comprehensive analysis of 412 muscle-invasive bladder cancers (MIBCs) as part of the Cancer Genome Atlas project.[33] In clinical trials of checkpoint inhibitor use in advanced UC, high TMB has been associated with a longer OS and high ORR.[22,30] However, broader application of TMB to clinical practice remains limited by a lack of consensus regarding optimal TMB cut-offs predictive of response and methodological inconsistencies across quantitative genomic assays.

Efforts to identify biomarkers predictive of response to checkpoint inhibition also centered on quantitative analysis of PD-L1 expression by tumor cells. The lack of standardization across immunohistochemical assays and the dynamic nature of PD-L1 expression both temporally and spatially have complicated the interpretation of results. Furthermore, the extent to which PD-L1 is expressed by tumor-infiltrating lymphocytes as compared with tumor cells may also variably inform the likelihood of response to anti-PD-1/PD-L1 antibodies.[34] The PD-L1 CPS assessed using the DAKO 22C3 assay is measured as the percentage of both tumor cells and infiltrating immune cells that express PD-L1 relative to the total number of tumor cells, and has shown promise as a predictive biomarker in recent clinical trials, including both the KEYNOTE-045 and KEYNOTE-052 studies of pembrolizumab in advanced UC. More recently, researchers have identified an 18-gene T-cell inflamed signature using GEP that may be more sensitive in capturing those who respond to PD-1/PD-L1 checkpoint inhibitors and may complement PD-L1 expression testing. The analysis was first used in the setting of melanoma but was subsequently applied to nine other cancers. A post hoc analysis of the KEYNOTE-052 study was presented at the 2017 ASCO annual meeting and showed that the T-cell-inflamed GEP signature significantly correlated with response rates and that all 18 genes incorporated in the scoring system were independently associated with a response.

Presently, the front-line use of checkpoint inhibitors in cisplatin-ineligible patients is the only indication that has a biomarker-based requirement for approval. None of the anti-PD-1 or anti-PD-L1 antibodies approved for second-line use have a biomarker-based requirement.

Pembrolizumab and immune-related adverse events

Based on the rapidly expanding body of literature that stems from clinical trials using immune checkpoint inhibitors in the treatment of solid tumors, the adverse drug effect profile of immuno-oncologic treatments has become increasingly well characterized. The novel mechanism through which checkpoint inhibitors target cancer cells, namely by disrupting inter-cellular signaling with the intention of invigorating an immune response to cancer-derived antigens, has given rise to an equally novel category of adverse drug effects known as immune-related adverse events (irAEs). This term refers to inflammatory side effects caused by the nonspecific

immune response generated by blocking the negative regulators of T-cell-mediated immunity. While generally well-tolerated, especially relative to cytotoxic chemotherapy, immune checkpoint inhibitors are associated with a distinct side-effect profile, and the timeframe in which adverse effects can occur with respect to treatment initiation is generally less predictable than with chemotherapy. In the KEYNOTE-045 study, treatment-related adverse events were reported in 60.9% of patients receiving pembrolizumab **versus* 90.2% of those receiving chemotherapy. Severe adverse events (those categorized as grade 3–5) were less frequently observed in the pembrolizumab group relative to chemotherapy (15.0% *versus* 49.3%, respectively). Treatment-related events leading to death were similar between groups. In the KEYNOTE-045 study, the only adverse events in the pembrolizumab arm that occurred with a frequency ⩾10% were pruritus, fatigue, and nausea.[19]

The safety data from the KEYNOTE-052 study was expectedly similar to the KEYNOTE-045 study, with 62% of patients reporting any treatment-related adverse event and 16% reporting treatment-related adverse events categorized as grade 3 or greater. The most commonly occurring treatment-related adverse events in this group were fatigue, elevated alkaline phosphatase, colitis, or muscle weakness, all of which occurred with a frequency ⩽2%. The KEYNOTE-052 study also reported data for irAEs with a frequency of 17%. The most commonly reported irAEs, occurring in two patients or more, were hypothyroidism (6%), hyperthyroidism (2%), colitis (2%), pneumonitis (2%), adrenal insufficiency (1%), type 1 diabetes (1%), hepatitis (1%), diabetic ketoacidosis (1%), and thyroiditis (1%).[27] KEYNOTE-045 and KEYNOTE-052 reported similar rates of treatment-related discontinuation of therapy among patients receiving pembrolizumab at 5.6% and 5% respectively, which compared favorably to chemotherapy-related discontinuation of therapy, which was 11%.[19,28] These findings suggest that pembrolizumab has a tolerable side-effect profile even among the subgroup of patients who have limited treatment options because of their comorbid medical conditions or poor functional status. The safety profile and incidence of treatment-related adverse events with pembrolizumab is similar to those associated with the other US FDA-approved checkpoint inhibitors used in the treatment of advanced UC.[35] The similar toxicity profile of these agents suggests a class-wide effect of antibodies that target either PD-1 or PD-L1.

Future directions: pembrolizumab combination studies and checkpoint inhibition in early-stage disease

After decades of stagnation with respect to progress in improving clinical outcomes in advanced UC, immune checkpoint inhibitors have already shifted treatment paradigms. Despite these advances, only a minority of patients benefit from single-agent checkpoint inhibition. Numerous clinical trials are now investigating ways to enhance response rates so that a greater proportion of patients benefit from therapy. Several actively accruing studies are comparing single-agent checkpoint inhibition to checkpoint inhibition in combination with another treatment. Combination strategies currently under investigation include the addition of chemotherapy, tyrosine kinase inhibitors, radiation, or investigational agents designed to further enhance immune response (Table 2). Part of the rationale for combining checkpoint inhibitors with conventional cytotoxic therapies is the hope that circulating T-cells will encounter higher levels of tumor-derived neoantigens, resulting in an enhanced anti-cancer immune response.

The optimal sequencing strategy with respect to checkpoint inhibition and cytotoxic chemotherapy is also the focus of ongoing investigation.

The success of checkpoint inhibitors in the treatment of metastatic UC, suggests that they may also be useful in patients with earlier-stage disease including in those with MIBC, as well as NMIBC.

For patients with MIBC undergoing radical cystectomy, it may be better tolerated over cisplatin-based systemic chemotherapy in either the neoadjuvant or adjuvant settings. In patients undergoing bladder-sparing therapy for the management of MIBC (poor surgical candidates or refusing radical cystectomy), they may be used in conjunction with radiation and systemic chemotherapy as a means to augment immune responses (NCT02621151).

Given the high rate of recurrence of NMIBC, even with the use of intravesical BCG, checkpoint inhibitors may be useful in this setting either in conjunction with BCG or alone. The two particular groups of patients who could benefit include those with high-risk recurrence following induction BCG and those with BCG nonresponsive NMIBC hoping to avoid early radical cystectomy; two studies of pembrolizumab, KEYNOTE-676 and KEYNOTE-057 are focusing on these populations, respectively.

Table 2. Ongoing trials of pembrolizumab-based combinations in advanced UC.

Drug class	Clinical setting	Study ID	Phase	Intervention	Primary endpoints
Chemotherapy	First-line	NCT02853305/ KEYNOTE-361	III	Pembrolizumab ± cisplatin/ carboplatin + gemcitabine *versus* cisplatin/carboplatin + gemcitabine	PFS, OS
Chemotherapy	First-line	NCT02500121	II	Pembrolizumab maintenance *versus* placebo following standard first-line platinum-based chemotherapy	PFS
Chemotherapy	First-line cisplatin-ineligible	NCT03240016	II	Pembrolizumab + abraxane (nab-paclitaxel)	ORR
Chemotherapy	Second-line	NCT03464734	II	Pembrolizumab + nab-paclitaxel	PFS
Chemotherapy	Second-line	NCT02581982	II	Pembrolizumab + paclitaxel	ORR
Chemotherapy	Second-line	NCT02437370	I	Pembrolizumab + gemcitabine *versus* pembrolizumab +docetaxel	MTD/Safety
Radiation therapy	First-line cisplatin-ineligible or second-line platinum-refractory	NCT03486197	II	Pembrolizumab + neutron radiation therapy	ORR
Radiation therapy	Second-line	NCT03287050	I	Pembrolizumab + SBRT	Percentage of patients who receive four doses of pembrolizumab + ⩾1 session of SBRT
Targeted therapy	First-line, cisplatin-ineligible	NCT03534804	II	Pembrolizumab + cabozantinib	ORR
Targeted therapy	Second-line	NCT02717156	II	Pembrolizumab + EphB4-HSA	Feasibility, OS
Targeted therapy	Second-line	NCT02443324	I	Pembrolizumab + ramucirumab	Safety
Targeted therapy	Second-line	NCT03123055	IbII	Pembrolizumab + B-701 (anti-FGFR3 antibody)	Safety
Targeted therapy	Second-line	NCT02619253	Ib/II	Pembrolizumab + vorinostat (HDAC inhibitor)	Safety
Immuno-oncologic agent	Second-line	NCT02351739/ KEYN OTE143	II	Pembrolizumab ± ACP-196	ORR
Immuno-oncologic agent	First-line cisplatin-ineligible or Second-line, platinum-refractory	NCT03236935	Ib	Pembrolizumab + L-NMMA (nitric oxide synthase inhibitor)	Safety

HDAC, histone-deacetylase inhibitors; NCT, ClinicalTrials.gov identifier; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; SBRT, stereotactic body radiation therapy; UC, urothelial carcinoma.

The extent to which such approaches will decrease the incidence of advanced UC remains unknown, however will be better understood with long-term follow up from these studies.

Conclusion

Pembrolizumab has emerged as the new standard of care in the treatment of platinum-refractory advanced UC based on level one evidence from the randomized phase III KEYNOTE-045 study showing a median OS benefit of about 3 months relative to investigator's choice second-line chemotherapy regardless of PD-L1 status. Pembrolizumab is one of two checkpoint inhibitors to have approval in the front-line, cisplatin-ineligible setting with durable responses seen among responders. Toxicity profiles of pembrolizumab are favorable to chemotherapy and our understanding of irAEs and how best to manage them continues to improve with the continued use of these agents. Combination strategies and how best to sequence checkpoint inhibitors in the treatment of UC is the focus of ongoing clinical investigation.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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