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Anti-programmed cell death-1/ligand-1 (PD-1/PD-L1) antibodies for the treatment of urothelial carcinoma: state-of-the-art and future development

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Abstract

Introduction/Background—Immunotherapy with programmed cell death-1/ligand-1 (PD-1/PD-L1) checkpoint inhibitors has expanded a previously limited pool of effective treatment options for patients with metastatic urothelial carcinoma, particularly those with recurring or refractory disease and those who are ineligible for cisplatin. This review reports key findings from completed and ongoing clinical trials that highlight the potential of PD-1/PD-L1 blockade in urothelial carcinoma.

Materials and Methods—A literature search was performed using PubMed®, Embase®, ClinicalTrials.gov, and selected annual congress abstracts. Prospective studies, reviews, editorials, and descriptions of ongoing anti-PD-1/PD-L1 studies in bladder cancer were included.

Results—Anti-PD-1/PD-L1 monoclonal antibodies have shown efficacy and safety across patient subgroups with urothelial carcinoma, including those with poor prognostic factors. Efficacy was similar across different anti-PD-1/PD-L1 agents. Although these antibodies have demonstrated

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durable responses in a subset of patients with urothelial carcinoma, clinicians are currently unable to predict which patients may derive benefit from immune checkpoint blockade.

Conclusion—Anti–PD-1/PD-L1 antibodies have shown favorable clinical activity and tolerability in patients with metastatic urothelial carcinoma refractory to platinum-based therapy or who are ineligible for cisplatin. The activity of PD-1/PD-L1 inhibitors is now also being studied as first-line monotherapy in cisplatin-eligible patients, in combination with chemotherapy, as maintenance therapy following first-line chemotherapy, and in earlier disease states, such as muscle-invasive and non–muscle-invasive bladder cancer. Better predictive tools to define target patient populations are needed as are further investigations to define optimal combinations or sequencing of treatments.

Keywords

immunotherapy; CD274; biomarkers; urinary bladder neoplasms; clinical trials

Introduction

Urothelial carcinoma of the bladder and upper tract represent 4.6% of new cancer cases worldwide, predominantly in elderly males.[1–3] Cytotoxic therapies have been the dominant treatment modality for these cancers for the past 40 years.[4] The most commonly used first-line regimens include gemcitabine plus cisplatin and dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (DDMVAC) in cisplatin-eligible patients which result in median survival of 14–15 months.[5,6] However, for patients with known negative prognostic factors, such as poor Eastern Cooperative Oncology Group (ECOG) performance status (PS) and baseline visceral metastases, these treatments provide minimal survival benefit, as shown by real-world evidence-based analyses in patients with advanced urothelial carcinoma.[7,8]

Approximately one-half of patients with metastatic disease are ineligible for cisplatin-based therapies due to renal impairment, poor ECOG PS, or other comorbidities. First-line treatment options for these patients include carboplatin-based combinations or other non-platinum–containing chemotherapy regimens that show response rates and survival outcomes that are comparable to, although less efficacious than, cisplatin-based therapies.[9] Vinflunine has been approved as a treatment option for recurrent disease in Europe[10,11]; in the United States, this patient population has typically received paclitaxel, docetaxel, gemcitabine, pemetrexed, or other monotherapy or combination chemotherapy.[4,12]

The high prevalence of tumor somatic mutations in advanced urothelial carcinoma,[13] which may generate neoantigens recognized by activated antitumor T cells,[14] provides a rationale for assessing immune checkpoint inhibitors in this disease. Immunotherapy with bacillus Calmette-Guérin (BCG) alone or in combination with interferon (IFN)–α has been used to treat urothelial cancers since the 1980s, although the associated clinical benefit is limited to noninvasive muscle bladder cancer (NIMBC).[15–17] Nevertheless, these therapies helped to establish urothelial carcinoma as immunogenic, and $CD4^+$ T cells, $CD8^+$ cytotoxic T cells, and natural killer cells have been shown to drive antitumor activity in response to BCG therapy.[17]

The current treatment landscape for urothelial carcinoma is rapidly advancing (Figure 1). Antibodies targeting programmed cell death-1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1), enhance antitumor T-cell immunity by blocking inhibitory signals generated by these immune checkpoint proteins.[18] Between May 2016 and May 2017, the Food and Drug Administration (FDA) granted accelerated approval for use of atezolizumab, durvalumab, and avelumab (monoclonal anti–PD-L1 antibodies) and nivolumab (a monoclonal anti–PD-1 antibody) for patients with locally advanced or metastatic urothelial carcinoma that had recurred following platinum-containing chemotherapy (given for first-line metastatic disease or within 12 months of neoadjuvant or adjuvant chemotherapy for muscle-invasive bladder cancer [MIBC]); another monoclonal anti–PD-1 antibody, pembrolizumab, has received full FDA approval in this setting.[19–28] Atezolizumab and pembrolizumab were also recently granted accelerated approval by the FDA for the first-line treatment of cisplatin-ineligible patients.[19,28–30] Preclinical studies support the use of checkpoint inhibitors in urothelial carcinoma and have shown that blocking the PD-L1/PD-1 interaction increases the numbers and cytolytic activity of tumor-specific T cells and modulates levels of proinflammatory and anti-inflammatory cytokines (Figure 2).[31,32]

Although tumor PD-L1 expression is used as a biomarker to predict response to anti-PD-L1/PD-1 treatments in cancers such as non-small cell lung cancer (NSCLC),[33] clinicians are currently unable to predict which patients with advanced urothelial carcinoma are most likely to benefit from immune checkpoint blockade, and better predictive tools are needed in standard clinical practice.[34] The FDA has approved the Ventana PD-L1 SP142 and SP263 complementary immunohistochemistry (IHC) assays to detect PD-L1 protein expression levels on tumor-infiltrating immune cells (IC [SP142 antibody]) and on tumor cells (TC) and ICs (SP263 antibody) in formalin-fixed, paraffin-embedded tissues, based on the assays identifying those patients with metastatic urothelial carcinoma most likely to respond to either atezolizumab (IMvigor 210, described below) or durvalumab in single-arm trials.[19,20,23,24,35] Safety and efficacy of atezolizumab and durvalumab were not dependent on this assay; therefore, the FDA did not mandate its use as a companion diagnostic.[19,24] Other experimental biomarkers of interest include soluble mediators such as cytokines, chemokines, and tumor antigen-specific antibodies in blood; tumor mutational burden and neoantigens in tumor tissues; and gene signature expression within the tumor microenvironment.[36] We review the role of anti-PD-L1/PD-1 checkpoint inhibitors and major clinical trials in the treatment of urothelial carcinoma.

MATERIALS AND METHODS

We conducted a literature search using PubMed®, EMBASE®, ClinicalTrials.gov, and selected websites of annual congress abstracts (American Society of Clinical Oncology, European Society for Medical Oncology, European Cancer Congress, Genitourinary Cancers Symposium, Society for Immunotherapy of Cancer, American Urological Association, and European Association of Urology). The search dates queried were January 1, 2011, to May 1, 2017, and original articles of prospective studies, and descriptions of ongoing studies pertaining to use of immunotherapy regimens in urothelial carcinoma were reviewed. Additional manuscripts and congress abstracts published after these search dates were manually queried based on relevance. The following search terms were used to identify

publications of interest: “PD-L1” and “PD-1,” and relevant generic and investigational drug names of immune checkpoint inhibitors: atezolizumab/MPDL3280A, avelumab/MSB0010718C, durvalumab/MEDI4736, nivolumab/BMS-936558, and pembrolizumab/MK-3475. Additional query search terms were “bladder,” “urothelial,” “carcinoma,” and “cancer,” and we limited our search to peer-reviewed articles written in English (Figure 3).

RESULTS

Anti-PD-L1/PD-1 Clinical Trials Reported to Date

The potential of PD-1/PD-L1 blockade in bladder cancer and urothelial carcinoma has been observed in multiple clinical trials (Tables 1 and 2). Anti–PD-L1/PD-1 monoclonal antibodies have generally shown manageable safety profiles and have been associated with encouraging durability and tumor response rates in patients with metastatic urothelial carcinoma (Table 1).[20,22,23,25,27,29,35,37–41] Ongoing trials are assessing the efficacy of first- and second-line use of anti-PD-L1/PD-1 therapies for all stages of bladder cancer, including NIMBC, MIBC, and metastatic urothelial carcinoma (Table 2). We present a chronological summary of phase 1, 2, and 3 trials that are assessing efficacy and safety of anti–PD-L1/PD-1 antibodies in the following disease settings: after progression of platinum-refractory metastatic urothelial carcinoma (post–first-line or post-perioperative treatment) and in cisplatin-ineligible patients with metastatic urothelial carcinoma.

Second-Line Anti-PD-L1/PD-1 Therapies After Progression on Platinum-Based Chemotherapy

Phase 1 Studies: Atezolizumab was the first anti–PD-L1/PD-1 antibody observed to show antitumor activity in urothelial carcinoma, based on findings from a phase 1 trial of 85 platinum-treated chemotherapy-resistant patients (NCT01375842), although these findings were not confirmed in the subsequent phase 3 study described below.[42] In the phase 1 study, responses were associated with PD-L1 expression on ICs, and patients with higher PD-L1 expression (IHC 2/3) had an objective response rate (ORR) of 46% compared with 16% in patients with low PD-L1 expression (IHC 0/1) (Table 1); median progression-free survival (PFS) was 24 vs 8 weeks in these subgroups, respectively.[37,41] Similarly, patients with baseline metastases and high PD-L1 expression had better responses to treatment than counterparts with low PD-L1 expression (32% compared with 12%). Treatment related adverse events (TRAE) of any grade occurred in 64% of 85 evaluable patients, including fatigue, asthenia, and nausea; grade 3 events were reported in 8% of patients.

CheckMate 032 (NCT01928394) is a phase 1/2 study that evaluated the efficacy and safety of nivolumab in 78 patients with advanced urothelial carcinoma who had received ≥1 prior line of platinum-based therapy.[39] ORR was 24%, with responses ongoing in 63% of responders at last follow-up; median overall survival (OS) was 9.7 months. Although patients with PD-L1+ tumors had a median OS of 16 months and a median PFS of 5.5 months compared with 10 months and 2.8 months in patients with PD-L1- tumors, there was no difference in overall clinical activity in patients based on PD-L1 expression (Table 1). TRAEs of any grade, including fatigue, pruritus, rash, elevated lipase level, nausea, arthralgia, and anemia, occurred in 81% of patients. Twenty-two percent of patients had a

grade ≥3 TRAE, which included elevated amylase and lipase levels in ≥4% of patients. Following results from this study, the FDA granted accelerated approval of nivolumab for the treatment of patients with unresectable locally advanced or metastatic urothelial carcinoma after the failure of a platinum-containing regimen.[21]

Durvalumab showed a manageable safety profile and evidence of clinical activity in a phase 1 expansion cohort of 191 patients with advanced disease that had progressed during or after any number of prior therapies (NCT01693562) (Table 1).[43] ORR was 18% in all patients, with responses ongoing in 77% of responders at the time of last follow-up; median OS was 18.2 months, but was considered immature at the time of data cut-off. Further subgroup analyses revealed ORRs of 28% and 5% in patients with tumors that had PD-L1 expression of ≥25% (PD-L1 high; either TCs or ICs staining for PD-L1) and <25% (PD-L1 low/negative; both TCs and ICs staining for PD-L1); median PFS was 2.1 vs 1.4 months in these subgroups, respectively. TRAEs of any grade occurred in 61% of patients; grade 3/4 events occurred in 7% of patients. Fatigue occurred in 19% of patients, with grade 3/4 events of elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyltransferase (GGT), and hypertension in ≥2 patients; there were 2 deaths resulting from TRAEs (autoimmune hepatitis and pneumonitis). Based on results from this study,[23] durvalumab received accelerated FDA approval for patients with locally advanced or metastatic urothelial carcinoma that progressed during or after, or within 12 months of neoadjuvant or adjuvant treatment with standard platinum-based chemotherapy.[24]

JAVELIN Solid Tumor (NCT01772004) is a phase 1, dose-expansion trial designed to investigate clinical activity and safety of avelumab in patients with metastatic solid tumors, including urothelial carcinoma (Table 1). An initial cohort of avelumab-treated patients with advanced urothelial carcinoma that had progressed after platinum chemotherapy showed encouraging antitumor responses and a manageable safety profile (N=44).[25] An additional efficacy cohort of 205 patients with advanced urothelial carcinoma was enrolled in the JAVELIN study. A pooled analysis of the initial and efficacy cohorts, which constituted the basis of the FDA's accelerated approval of avelumab for this patient population, resulted in an ORR of 17% in those patients with ≥6 months of follow-up, with 82% of responses ongoing at the time of data cutoff.[38] The ORR in patients with or without baseline visceral metastases was 14% compared with 38%, respectively. Patients with historically poor prognostic factors also responded to avelumab, albeit with decreased response rates, and there was a trend toward lower ORR in patients with increased Bellmunt risk score.[44] ORR was 3% and 21% in patients with low and normal levels of albumin at baseline and 4% and 20% in patients with baseline hemoglobin levels of <10 g/dL compared with >10 g/dL, respectively. Despite a trend of PD-L1-positivity association with clinical activity in the initial cohort of patients with metastatic urothelial carcinoma, antitumor activity could not be linked to PD-L1 expression based on the pooled analysis. With a ≥5% cutoff for staining on TCs, the ORR was 25% in patients with PD-L1+ tumors and 13% in patients with PD-L1- tumors (P=0.082); median PFS was 12 vs 6 weeks in PD-L1+ and PD-L1- patients, respectively. Median OS in all postplatinum avelumab-treated patients was 7 months. TRAEs of any grade occurred in 67% of patients and included infusion-related reactions, fatigue, and rash in ≥10% of patients; 7% of patients had grade ≥3 TRAEs, including fatigue in ≥1% of patients.

Similarly, a phase 1 cohort of 33 PD-L1+ patients (TC or stromal) with advanced urothelial carcinoma that had progressed following prior systemic therapies showed preliminary antitumor activity with pembrolizumab (KEYNOTE-012; NCT01848834) (Table 1).[40] In 27 evaluable patients with measurable disease at baseline, ORR was 26%, with ongoing responses in 7% of patients at the time of data cutoff. In a post hoc analysis of PD-L1 expression, 56% of patients had PD-L1+ TCs. When ICs were also included in this scoring, a larger population of patients (84%) was considered PD-L1+. The ORR in the subset of evaluable patients with PD-L1+ or PD-L1- staining in TCs and ICs was 24% and 0%, respectively. Median OS for all patients was 13 months. Adverse events (AE) were common, with TRAEs of any grade, including fatigue and peripheral edema, occurring in 60% of patients. Grade ≥3 events included elevated AST level, myalgia, myositis, dehydration, hypercalcemia, thrombocytopenia, rhabdomyolysis, neuromyopathy, toxic encephalopathy, and maculopapular and pruritic rash in 15% of patients.

Phase 2 Studies: Given the encouraging reports of antitumor activity and safety in phase 1 studies, phase 2 and 3 trials have subsequently been conducted to further characterize efficacy of anti-PD-L1/PD-1 therapies in larger populations of patients with advanced urothelial carcinoma. Following the previously reported phase 1 study of atezolizumab in 85 patients, a separate large phase 2, single-arm study (IMvigor 210; NCT02108652) (Table 1) confirmed the efficacy of atezolizumab as second-line therapy in an expanded cohort of 310 patients with metastatic urothelial carcinoma that had progressed after chemotherapy.[20,35] ORR was 16% in patients unselected for PD-L1 expression, whereas patients in the IC1/2/3 (≥1%) and IC2/3 (≥5%) PD-L1 expression subgroups had ORRs of 19% and 28%, respectively. Median OS was 7.9 months in the overall population, 11.4 months in the IC2/3 group, and 8.8 months in the IC1/2/3 group. The safety profile of atezolizumab was consistent with that seen in the phase 1 trial,[37,41] and TRAEs of any grade occurred in 70% of patients, with fatigue, nausea, decreased appetite, and pruritus in ≥10% of patients. Grade ≥3 TRAEs occurred in 16% of patients, with fatigue the most common at 2%. The FDA granted accelerated approval of atezolizumab for patients with locally advanced or metastatic urothelial carcinoma that progressed during or following any platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant chemotherapy based on the IMvigor 210 second-line results.[19] A subsequent phase 3 study (IMvigor 211), discussed below, failed to confirm these studies and did not meet its primary endpoint of OS; a confirmatory trial assessing clinical efficacy and safety of atezolizumab in cisplatin-ineligible patients is ongoing.

CheckMate 275 (NCT02387996) is a phase 2 study that investigated the efficacy and safety of nivolumab in 265 patients with metastatic urothelial carcinoma who had received prior treatment.[22] ORR was 20% in all patients and 16% and 24% in patients with tumors with negative (≤1%) and positive (>1%) PD-L1 expression on TCs, respectively. Responses were ongoing in 77% of responders at last follow-up, and median OS was 8.7 months in the overall population and 6.0 vs 11.30 months in PD-L1- vs PD-L1+ patients. The safety analysis of CheckMate 275 showed that grade ≥3 TRAEs occurred in 18% of patients, with fatigue and diarrhea each in 2% of patients. The encouraging safety and efficacy observed in

this study were the basis for FDA accelerated approval of nivolumab in the second-line setting.[21]

Phase 3 Studies: With multiple phase 1 and 2 trials completed, ongoing phase 3 trials have further distinguished the efficacy and safety of anti-PD-L1/PD-1 agents in urothelial carcinoma. KEYNOTE-045 (NCT02256436) (Table 2), a randomized phase 3 trial that compared pembrolizumab with investigator choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with metastatic or advanced urothelial carcinoma that recurred or progressed following platinum-based chemotherapy, showed an ORR for pembrolizumab of 21% compared with 11% for chemotherapy.[27,45] OS, regardless of PD-L1 expression, was superior with pembrolizumab compared with chemotherapy (10.3 vs 7.4 months), and there was a 30% reduction in the risk of death.[45] In the subgroup of patients with enriched PD-L1 expression (≥10%), median OS was longer in the pembrolizumab-treated arm compared with the chemotherapy-treated arm (hazard ratio of 0.57), and a similar trend was noted for patients with low PD-L1 expression (<10%).[45] There was no difference in PFS in patients treated with either pembrolizumab or chemotherapy in the overall population[45] and according to PD-L1 expression status (hazard ratio 0.89).[27] Pembrolizumab was tolerated better than chemotherapy; 61% of patients in the pembrolizumab arm compared with 90% of patients in the chemotherapy arm experienced TRAEs of any grade, including those of grade ≥3 (17% and 50% for pembrolizumab and chemotherapy, respectively).[45] Results from KEYNOTE-045 led to full FDA approval for treatment of this patient population with metastatic urothelial carcinoma.[28]

IMvigor 211 (NCT02302807), a randomized phase 3 study that compared atezolizumab with investigator choice of chemotherapy (paclitaxel, docetaxel, or vinflunine) in the post-platinum setting enrolled 932 patients. ORR for both atezolizumab- and chemotherapy-treated patients was 13%. Although atezolizumab treatment provided a benefit over chemotherapy with a median OS of 8.6 months vs 8.0 months, respectively (P=0.038), the trial failed to achieve its primary objective in showing superiority of atezolizumab compared with chemotherapy based on PD-L1 expression in the IC2/3 subgroup. In patients with high PD-L1 expression (IC 2/3; ≥5% staining), atezolizumab and chemotherapy regimens resulted in OS of 11.1 and 10.6 months, respectively (P=0.41). Median OS in the atezolizumab and chemotherapy arms was 8.9 vs 8.2 months in the IC1/2/3 subgroup (≥1% PD-L1 expression; P=0.14). The safety profile was consistent with that seen in previous studies of atezolizumab; TRAEs of all grades occurred in 70% vs 89% of patients treated with atezolizumab and chemotherapy, respectively; grade 3–4 TRAEs occurred in 20% vs 43% of atezolizumab and chemotherapy treated patients.[42]

First-Line Anti-PD-L1/PD-1 Therapies in Cisplatin-Ineligible Patients

Phase 2 Studies: Many patients are unable to tolerate standard-of-care first-line treatment of advanced urothelial carcinoma with cisplatin because of impaired renal function, poor PS, or other comorbidities.[46] To address this population of patients, IMvigor 210, the same study of atezolizumab that assessed a population of postplatinum patients with metastatic urothelial carcinoma, enrolled a second cohort of 119 cisplatin-ineligible patients who received atezolizumab as first-line treatment.[20,29] In this population, ORR was 23%, median OS was

15.9 months, and there was no significant enrichment of clinical activity by PD-L1 expression (median OS and PFS were 12.3 and 4.1 months in the IC2/3 subgroup [≥5% PD-L1 expression] vs 19.1 and 2.6 months in the IC0/1 subgroup [<5% PD-L1 expression]) or by other clinical subgroups assessed, including patients with poor prognostic factors, such as visceral (non–lymph node) and liver metastases and ECOG PS of 2. Additional exploratory biomarkers included tumor mutation load, which was associated with significantly higher numbers of responding patients. The overall incidence of TRAEs of any grade was 66%, and fatigue, diarrhea, and pruritus occurred in ≥10% of patients. Grade 3/4 TRAEs occurred in 16% of patients, most commonly fatigue and elevated ALT and AST levels (3% each).

KEYNOTE-052 (NCT02335424) (Table 1), a phase 2 study that similarly assessed pembrolizumab as first-line therapy in 370 cisplatin-ineligible patients with metastatic urothelial carcinoma,[30,47] resulted in an ORR of 29%, with high-level PD-L1 expression predicting patients most likely to respond to treatment. Moreover, ORR in patients with tumor PD-L1 expression of ≥10% was 37%. TRAEs of any grade were common in these pembrolizumab-treated patients (66%), 19% of whom had a grade ≥3 event.[47] Based on these studies, both atezolizumab and pembrolizumab were granted accelerated approval by the FDA for first-line treatment of cisplatin-ineligible patients.[19,28–30]

Combination Immunotherapy in Chemotherapy-Refractory Urothelial Carcinoma

Multiple agents, including other immunotherapy, targeted therapy, chemotherapy, and radiation therapy, may enhance the immune response to checkpoint inhibition. The combination of checkpoint inhibitors targeting different molecules, such as PD-L1 and CTLA-4, may enhance the antitumor efficacy seen with monotherapy in urothelial carcinoma. In addition to testing nivolumab as a monotherapy in previously treated patients, CheckMate 032 tested therapy with 2 combination schedules of ipilimumab plus nivolumab (nivolumab 1 mg/kg + ipilimumab 3 mg/kg [N1I3; n=26] or nivolumab 3 mg/kg + ipilimumab 1 mg/kg [N3I1; n=104]) and yielded early encouraging clinical responses. ORR was 39% and 26% in the N1I3 and N3I1 cohorts compared with 26% for nivolumab monotherapy; median OS for the combination was 10.2 and 7.3 months for N1I3 and N3I1, respectively. Safety was consistent with that of nivolumab monotherapy (grade ≥3 TRAEs occurred in 31% and 23% of patients treated with N1I3 and N3I1, respectively, compared with 23% for nivolumab monotherapy).[48]

Several phase 1/2 studies are addressing the combination approach with other novel therapies in patients with advanced or metastatic urothelial carcinoma that has progressed after previous platinum-based therapy. A phase 1 trial (NCT02496208) has shown clinical response to the doublet combination of cabozantinib plus nivolumab (n=30) or the triplet combination of cabozantinib plus nivolumab plus ipilimumab (n=18) in previously treated patients with metastatic urothelial carcinoma or other genitourinary tumors. Treatment was tolerable (most common grade ≥3 AEs were neutropenia, elevated lipase level, hypophosphatemia, and fatigue in patients treated with the doublet combination and hypophosphatemia, elevated ALT level, hypertension, elevated lipase level, and fatigue, in patients treated with the triplet combination [≥10% of patients]). ORR was 37% for all genitourinary tumors and 44% for patients with urothelial carcinoma, with all patients with

urothelial carcinoma experiencing ongoing responses at the time of data cutoff.[49] Phase 1 studies with combination regimens with pembrolizumab include a phase 1a/b trial that enrolled 24 patients who were treated with a combination of pembrolizumab and the anti–vascular endothelial growth factor receptor 2 antibody ramucirumab.[50] Preliminary ORR was 8%. TRAEs occurred in 54% of patients, most commonly fatigue, nausea, pyrexia, and elevated ALT and AST levels in ≥10% of patients (3 patients [13%] had grade 3 TRAEs). Pembrolizumab with either docetaxel or gemcitabine has also been assessed in 12 patients with advanced or metastatic urothelial carcinoma that progressed on ≥1 previous platinum-based therapy.[51] Encouraging antitumor activity was noted in this study, particularly with pembrolizumab plus docetaxel (ORR 50%); ORR was 17% for the pembrolizumab plus gemcitabine regimen. The overall incidence of grade ≥3 TRAEs was 54%, most commonly anemia, fatigue, and neutropenia. ECHO-202/KEYNOTE-037 (NCT02178722) is a phase 1/2 study of pembrolizumab plus epacadostat, an IDO1 inhibitor, in multiple advanced cancers, including a cohort in UC that has enrolled 40 patients. In a preliminary analysis, ORR was 35%, and 7 of 11 patients with PD-L1+ tumors had a response (ORR, 64%). Grade 3/4 TRAEs occurred in 23%.[52]

Safety Profile for Anti-PD-L1/PD-1 Agents in Metastatic Urothelial Carcinoma

In addition to the encouraging efficacy results demonstrated in several clinical trials, anti–PD-L1 agents have also been associated with fewer adverse events compared with chemotherapy.[20,22,23,25,29,30,37–40] Although serious TRAEs, renal toxicity, and serious immune-related AEs affecting the dermatologic, gastrointestinal, hepatic, and endocrine systems have been noted in patients with metastatic urothelial carcinoma receiving treatment with anti–PD-L1/PD-1 agents, they are reported less frequently than during treatment with chemotherapy regimens.[53] Indeed, immunotherapy appears to be generally better tolerated than chemotherapy, including in elderly patients or patients with comorbidities who have historically had limited treatment options due to toxicity.[1,46] Despite the general tolerability of anti–PD-L1/PD-1 antibodies, challenges associated with their use include acquired resistance attributable to upregulation of alternative immune checkpoints, a phenomenon noted in other tumor types.[54]

Treatment Sequencing and Combination Treatment Strategies with Anti-PD-L1/PD-1 Agents

Combination regimens with anti–PD-L1/PD-1 agents and platinum-based chemotherapy for patients with metastatic urothelial carcinoma are also being evaluated in phase 3 trials (Table 2). KEYNOTE-361 is assessing efficacy and safety of first-line pembrolizumab treatment with or without platinum-based chemotherapy in patients with advanced or metastatic urothelial carcinoma, compared with platinum-based chemotherapy (cisplatin with gemcitabine or carboplatin with gemcitabine doublet) in treatment-naive patients with metastatic urothelial carcinoma.[55] CheckMate 901 (NCT03036098) will assess the efficacy of nivolumab in combination with ipilimumab vs platinum-based chemotherapy in patients with untreated inoperable or metastatic urothelial carcinoma.[56] DANUBE will determine the efficacy and safety of first-line durvalumab treatment with or without tremelimumab vs platinum-based chemotherapy in cisplatin-eligible and -ineligible patients.[57] IMvigor 130 is analyzing first-line treatment with atezolizumab plus gemcitabine/carboplatin chemotherapy

vs placebo plus gemcitabine/carboplatin in a cohort of randomized cisplatin-ineligible patients with advanced metastatic urothelial carcinoma.[58]

Following completion of first-line platinum-based chemotherapy without progressive disease, patients are typically managed with best supportive care (BSC) because effective maintenance regimens resulting in durable responses in these patients have not been established. Maintenance treatment thus offers the possibility of prolonging PFS in patients who achieve a response to first-line chemotherapy. However, there are currently no approved agents for maintenance treatment of patients with metastatic urothelial carcinoma. In a recent phase 2 study of 88 patients with advanced urothelial carcinoma who achieved stable disease after first-line cisplatin and gemcitabine treatment (MAJA, SOGUG 2011/02; NCT01529411), maintenance vinflunine resulted in longer PFS compared with BSC.[59] Median PFS was 6.5 months in patients treated with maintenance vinflunine compared with 4.2 months in those patients receiving BSC (hazard ratio of 0.59). Although patients treated with vinflunine maintenance had an increased incidence of adverse events versus those treated with BSC, all grade 3–4 adverse events were manageable. Maintenance treatment with checkpoint inhibitors for controlled urothelial carcinoma is also being assessed in several studies, including a phase 2 study of pembrolizumab as maintenance therapy after initial chemotherapy in urothelial carcinoma is currently ongoing (NCT02500121).[60] Furthermore, a phase 3 study of maintenance therapy with avelumab plus BSC compared with BSC in patients with metastatic urothelial carcinoma that did not worsen during or after first-line treatment with platinum-based chemotherapy (JAVELIN Bladder 100; NCT02603432) is also ongoing.[61] Combination therapy for patients with metastatic urothelial carcinoma who have failed at least one prior platinum regimen is also being assessed in BISCAY (NCT02546661), a biomarker-directed multidrug umbrella study combining next-generation targeted small molecules and durvalumab.[62]

Cisplatin-based neoadjuvant chemotherapy is standard with radical cystectomy, given the high risk of relapse with surgery alone.[63] In the neoadjuvant setting, multiple trials with immune checkpoint inhibitors are ongoing or planned. Among these studies are two phase 2 studies that are currently enrolling patients to receive atezolizumab (NCT02662309) or pembrolizumab (NCT02736266), with pathological complete response as the primary endpoint.[64,65] In the adjuvant setting after radical cystectomy for MIBC, there is currently no standard treatment,[4] and adjuvant treatment with anti-PD-L1/PD-1 therapies for these patients is being assessed in several phase 3 trials. IMvigor 010 and CheckMate 274 are assessing adjuvant treatment with atezolizumab and nivolumab, respectively. In IMvigor 010, patients with PD-L1–selected MIBC who are at high risk for recurrence following cystectomy will be treated with atezolizumab or observation. In CheckMate 274, these patients will be randomized and treated with nivolumab or placebo and stratified by PD-L1, lymph node, and previous cisplatin neoadjuvant chemotherapy status.[66] Finally, an intergroup trial of pembrolizumab versus observation in the adjuvant treatment of MIBC and high-grade upper tract urothelial carcinoma has initiated enrollment (AMBASSADOR; NCT03244384).[67]

Evidence for Potential Biomarkers

PD-L1 as a Predictive Biomarker—Levels of tumor PD-L1 expression have been associated with urothelial carcinoma severity and treatment outcome; thus, assessment of PD-L1 expression has consistently been an integral part of clinical studies of checkpoint inhibitors in urothelial carcinoma.[20,22,25,29,35,38–41] The use of PD-L1 as a biomarker in bladder cancer is complex due to several factors, including heterogeneity of PD-L1 expression level within tumors, variability in tissue collection requirements across trials (fresh or archival samples), differences among antibody clones used for IHC, definitions of PD-L1 positivity based on protocol-specific staining cutoffs, and use of nonstandardized test designs.[34]

There are currently several PD-L1 assays used in trials for each of the anti–PD-L1/PD-1 inhibitors described in this review. Although the Ventana PD-L1 assay (SP142; OptiView DAB IHC detection kit with OptiView amplification) stains both TCs and ICs, the FDA approved it as a complementary assay for atezolizumab based on the clinical benefit that was associated with enriched IC PD-L1 staining in 310 postplatinum patients from IMvigor 210.[19,20,35] However, the FDA's accelerated approval of atezolizumab did not include a requirement for PD-L1 expression testing,[4,19] and indeed, no significant enrichment of response by PD-L1 expression was seen in the cohort of first-line, cisplatin-ineligible patients treated with atezolizumab, in contrast to responses from the postplatinum patient cohort.[29] Although analyses are ongoing, top-line results from IMvigor 211 suggest that the biomarker was not indicative of clinical efficacy.[42] In KEYNOTE-012 and KEYNOTE-052, pembrolizumab showed enhanced antitumor activity in patients with recurrent or metastatic PD-L1+ urothelial carcinoma based on ≥1% and ≥10% PD-L1 expression, respectively.[30,40,47] PD-L1 was assessed using the Dako PD-L1 IHC 22C3 pharmDx assay, a qualitative IHC assay using the anti-PD-L1 clone 22C3 performed on formalin-fixed, paraffin-embedded tissues, which is currently approved by the FDA as a companion diagnostic test to identify patients with NSCLC for treatment with pembrolizumab.[28] Durvalumab showed enhanced antitumor activity in a population of patients with ≥25% PD-L1 expression on ICs or TCs as a combined measure. PD-L1 was assessed using the FDA-approved Ventana SP263 PD-L1 assay, which stains TCs and ICs at a threshold of ≥25%. Notably, PD-L1 expression was not predictive of durvalumab efficacy when assessed in TCs or ICs separately but was predictive of efficacy when assessed in TCs and ICs combined.[23] In the JAVELIN Solid Tumor trial of avelumab, testing has been performed using the proprietary Dako PD-L1 IHC 73-10 pharmDx assay. Although potential differences in efficacy per PD-L1 expression have been seen, durable efficacy has also been observed in PD-L1- subgroups.[25,38] The role of tumor PD-L1 expression has similarly been investigated across several nivolumab trials, and phase 1 and 2 nivolumab trials used the Dako PD-L1 IHC 28-8 pharmDx assay to determine TC PD-L1 expression at ≥1% or ≥5% staining and at any intensity. These studies showed that patients with PD-L1- and PD-L1+ tumors benefited equally.[22,39]

Despite wide usage of PD-L1 in clinical trials, its predictive role in urothelial carcinoma remains uncertain, with trends suggesting different clinical outcomes by PD-L1 expression based on staining in ICs, TCs, or both. Furthermore, each of the PD-L1 assays has been

designed for use with a specific inhibitor, and it is currently unknown whether these assays are interchangeable. Although one recent study reported that in NSCLC, the 22C3, 28-8, and E1L3N anti–PD-L1 antibodies appeared to be interchangeable,[68] this has not been verified in urothelial carcinoma. The ongoing FDA Blueprint initiative for companion diagnostics, whose goal is to standardize analytical and clinical performance across various PD-L1 diagnostic assays, was undertaken to address this controversy.[69]

Next-Generation Predictive Biomarkers—In addition to tumor PD-L1 expression, mutational load has been explored for its association with clinical outcomes in patients treated with PD-L1/PD-1 checkpoint inhibitors.[70] Other biomarkers that may predict response to immunotherapies include IFNγ gene signatures, expanded immune gene signatures, and tumor subtypes based on The Cancer Genome Atlas (TCGA).[71,72] Studies to identify peripheral blood immune biomarkers have determined that blockade of the PD-L1/PD-1 axis can increase effector T-cell proliferation and production of inducible T-cell α chemoattractant, IFNγ, and interleukin 18, although these responses were not indicative of significant response or progression.[72]

The TCGA project analyzed gene expression data sets relative to clinical and pathological data in chemotherapy-naive patients with MIBC. As part of these analyses, bladder cancer subtypes were grouped based on luminal- and basal-like gene signatures.[71] Further analyses revealed that certain TCGA subtypes were associated with prognostic differences in survival, with basal tumors associated with decreased survival.[73] IMvigor 210 and CheckMate 275 included analyses of urothelial carcinoma subtype and immune gene signature expression as predictive biomarkers.[20,22] In IMvigor 210, TCGA molecular subtypes were independently associated with clinical responses to atezolizumab. IC PD-L1 expression was highly enriched in the basal urothelial carcinoma subtype, which also had the strongest IFNγ gene signature expression, compared with the luminal subtype. Additionally, mutational burden was significantly higher in responders than in nonresponders. CheckMate 275 also showed an association between high IFNγ expression and urothelial carcinoma molecular subtype with clinical outcome of nivolumab treatment.[22] Finally, the BISCAY trial is exploring whether the addition of targeted small molecules to durvalumab treatment in patients with specific biomarkers may result in enhanced neoantigen release and immunosensitization.[62]

Health-related quality of life (HRQOL) as a Marker of Treatment Benefit With Immune Checkpoint Inhibitors

Measurement of patient-reported outcomes, including HRQOL, is a rapidly expanding initiative that has been included as an endpoint in multiple clinical trials following validation of self-report questionnaires. There are growing amounts of data supporting the benefit of immune checkpoint inhibitors relative to HRQOL measures reported by patients with urothelial carcinoma, and nearly all ongoing phase 3 trials for patients with urothelial carcinoma have begun to incorporate HRQOL measures as key secondary objectives. For example, in KEYNOTE-045, pembrolizumab was associated with improved HRQOL measures compared with chemotherapy, including increased rates of improvement for most social functioning and symptom domains (31.2% vs 22.0%) and lower rates of deterioration

for all social functioning and symptom domains (28.9 vs 40.6%).[74] IMvigor 211 measured patient-reported global health status, physical functioning, and fatigue occurring during treatment with atezolizumab based on European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 quality of life questionnaires. In evaluable patient reported outcomes, an overall numerical trend toward better global health status and less fatigue was seen with atezolizumab. Mean global health status scores worsened initially but returned to baseline values more quickly with atezolizumab than with chemotherapy. Similar results were seen for physical functioning. Furthermore, the initial worsening of fatigue levels rapidly improved with atezolizumab.[42] Additionally, IMvigor 130 will also measure median time to deterioration during atezolizumab treatment based on EORTC QLQ-C30 reports, and disease-related symptoms and health status of patients with metastatic urothelial carcinoma will be assessed in JAVELIN Bladder 100 (avelumab) and DANUBE (durvalumab).[57,61]

CONCLUSIONS

Bladder cancer remains an area of great unmet medical need, with 5-year OS rates of 5% for metastatic disease.[1] Although platinum-based combination chemotherapy leads to high response rates in patients with urothelial carcinoma, most of these patients will ultimately experience disease progression. Therefore, improved treatments for advanced or metastatic urothelial carcinoma must still be determined.[4] The recent approvals of anti-PD-L1/PD-1 therapies has expanded the treatment landscape for patients with bladder cancer, for whom there have been few options with durable responses. Additional examination of data from recent trials may prompt re-evaluation of key study design assumptions made given the success of KEYNOTE-045 and the failure of IMvigor 211 to meet its primary endpoint.[27,28,42] Anti-PD-L1/PD-1 monoclonal antibodies have shown efficacy and safety in patients with advanced disease, particularly in those with poor prognostic factors. In general, efficacy appears to be similar among different anti-PD-L1/PD-1 agents tested to date in populations unselected for PD-L1 status, although head-to-head data are not available. Differences have been seen between the predictive value of different assays used for PD-L1 detection, consistent with the use of different antibodies and methodologies in the various trials.

Future considerations to improve the probability of benefit provided by PD-L1/PD-1 checkpoint inhibitors include the use of biomarkers or a combination of biomarkers, as well as HRQOL reports, to identify the patient populations most likely to respond to these treatments. Trials with checkpoint inhibitors combined with other active anticancer agents have shown improved response rates compared with monotherapies in other tumors,[75] and evaluation of similar combinations are ongoing in urothelial carcinoma with promising preliminary efficacy and safety data. Treatment sequencing strategies in patients with metastatic urothelial carcinoma that has not responded to anti-PD-L1/PD-1 monotherapy is needed. Finally, investigation of checkpoint inhibitors during earlier disease stages has the potential to expand the use of immunotherapy within the urothelial carcinoma treatment landscape.

Expert Opinion

Anti–PD-L1/PD-1 inhibitors have shown activity in patients with metastatic urothelial carcinoma in both the first- and second-line settings. Based on the evolving landscape, our recommendations for treating patients with urothelial carcinoma are as follows:

1. Current evidence supports the use of anti–PD-L1/PD-1 agents for second-line treatment of patients with urothelial carcinoma
2. Use of anti–PD-L1/PD-1 inhibitors is encouraged for first-line treatment of cisplatin-ineligible patients with urothelial carcinoma
3. In the context of ongoing clinical trials, for which data are eagerly awaited, anti–PD-L1/PD-1 therapy may be incorporated during earlier disease settings, including during the maintenance line, and may include combinations with chemotherapy or novel small molecule inhibitors; when possible we favor patients be enrolled in an anti–PD-L1/PD-1 trial
4. Trends in clinical trial designs suggest the potential for post-progression rechallenge with combination anti–PD-L1/PD-1 therapy coupled with intervening chemotherapy or radiation for treatment of checkpoint inhibitor-refractory urothelial carcinoma

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Abbreviations

FDA	Food and Drug Administration
PD-1/PD-L1	programmed cell death-1/ligand-1

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Clinical practice points

- Anti–PD-L1/PD-1 treatments are generally considered preferable to second-line chemotherapy, enabling treatment of a wider patient population including patients with historically adverse prognostic risk factors
- The relative benefits of anti–PD-L1/PD-1 inhibitors are highlighted through measures that include safety, OS, ORR, PFS, and HRQOL
- Novel biomarkers are a strong focus and include genomic subtypes, mutational profiles, and gene signatures; uncertainty and skepticism exists about the clinical value of PD-L1 expression as a predictive biomarker, and data for next-generation biomarkers with anti–PD-L1/PD-1 antibodies may help identify patient populations more likely to respond to these immunotherapy regimens

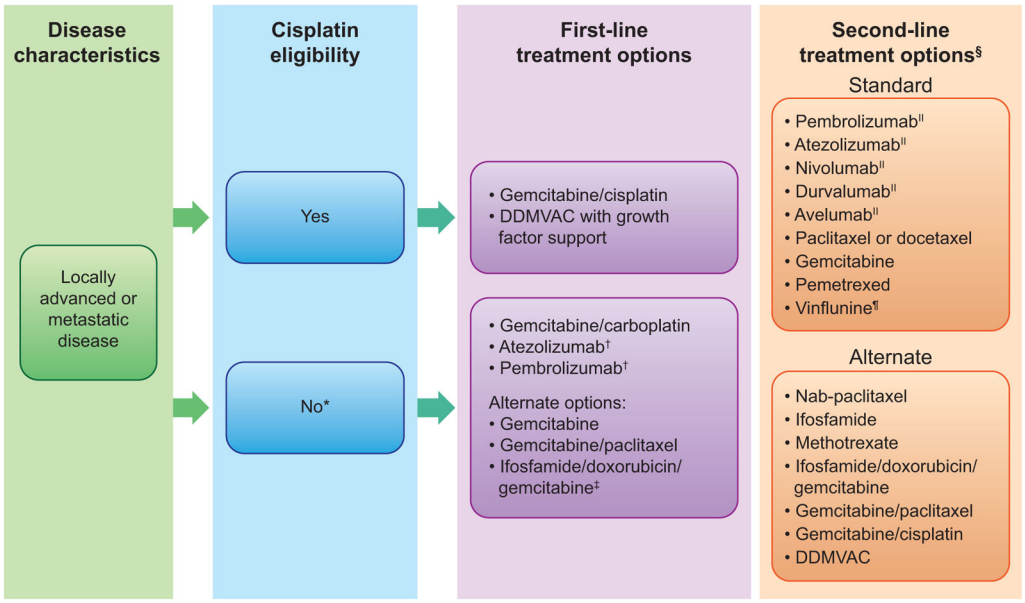


Figure 1.

Systemic treatment of locally advanced or metastatic urothelial carcinoma. Treatment guidelines for urothelial carcinoma based on NCCN Clinical Practice Guidelines in Oncology (bladder).[4] * Participation in clinical trials of new or more tolerable therapy is recommended for patients who cannot receive cisplatin-based chemotherapy. † Accelerated US Food and Drug Administration approval of atezolizumab and pembrolizumab for treatment of locally advanced or metastatic urothelial carcinoma in cisplatin-ineligible patients. ‡ For patients with good kidney function and good performance status. § No global second-line treatment options currently exist; participation in clinical trials of new agents is recommended. II Accelerated US Food and Drug Administration approval of atezolizumab, nivolumab, durvalumab, and avelumab and full approval of pembrolizumab for treatment of locally advanced or metastatic urothelial carcinoma that has progressed during or following platinum-containing chemotherapy or has progressed within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. ¶ Approved in Europe as a standard treatment for patients in the second-line setting.[10,11] **Abbreviations**: DDMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin.

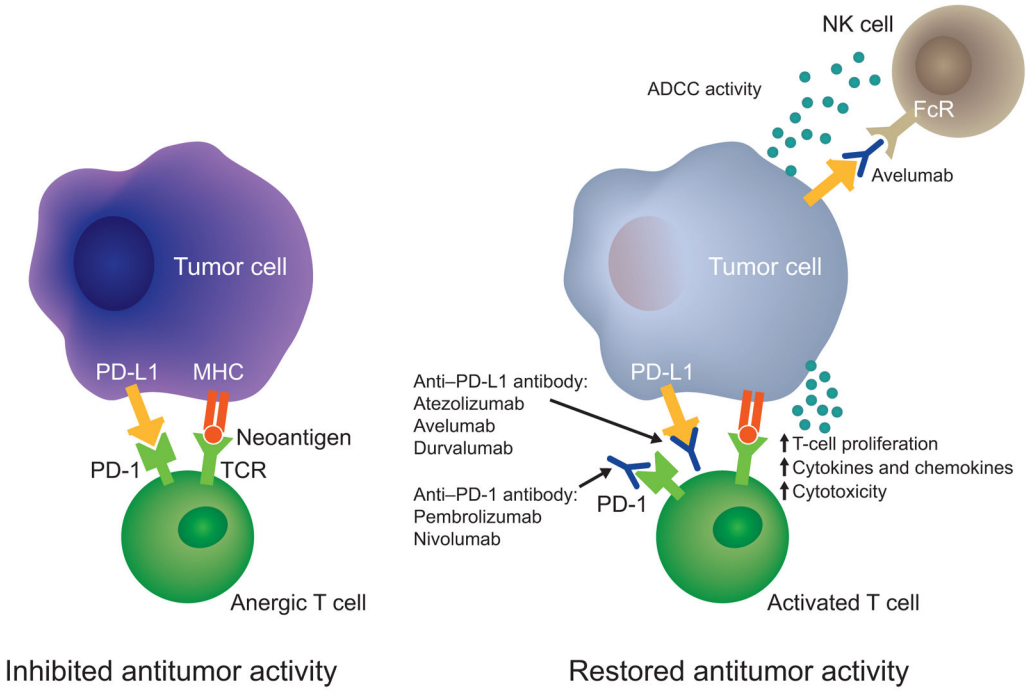
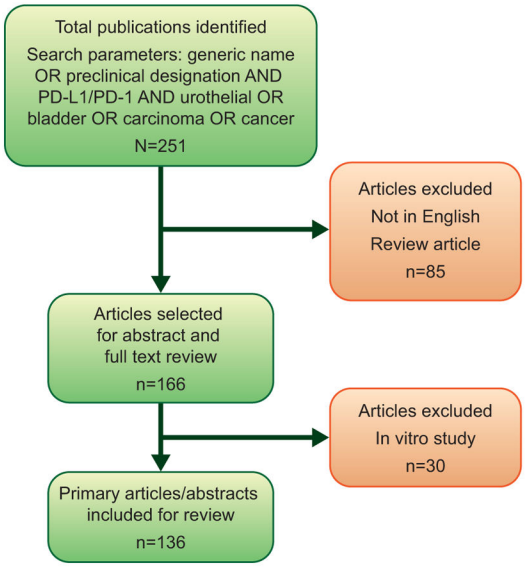


Figure 2.

Mechanism of action of anti-PD-L1/PD-1 checkpoint inhibitors. The PD-L1/PD-1 axis in the tumor microenvironment and the roles of PD-L1 and PD-1 inhibitors in restoring antitumor activity. T cells are inactivated in response to co-inhibitory signals from tumor cells (ie, engagement of PD-1 on T cells by PD-L1). Anti–PD-L1/PD-1 inhibitors block these co-inhibitory signals, resulting in increased T-cell proliferation, increased proinflammatory cytokine and chemokine production, and increased cytotoxicity. A potential role for NK cells and ADCC in avelumab's mechanism of action is also depicted.

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; FcR, Fc receptor; MHC, major histocompatibility complex; NK, natural killer; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; TCR, T-cell receptor.



Search Parameters	No. of Articles, All Types	No. of Articles and Abstracts Included
Atezolizumab or MPDL3280A	39	8
Avelumab or MSB0010718C	11	3
Durvalumab or MEDI4736	9	3
Nivolumab or BMS-936558	21	6
Pembrolizumab or MK-3475	32	11
Total	**113**	**32**

Figure 3.

Literature search results for anti–PD-L1/PD-1 therapies in bladder cancer. Flow chart of literature search results for studies examining the effects of anti–PD-L1/PD-1 therapies in bladder cancer performed using the PubMed database and major congresses as outlined in Materials and Methods. An independent search replacing the PubMed database with the Embase database produced similar results.

Table 1

Phase 1 and phase 2 trials for treatment of patients with urothelial carcinoma

Drug (target)	Phase	Trial Identifier	Treatment Schedule	No. Patients	No. Treatment Lines	Patient Population	Safety (%)	ORR (%)	OS (mos)	PD-L1 Expression Assay	Reference No.
	Second-line anti-PD-L1/PD-1 therapies in patients with disease that progressed after platinum-based chemotherapy										
Atezolizumab (PD-L1)	1	NCT01375842	15 mg/kg or 1200 mg Q3W	85	1L: 2 ≥2L: 83	Platinum-resistant advanced UC	Any TRAE: 64 Grade ≥3: 8 irTRAE: NR	All patients: NR PD-L1+ 2/3: 46 PD-L1+ 0/1: 16	NR	Ventana SP142: IC0 (<1%), IC1 (≥1%/ <5%), IC2/3 (≥5%)	41
	2	IMvigor 210; NCT02108652	1200 mg Q3W	310	1L: 58 2L: 120 ≥3L: 132	Platinum-refractory or -resistant advanced UC	Any TRAE: 70 Grade ≥3: 16 irTRAE: 7	All patients: 16 PD-L1+ 2/3: 28 PD-L1+ 1/2/3: 19	All patients: 7.9 PD-L1+ 2/3: 11.4 PD-L1+ 1/2/3: 8.8	Ventana SP142: IC0 (<1%), IC1 (≥1%/ <5%), IC2/3 (≥5%)	35
Nivolumab (PD-1)	1	CheckMate 032; NCT01928394	3 mg/kg Q2W	78	1L: 0 2L: 26 ≥3L: 52	Platinum-resistant advanced UC	Any TRAE: 81 Grade ≥3: 22 irTRAE: NR	All patients: 24 PD-L1+: 24 PD-L1-: 26	All patients: 9.7 PD-L1+: 16 PD-L1-: 10	Dako 28-8: ≥1% PDL1	39
	2	CheckMate 275; NCT02387996	3 mg/kg Q2W	270	1L: 77 2L: 114 ≥3L: 79	Platinum-resistant advanced UC	Any TRAE: 64% Grade ≥3: 18 irTRAE: NR	All patients: 20 PD-L1 ≥5%: 28 PD-L1 <1%: 16	All patients: 8.7 PD-L1+: 11.3 PD-L1-: 6.0	Dako 28-8: ≥5% PDL1	22
Durvalumab (PD-L1)	1	NCT01693562	10 mg/kg Q2W	191	1L: 9 2L: 118 ≥3L: 64	Pretreated advanced UC	Any TRAE: 61 Grade 3/4: 7 irAE: 12	All patients: 18 PD-L1+: 28 PD-L1-: 5	All patients: 18.2 PD-L1+: 20.0 PD-L1-: 8.1	Ventana SP263: ≥25% PDL1	43
Avelumab (PD-L1)	1	JAVELIN Solid Tumor; NCT01772004	10 mg/kg Q2W	249	1L: 8 2L: 111 ≥3L: 124	Platinum-refractory advanced UC or cisplatin ineligible	Any TRAE: 67 Grade ≥3: 8 irAE: 34	All patients: 17 PD-L1+: 25 PD-L1-: 13	All patients: 7.4 PD-L1+: 7.7 PD-L1-: 6.3	Dako 73-10: ≥5% PDL1	38
Pembrolizumab (PD-1)	1	KEYNOTE-012; NCT01848834	10 mg/k Q2W	33	1L: 8 2L: 8 ≥3L: 17	Pretreated advanced UC and ≥1% PD-L1 expression level	Any TRAE: 60 Grade ≥3: 15 irTRAE: NR	All patients: 26 PD-L1+: 24 PD-L1-: 0	All patients: 13 PD-L1+: NR PD-L1-: NR	Dako 22C3: ≥1% PDL1	40
	First-line anti-PD-L1/PD-L1 therapies in cisplatin-ineligible patients										
Atezolizumab (PD-L1)	2	IMvigor 210; NCT02108652	1200 mg Q3W	119	1L: 119	Cisplatin-ineligible advanced UC	Any TRAE: 66 Grade ≥3: 16 irTRAE: NR	All patients: 23 PD-L1+ 2/3: 28 PD-L1+ 1/2/3: 24 PD-L1+ 1: 21 PD-L1+ 0: 21	All patients: 15.9 PD-L1+ 2/3: 12.3 PD-L1+ 0/1: 19.1	Ventana SP142: IC0 (<1%), IC1 (≥1%/ <5%), IC2/3 (≥5%)	29
Pembrolizumab (PD-1)	2	KEYNOTE-052; NCT02335424	200 mg Q3W	370	1L: 370	Platinum-resistant advanced UC	Any TRAE: 66 Grade ≥3: 19 irTRAE: NR	All patients: 29 PD-L1+ ≥10%: 47	NR	Dako 22C3: ≥10% PDL1	30

Abbreviations: 1L, first line 2L, second line; 3L, third line; irAE, immune-related adverse event; irTRAE, immune-related treatment-related adverse event; IC, immune cell; mos, months; NR, not reported; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; TRAE, treatment-related adverse event; UC, urothelial carcinoma.

Table 2

Planned/ongoing phase 3 clinical trials for treatment of patients with urothelial carcinoma

Drug (target)	Trial Identifier	Treatment Schedule	Planned Treatment Regimen	Planned No. Patients	Planned Patient Population	Results
Atezolizumab (PD-L1)	IMvigor 211; NCT02302807	Q3W	Arm 1: atezolizumab 1200 mg Arm 2: vinflunine 320 mg/m^2, paclitaxel 175 mg/m^2, or docetaxel 75 mg/m^2	932	Locally advanced or metastatic UC that progressed following platinum therapy	Failed to meet its primary endpoint of OS compared with chemotherapy[42]
	IMvigor 130; NCT02807636	Q3W	Arm 1: atezolizumab 1200 mg + gemcitabine 1000 mg/m^2 (on days 1 and 8 of each cycle) + cisplatin 70 mg/m^2 ***or*** carboplatin AUC 4.5 Arm 2: gemcitabine 1000 mg (on days 1 and 8 of each cycle) + cisplatin 70 mg/m^2 ***or*** carboplatin AUC 4.5 Arm 3: atezolizumab 1200 mg	1200	Previously untreated locally advanced or mUC	NA
	IMvigor 010; NCT02450331	Q3W	Arm 1: atezolizumab 1200 mg Arm 2: observation	700	After radical surgery for high-risk MIBC (PD-L1+)	NA
Avelumab (PD-L1)	JAVELIN BLADDER 100; NCT02603432	Q2W	Arm 1: avelumab 10 mg/kg in combination with BSC Arm 2: BSC alone	668	Locally advanced or metastatic UC that did not progress following 1L treatment with 4–6 cycles of gemcitabine + cisplatin or carboplatin	NA
Durvalumab (PD-L1)	DANUBE; NCT02516241	Q4W	Arm 1: durvalumab 1500 mg Arm 2: durvalumab 1500 mg + tremelimumab 75 mg Arm 3: gemcitabine + cisplatin ***or*** carboplatin (6 cycles)	1005	Advanced/unresectable or metastatic UC	NA
Nivolumab (PD-1)	CheckMate 274; NCT02632409	Q2W	Arm 1: nivolumab Arm 2: placebo	640	Undergone radical surgery for high-risk MIBC (PD-L1 status known)	NA
	CheckMate 901; NCT03036098	NA	Arm 1: nivolumab + ipilimumab Arm 2: gemcitabine/cisplatin or gemcitabine/carboplatin Arm 3: nivolumab + gemcitabine/cisplatin followed by nivolumab Arm 4: gemcitabine-cisplatin	897	Previously untreated unresectable or metastatic UC	NA
Pembrolizumab (PD-1)	KEYNOTE-045; NCT02256436	Q3W	Arm 1: pembrolizumab 200 mg Arm 2: paclitaxel 175 mg/m^2, docetaxel 75 mg/m^2, ***or*** vinflunine 320 mg/m^2	542	Metastatic or locally advanced unresectable UC that recurred or progressed following platinum-based chemotherapy	Co-primary endpoint reached; pembrolizumab superior to

Drug (target)	Trial Identifier	Treatment Schedule	Planned Treatment Regimen	Planned No. Patients	Planned Patient Population	Results
						investigator choice chemotherapy (median OS 10.3 vs 7.4 months)[27,45]
	KEYNOTE-361; NCT02853305	Q3W	Arm 1: pembrolizumab 200 mg Arm 2: pembrolizumab 200 mg + gemcitabine 1000 mg/m^2 (on days 1 and 8 of each cycle) + cisplatin 70 mg/m^2 ***or*** carboplatin AUC 5 Arm 3: gemcitabine 1000 mg/m^2 (on days 1 and 8 of each cycle) + cisplatin 70 mg/m^2 ***or*** carboplatin AUC 5	990	Advanced/unresectable or metastatic UC	NA

Abbreviations: 1L, first line; AUC, area under the curve; BSC, best supportive care; MIBC, muscle-invasive bladder cancer; NA, not available; OS, overall survival; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand 1; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; UC, urothelial carcinoma.