# Advances and Controversies With Checkpoint Inhibitors in Bladder Cancer

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**ABSTRACT:** Immune checkpoint inhibitors have revolutionized the treatment of bladder urothelial cancers and have wide application in almost all disease states. Although several drugs have initially been shown to be beneficial in the second-line metastatic setting, there are still ongoing controversies and debate, including voluntary withdrawals of durvalumab and atezolizumab, along with the approval of agents in the first-line setting in the cisplatin-ineligible state based on inconsistent confirmatory phase III trials. As novel immunotherapy drugs are discovered and studied in various phases of clinical trials, these agents will continue to change the treatment landscape for bladder cancer patients. This review will discuss current available evidence and information and key pivotal trials using checkpoint inhibitors in bladder cancer.

**KEYWORDS:** Bladder cancer, immune checkpoint inhibitors, pembrolizumab, avelumab, atezolizumab, durvalumab, nivolumab

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## Introduction

Bladder cancer is the ninth most common cancer in the world, and the most common malignancy of the urinary tract. In the United States alone, 83 730 new cases are expected to be diagnosed in 2021, the vast majority of cases occurring in men.[1,2] It has become the second most prevalent malignancy in middle-aged and older adult men.[3] Urothelial carcinomas, or transitional cell carcinomas, accounts for majority of bladder cancer cases in the United States and Western Europe. Non-urothelial forms, typically those secondary to endemic schistosomiasis, are growing in numbers in other parts of the world. Over the past 50 years, the US 5-year survival rate has increased to approximately 80%, especially as superficial bladder cancers remain the most common presentation of bladder cancer.[1]

Although most bladder cancers are diagnosed in the superficial stages, up to a quarter of patients present with muscle-invasive disease that can progress to metastatic disease. Multimodality therapy is the cornerstone of treatment with platinum-based chemotherapy forming an important backbone of treatment.[4] Treatment for metastatic bladder cancer often involves platinum-based chemotherapy for those who are considered cisplatin-fit or platinum-eligible, although use of first-line immunotherapy remains for those who have high expression of PD-L1 (programmed death-ligand 1) or platinum-ineligible.[5]

The earliest touted use of immunotherapy in bladder cancer dates back to 1990, when intravesical Bacillus Calmette-Guerin (BCG), a live attenuated form of *Mycobacterium bovis*, was approved for the treatment of non-muscle-invasive disease. It has become standard for adjuvant treatment for high-risk non-muscle-invasive disease following transurethral resection of the bladder tumor (TURBT).[6] While the full effects of BCG are not entirely elucidated, it is thought to lead to a series of local immune responses through various mechanisms, including induction of CD4+ T cells and macrophages, increased interferon gamma expression, increased recruitment of urinary cytokines, trained immunity, and tumor growth suppression.[7-12] As evolution of our understanding of cancer biology and immunology have expanded, novel agents focused on using the patient's immune system to help fight and control malignancy have become increasingly effective in various tumor types. One such therapy of immune checkpoint inhibition, primarily those targeting programmed cell death-1 protein (PD-1) or its ligand (PD-L1), has become widely studied in oncology, including bladder cancer.[13] Based on durable responses and favorable overall survival (OS) in clinical trials, antibodies inhibiting PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, and durvalumab) are used for a number of clinical indications. While all 5 of those agents were initially approved by the US Food and Drug Administration (FDA) as second-line therapy for patients who have progressed during or after platinum-based therapy (see Table 1), and have not received prior immunotherapy, the approval for durvalumab was recently voluntarily withdrawn given inability to meet primary endpoints for the confirmatory DANUBE trial,[14] with atezolizumab soon following voluntary withdrawal in March 2021 given failure to meet primary endpoint for the IMvigor211. In addition, the initial accelerated approval for pembrolizumab and atezolizumab[15] has been called into question given controversial results for the confirmatory trials KEYNOTE-361 and IMvigor010, respectively. Table 1 provides a data summary from landmark trials that used immune checkpoint inhibitor therapy in the second-line setting, including their primary endpoints, findings, and FDA

**Table 1.** Landmark trials using immune checkpoint inhibitors as second-line therapy.

| TRIAL | PHASE OF TRIAL | EXPERIMENTAL ARMS | PRIMARY ENDPOINTS | FINDINGS | COMMENTS |
|---|---|---|---|---|---|
| IMvigor210 | II | Atezolizumab 1200 mg IV every 3 wk (n = 310) | PFS in PD-L1+; OS in ITT | ORR: 15.0% (11%-20%) mPFS 2.7 mo (2.1-4.2 mo) | FDA approved 2016; voluntarily withdrawn March 2021 |
| KEYNOTE-045 | III | Pembrolizumab 200 mg IV every 3 wk (n = 266) | OS and PFS in ITT and PD-L1+ | ORR: 21.1% (16.4%-26.5%) mPFS 2.1 mo (2.0-2.2 mo) | FDA approved 2017 |
| Javelin Solid tumor | Ib | Avelumab 10 mv/kg IV every 2 wk (n = 44) | DLT and BOR | ORR: 18.2% (8.2%-32.7%) mPFS 11.6 wk (6.1-17.4 wk) | FDA approved 2017 |
| CheckMate 275 | II | Nivolumab 240 mg IV every 2 wk (n = 270) | ORR in ITT and PD-L1+ | ORR: 19.6% (15.1%-24.9%) mPFS 2 mo (1.87-2.63 mo) | FDA approved 2017 |
| Study 1108 | I/II | Durvalumab 10 mg/kg IV every 2 wk (n = 182) | DLT and antitumor efficacy | ORR: 17.0% (11.9%-23.3%) mPFS 2.2 mo (1.4-2.7 mo) | FDA approved 2017; voluntarily withdrawn February 2021 |

Abbreviations: BOR, best overall response; DLT, dose limiting toxicity; FDA, US Food and Drug Administration; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

approval information. This review will discuss summary approval of these agents and implications for use as well as recent controversies surrounding its use in bladder cancer.

## Second-Line Immune Checkpoint Inhibitors Post-Chemotherapy Failure in Metastatic Urothelial Cancers

Immune checkpoint inhibitors were first studied and approved for second-line metastatic urothelial cancers. The following section discusses the pivotal trials that used these drugs (see Table 1).

### *Atezolizumab*

Atezolizumab is an IgG1 monoclonal antibody against PD-L1 and was the first agent of its class found effective in patients with metastatic bladder cancer as second-line therapy.[16] Atezolizumab was one of the first initially granted accelerated approval in the United States with the indications for patients with locally advanced or metastatic urothelial bladder cancer. Atezolizumab was initially studied at a dose of atezolizumab of 1200 mg IV every 3 weeks. The initial trial that showed use of atezolizumab was based on the phase II, single-arm IMvigor210 trial (NCT02108652) which enrolled 2 cohorts: the first which included 119 patients with treatment-naïve cisplatin-ineligible patients was initially reported as part of a different study (NCT02951767) while the other cohort of 310 patients were treated with prior platinum-based chemotherapy as second-line, with the primary endpoint of overall response rate (ORR) which was shown to be 15% in the whole cohort regardless of PD-L1 expression. Higher responses were noted in the IC2/3 group with an ORR of 27%, and the definition of PD-L1 positivity was based on percentage of immune cells at <1% expression considered as IC0, IC1 at immune cell positivity of ⩾1% but ⩽5% expression, and IC 2/3 as immune cell expression of ⩾5% expression. The most common adverse event noted was fatigue, which occurred in 31% of patients. Grade 3/4 events occurred in 16% of patients, and immune-related adverse events (IRAEs) occurred in 5% of patients which included rash, transaminitis, and pneumonitis. Overall, there were no treatment-related deaths reported, with low discontinuation rates because of toxicity. This study was the first to correlate responses of checkpoint inhibitors according to the different The Cancer Genome Atlas (TCGA) subtypes, and to highlight the importance of mutational burden as a predictive measure for treatment response in advanced urothelial carcinoma.[17]

This trial also led to the confirmatory phase III registrational trial called IMvigor211 which enrolled a total of 931 patients with metastatic urothelial carcinoma who had previously received platinum-based chemotherapy and were randomized to receive either atezolizumab or investigator's choice chemotherapy (which included vinflunine, paclitaxel, or docetaxel). However, the study did not meet its primary endpoint of OS which showed that the atezolizumab compared with the standard comparator chemotherapy arms had median overall survival (mOS) times of 11.1 versus 10.6 months, with similar overall responses of 23% versus 22%, respectively, despite seemingly longer duration of response in the atezolizumab arm compared with the chemotherapy arm of 15.9 versus 8.3 months. An additional exploratory analysis of the intention-to-treat population found no difference in ORR (equal at 13.4%), although the duration of response was longer with atezolizumab (21.7 vs 7.4 months). Other features of atezolizumab included better tolerance and duration of response with 13.1% of patients remaining on trial with the drug at the data cutoff of median follow-up of 17.3 months, while only 1.9% remained on chemotherapy. The toxicity profile also vastly favored the atezolizumab arm with fewer higher-grade toxicity at 20% compared with 43% as seen with chemotherapy, leading eventually to lower rates of drug discontinuation at 7% compared with chemotherapy where

discontinuation occurred in 18% of patients.[18] While the initial FDA approval of atezolizumab in 2016 was based on the positive results from the phase II IMvigor210 trial, failure to meet the primary endpoint of OS in patients with tumors expressing PD-L1 in this cohort, along with data from the confirmatory phase III IMvigor211 led to the voluntary withdrawal by Roche of atezolizumab's accelerated approval in the United States on March 8, 2021.

### *Pembrolizumab*

Pembrolizumab is a PD-1 monoclonal antibody receptor inhibitor, which is considered to have level 1 evidence of all the immune checkpoint inhibitors as second-line therapy after failure of prior platinum[19] after seminal studies showing prolongation of OS. Pembrolizumab has also been shown to have less toxicity compared with standard second-line chemotherapy along with improved quality of life outcomes in the randomized phase III KEYNOTE-045 trial.[20] The KEYNOTE-045 (NCT02256436) trial was a phase III international randomized trial that included 542 patients with metastatic, locally advanced or unresectable urothelial cancer. Randomization occurred with 1 arm receiving pembrolizumab intravenously at 200 mg every 3 weeks versus investigator's choice chemotherapy at standard doses intravenously given every 3 weeks (paclitaxel 175 mg/m$^2$, docetaxel 75 mg/m$^2$, or vinflunine 320 mg/m$^2$) with the primary endpoint of OS and progression-free survival (PFS) as assessed by investigators independently.

The trial results showed achievement of primary endpoints with improvement in the mOS at 10.1 months with use of pembrolizumab compared with chemotherapy at 7.3 months, with a median follow-up of 28 months. Comparison of patients with PD-L1-expressing tumor and infiltrating immune cells showed that those with a combined positive score (CPS) of $\geqslant$10% had a higher mOS (8.0 months) with pembrolizumab compared with the chemotherapy group (5.2 months), with secondary endpoints of PFS showing no difference between the groups regardless of PD-L1 expression. In addition, pembrolizumab was shown to be better tolerated and associated with fewer total treatment-related adverse events (TRAEs). The overall incidence of grade 3 or higher toxicity per the common toxicity grading criteria was 17% with pembrolizumab use compared with 50% in the chemotherapy arm, raising no new safety concerns as shown across other tumor subtypes of patients receiving pembrolizumab.[21,22] The favorable results particularly with longer OS in this phase III trial has garnered US FDA approval for pembrolizumab as the option for second-line therapy for platinum-refractory urothelial carcinoma with level 1 evidence.

### *Avelumab*

Avelumab is an anti-PD-L1 antibody that was evaluated in the JAVELIN Solid Tumor phase I dose-expansion clinical trial for various cancer types and included patients with metastatic urothelial cancers previously treated with chemotherapy which showed beneficial effects.[23,24] Avelumab was given in a total of 161 patients who were evaluated at a dose of 10 mg/kg IV every 2 weeks until progression, development of intolerable toxicity or voluntary discontinuation from trial. Avelumab resulted in an ORR of 17%, including complete response (CR) in 6%, partial response (PR) in 11%, and stable disease (SD) noted in 23% of patients, with ORRs greater in patients with tumors with PD-L1 expression at 24%, compared with 14% in those who are negative PD-L1 expressing tumors.[25] The safety profile appeared to be tolerable with the infusion-related reactions occurring in 29% and fatigue in 16% of patients (all grade 1 or 2) although grade 3 or higher events did occur in about 8% of patients, the most common of which was fatigue seen in 2% of patients with 1 death due to pneumonitis, attributable to avelumab.

Avelumab also garnered initial accelerated approval for use as second-line therapy given acceptable antitumor activity and associated acceptable safety profile for patients with platinum-refractory metastatic urothelial carcinoma.

### *Nivolumab*

Nivolumab is a PD-1 inhibitor that was first studied in bladder cancer with the phase II CheckMate 275 trial, an open-label, single-arm study that enrolled patients with metastatic or unresectable locally advanced bladder cancer, previously progressed on platinum-based therapy. The trial enrolled 270 patients who received single agent nivolumab 3 mg/kg IV every 2 weeks. In this cohort of patients, ORR was found to be 19.6%, and responses were noted regardless of PD-L1 expression. The mOS for the whole population was 8.7 months, with patients having higher PD-L1 expression yielding a higher mOS of 11.3 months for PD-L1 expression of $\geqslant$1% compared with mOS of 6.0 months for PD-L1 expression $<$1%. The safety profile showed that 18% of patients experienced grade 3 to 4 TRAEs, the most common of which were fatigue and diarrhea. Three treatment-related deaths were recorded and included cases of pneumonitis, acute respiratory failure, and cardiovascular failure.[26,27] Nivolumab provided evidence of significant clinical benefit with satisfactory safety profile, regardless of tumor PD-L1 expression, leading to FDA approval for nivolumab monotherapy in February 2017.

Ipilimumab is an anti-cytotoxic T lymphocyte antigen-4 (CTLA-4), that has been used in combination with nivolumab to harness a potentiated cancer immune response in multiple cancer types, often followed by nivolumab maintenance therapy. The open-label phase II multi-cohort study of CheckMate 032 trial enrolled 274 patients with advanced or metastatic urothelial carcinoma, who were previously treated with platinum-based chemotherapy. The primary endpoint of this trial was investigator-assessed response rate and duration of response. The patients were randomized to either single-agent nivolumab 3 mg/kg or combination therapies of nivolumab

3 mg/kg plus ipilimumab 1 mg/kg or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg.[26] The combination regimens were then followed by maintenance therapy with nivolumab 3 mg/kg. While the combination of nivolumab 1 mg/kg with ipilimumab 3 mg/kg showed the greatest response, achieving an ORR of 38% compared with 26% for nivolumab monotherapy alone, an ORR of 27% was seen for the combination of nivolumab 3 mg/kg plus ipilimumab 1 mg/kg; higher TRAEs were also seen in the higher ipilimumab dose, with grade 3 or 4 TRAEs seen in 26.9% in the nivolumab alone arm, compared with 30.8% in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg arm compared with 39.1% in the nivolumab 1 mg/kg and ipilimumab 3 mg/kg arm. Responses were seen regardless of PD-L1 expression, and overall PFS and OS were similar across the different arms. There were 2 cases of grade 5 pneumonitis considered to be a TRAE in the nivolumab alone and the combined nivolumab 3 mg/kg and ipilimumab 1 mg/kg arms.[28]

### *Durvalumab*

Durvalumab, another PD-L1 inhibitor, had initially been granted accelerated approval for treatment of advanced urothelial carcinoma based on information from a phase 1/2 study. In this earlier phase study, durvalumab was given 10 mg/kg every 2 weeks in patients with various solid tumor types, followed by more specific updates for patients with locally advanced or metastatic urothelial carcinoma. Objective responses were seen in 17.8% of patients, of the 191 patients studied, of whom 7 patients achieved CR. Similar to prior immune checkpoint inhibitor trials, responses were notably greater in those who had higher rates of PD-L1 expression (28% vs 5% in low-or-negative PD-L1 expression). Other endpoints including PFS, and OS was favorably seen with median PFS of 1.5 and median OS of 18.2 months, with 55% of patients alive in 1 year. High-grade (grade 3 or 4) TRAEs were noted in 7% of patients, and there were 2 treatment-related deaths noted from autoimmune hepatitis and pneumonitis.[29,30] While these data led to the initial accelerated FDA approval for durvalumab in patients with locally advanced or metastatic bladder cancer previously treated with chemotherapy, it was voluntarily withdrawn by the drug developer as the confirmatory trial that would have led to the regular approval did not meet the primary endpoint in the phase III DANUBE trial, which will be discussed in a later section of this article.

## First-Line Metastatic Urothelial Cancer: Role of Immune Checkpoint Inhibitor Therapy

Systemic immunotherapy can be considered as a first-line therapy alternative to platinum-based chemotherapy in patients with advanced or metastatic urothelial carcinoma, regardless of PD-L1 expression status, particularly for those considered cisplatin-ineligible but with high expression of PD-L1 based on an approved companion diagnostic assay with a corresponding drug, as well as those who are considered platinum-ineligible (see list of trials in Table 2). Table 2 further provides data summary from landmark phase III trials that used immune checkpoint inhibitor therapy in the first-line setting, including their primary endpoints, available findings, and FDA approval information, wherever applicable. However, platinum ineligibility is poorly defined although an arbitrary definition includes factors such as ECOG (Eastern Cooperative Oncology Group) Performance Status (PS) > 3, a creatinine clearance (Cr Cl) of < 30 mL/min, peripheral neuropathy > Grade 3, New York Heart Association (NYHA) Heart Failure Class > 3, or a combination of ECOG PS 2 and Cr Cl < 30 mL/min.[31] Although efficacy often correlates with PD-L1 expression, this is not universally so across multiple tumor types or in various clinical settings and different trials, and patients who are considered to have low to negative expression also do not preclude responses and therefore should not be a basis to withhold use of immune checkpoint inhibitors for those who are non-PD-L1 expressors. There are multiple other issues and controversies with use of biomarkers, including use of assays that are not well standardized across institutions or even use of different immunotherapy agents as different companion diagnostic assays have been approved for each particular immune checkpoint inhibitor drug, without adequate data to support interchangeable use across different assays for different drugs.[32] In addition, it is known that PD-L1 expression is not homogeneous within a tumor, differences may exist between the primary tumor and its corresponding metastasis and can also change expression over time with changes in the tumor microenvironment,[33] making interpretation and decisions regarding therapy based on PD-L1 expression alone extremely difficult and challenging.

There have been 2 candidate immunotherapy drugs that have been summarily approved for the PD-L1 high marker expressing tumors or for the platinum-ineligible population of metastatic urothelial cancer patients, to be used in the front-line setting, namely, atezolizumab and pembrolizumab.[15] However, confirmatory trials for maintaining conditional approval also came in the form of the phase III IMvigor130 and KEYNOTE-361, respectively, showing mixed results. This has also led to the recent FDA Oncologic Drugs Advisory Committee (ODAC) vote to retain the accelerated approval for both atezolizumab and pembrolizumab for the front-line setting indications.

### *Atezolizumab*

Atezolizumab was granted initial conditional accelerated approval as monotherapy by the FDA as first-line therapy for patients who are not candidates for platinum-based chemotherapy following analysis of the phase II IMvigor210 and phase III IMvigor130 trials. IMvigor210 was a phase II, single-arm multi-center trial that had the primary endpoint of objective response rates in both intent-to-treat overall population and the PD-L1 population. The trial enrolled 119 patients

**Table 2.** Landmark trials using immune checkpoint inhibitors as first-line therapy.

| TRIAL | PHASE OF TRIAL | EXPERIMENTAL ARMS | PRIMARY ENDPOINTS | FINDINGS | COMMENTS |
|---|---|---|---|---|---|
| IMvigor130 | III | Gemcitabine/Platinum<br>Atezolizumab<br>Gemcitabine/Platinum + Atezolizumab | PFS, OS, and toxicity | Improvement in PFS<br>8.2 vs 6.3 mo<br>HR 0.82; $P = .007$<br>OS 16 vs 13.4 mo<br>HR 0.83; $P = .027$ | |
| Javelin Bladder 100 | III | Gemcitabine/Platinum → Avelumab<br>Gemcitabine/Platinum → BSC | OS | Improvement in OS<br>21.4 vs 14.3<br>HR 0.69; $P = .001$ | FDA approved for maintenance therapy 2020 |
| KEYNOTE-361 | III | Gemcitabine/Platinum<br>Pembrolizumab<br>Gemcitabine/Platinum + Pembrolizumab | PFS and OS | Did not meet dual primary endpoints of OS and PFS | |
| DANUBE | III | Gemcitabine/Platinum<br>Durvalumab<br>Gemcitabine/Platinum + Durvalumab | OS in ITT and PD-L1+ | Failed to improve OS | |
| CheckMate 901 | III | Gemcitabine/Platinum<br>Gemcitabine/Platinum + Nivolumab<br>Nivolumab + Ipilimumab | OS in ITT and PD-L1+; PFS | Ongoing | |
| EV-302 | III | Enfortumab + Pembrolizumab ±<br>Gemcitabine/Platinum<br>Gemcitabine/Platinum | PFS and OS | Ongoing | |

Abbreviations: BSC, best supportive care; FDA, US Food and Drug Administration; HR, hazard ratio; ITT, intention to treat; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival.

who received atezolizumab 1200 mg every 3 weeks. Objective responses were noted in 23% of patients, at a median follow-up of 17 months, and responses also included 9% of patients who achieved CR. The mOS for the entire cohort was 16 months.[34]

Given promising results in the phase II trial, IMvigor130 was initiated as the phase III study (NCT02807638) that was meant to be the confirmatory registrational trial comparing atezolizumab with platinum-based chemotherapy versus atezolizumab alone versus platinum-based chemotherapy alone with a dual primary endpoint of PFS and OS as assessed by investigator with a sequential formal analyses only if OS was achieved to be positive for the combined chemotherapy and atezolizumab group (group A) versus the chemotherapy group alone (group C). IMvigor130 compared and randomized 1213 patients in a 1:1:1 fashion atezolizumab 1200 mg given intravenously at every 3-week cycles as monotherapy compared with atezolizumab given with platinum-based chemotherapy every 3-week cycles in patients with untreated metastatic urothelial carcinoma. There were 3 randomized groups studied including group A, which included 451 patients who received atezolizumab with platinum-based chemotherapy; group B, which included 362 patients who were randomized to atezolizumab monotherapy alone; and group C consisted of 400 patients treated with placebo and platinum-based chemotherapy.[35,36] Results revealed that PFS was favorable at 8.2 months with the addition of atezolizumab to the chemotherapy compared with 6.3 months PFS in those treated with chemotherapy alone, although mOS was similar between the 2 groups (16.0 and 13.4 months, respectively). Atezolizumab monotherapy had the lowest incidence of TRAEs at 6%, while the chemotherapy arms had similar, but increased adverse-event rates, affecting 34% of patients in both groups A and C. In all, 11% of patients treated with combination atezolizumab and chemotherapy were withdrawn due to atezolizumab-related adverse events. While PFS was considered prolonged in favor of the atezolizumab in combination with platinum-based chemotherapy arm, the OS data were not yet considered mature.

Further subgroup exploratory analysis of clinical outcomes based on PD-L1 status were also additionally reported,[37] and found that patients with PD-L1 expressing immune cells on ⩾5% of the tumor area had improved OS with atezolizumab monotherapy versus gemcitabine plus placebo in cisplatin-ineligible patients. Overall response rate also appeared to be higher with atezolizumab in this group. While additional OS follow-up is ongoing, these findings provide evidence of clinical benefit with atezolizumab monotherapy for patients who are ineligible for cisplatin with high PD-L1 scoring. The findings overall from IMvigor130 lends support to continued benefit for the first-line treatment of metastatic urothelial cancer cisplatin-ineligible population, leading to the continued upholding of the decision by the FDA ODAC vote on April 29, 2021, for this continued label and indication.

### *Pembrolizumab*

One of the first trials that investigated the safety and efficacy of pembrolizumab for the metastatic cisplatin-ineligible

population of patients came in the form of the KEYNOTE-052 trial. The KEYNOTE-052 was a multi-center phase II trial that enrolled 370 patients with cisplatin-ineligible metastatic urothelial carcinoma and was given a dose of pembrolizumab 200 mg intravenously on an every 3-week cycle until unacceptable toxicity, progression, or for up to 2 years. At the landmark 2-year follow-up, ORR was achieved at 29% for the whole intent-to-treat population, which was the primary endpoint, and this included CR, which was achieved in 9% of patients while PR was seen in another 20% of patients. Similar to other trials, the ORR was notably higher in patients who are overexpressing PD-L1 > 10% at 38% of the 110 patients, although responses were also seen regardless of PD-L1 expression. Ten percent of patients had serious TRAE. The overall duration of response was 30 months, with a median OS of 11.3 months seen in the whole cohort of patients.[38,39]

A phase I/II study EV-103 (NCT03288545) compared enfortumab vedotin, a Nectin-4 antibody-drug conjugate,[40] plus pembrolizumab for 45 cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma.[41] Enfortumab vedotin was given 1.25 mg/kg on days 1 and 8 while pembrolizumab 200 mg IV was given day 1 in 3-week cycles. Drugs were tested in dose escalation and dose-expansion cohorts. Overall response rate was 73.3% regardless of PD-L1 expression with a median PFS of 12.3 months and 81.6% of patients alive at 12 months (median OS was not reached), at a median follow-up time of 11.5 months. Responses appeared to be rapid and durable, with 88% of patients noting a response at first assessment and median duration of response not met. The safety profiles were similar to individual drugs, and most common TRAEs included fatigue, alopecia, and peripheral sensory neuropathy. A single treatment-related death that was felt to be from multiorgan dysfunction syndrome was reported. A phase III study EV-302 (NCT04223856) is already ongoing to evaluate enfortumab vedotin in combination with pembrolizumab with or without chemotherapy compared with gemcitabine and platinum therapy in a similar patient population in the first-line setting.

Pembrolizumab was also studied as monotherapy and in combination with chemotherapy versus chemotherapy alone for untreated advanced urothelial cancer in the KEYNOTE-361 phase III trial (NCT02853305).[42] A total of 1010 patients were randomized in 1:1:1 fashion, pembrolizumab arms were treated with pembrolizumab 200 mg IV every 3 weeks, while chemotherapy arms received were based on investigator's choice of chemotherapy with gemcitabine and cisplatin or carboplatin in 21-day cycles. Initial data from this study did not meet statistical significance for OS and PFS with the addition of pembrolizumab to chemotherapy, although results did favor the combination arm. However, multiple subsequent exploratory analyses attempted to describe and understand the different patterns of response with pembrolizumab monotherapy compared with carboplatin-based chemotherapy cohorts or progression-free analyses for subsequent lines of therapy.[43] Regardless, the inability to meet the primary endpoint from these seminal trials did bring into question whether the first-line therapy label for cisplatin-ineligible disease or platinum-ineligible patients should be retained although the US FDA ODAC voted to uphold the label indication as of April 29, 2021.

### *Durvalumab*

The phase III DANUBE trial (NCT02516241) enrolled 1032 patients with untreated locally advanced or unresectable metastatic urothelial carcinoma. This trial served as the confirmatory registrational trial for the continued approval of durvalumab that was granted initial accelerated approval for second-line therapy use in metastatic urothelial cancers. Patients in the DANUBE trial was randomized to durvalumab monotherapy, durvalumab plus tremelimumab (another monoclonal antibody targeting CTLA-4), or gemcitabine plus platinum-based chemotherapy. At a median follow-up of 41 months, durvalumab did not prolong OS compared with standard chemotherapy in the PD-L1 expressing tumor population, and the combination of durvalumab and tremelimumab did not improve OS versus chemotherapy in the intention-to-treat population.[14] For this reason, durvalumab is not recommended as first-line therapy for patients with metastatic urothelial carcinoma.

## Maintenance Therapy

Historically, patients with metastatic urothelial cancers are treated with platinum-based chemotherapy for 4 to 6 cycles and the platinum therapy is highly dependent on cisplatin-eligibility criteria. While responses are reasonable, majority would ultimately fail, recur, or progress. The standard of care following platinum-based chemotherapy had been observation and best supportive care (BSC) given limitation to give optimal platinum-based chemotherapy. Therefore, the Javelin Bladder 100 trial (see Table 2) was a phase III international randomized trial that sought to compare avelumab maintenance with BSC in metastatic urothelial cancer patients who have received 4 to 6 cycles of platinum-based chemotherapy and have achieved either a CR, PR, or SD.[44] The phase III study enrolled 700 patients with locally advanced, unresectable or metastatic urothelial bladder cancer and were randomized to either avelumab 10 mg/kg intravenously as maintenance with BSC versus BSC alone.[45] The primary endpoint OS was met with avelumab at a median 21 months compared with 14 months in the BSC arm, at a median follow-up of 19 months. Approximately 51% of the patients were considered PD-L1 positive tumors, with greater responses noted with PD-L1 positive tumors (median not reached vs 17 months). Avelumab also improved other secondary endpoints including median PFS at 3.7 months for the avelumab arm compared with

2 months for the BSC arm with higher PFS in the PD-L1 population at 5.7 months in the avelumab arm compared with 2.1 months in the BSC group. Treatment with maintenance avelumab was overall well tolerated, grade 3 or higher toxicity rates were greater in the avelumab population compared with BSC (47% vs 25%), and the IRAE rate was 7%, with about 9% of patients requiring high doses of corticosteroids for IRAEs. Two deaths (sepsis and ischemic stroke) were reported in patients who died from toxicity attributed to avelumab. Based on promising results of these data, the FDA granted approval for use of avelumab for maintenance therapy for locally advanced or metastatic urothelial carcinoma that had not progressed following first-line platinum-based chemotherapy. Maintenance avelumab is administered at 800 mg every 2 weeks which is considered an equivalent pharmacokinetic dose,[46] until disease progression or unacceptable toxicity after 4 to 10 weeks of completing therapy.

Although there is no other established role for maintenance therapy with other immunotherapy medications, a smaller phase II trial led by the Hoosier Oncology Group using pembrolizumab in a switch maintenance therapy approach did show improvement in PFS,[47] 108 patients were randomly assigned to pembrolizumab (n = 55) or placebo (n = 53), and the primary endpoint of PFS was met which was significantly longer with maintenance pembrolizumab versus placebo at 5.4 months compared with 3.0 months in the placebo arm, with a hazard ratio of 0.65; log-rank $P = .04$.

These data have further solidified the role of maintenance or switch maintenance immunotherapy in metastatic urothelial cancer after initial response or SD to chemotherapy, although questions regarding interchangeability across different agents is unknown but currently driven by availability of level 1 evidence with the use of avelumab given phase III trial with Javelin Bladder 100.

## Muscle-Invasive Bladder Cancers: Role of Immune Checkpoint Inhibitors

Given the effectiveness of checkpoint inhibitor immunotherapy in treating advanced or metastatic urothelial cancer, use of checkpoint inhibitors in an earlier disease setting in the form of neoadjuvant or adjuvant therapy in muscle-invasive bladder cancer (MIBC) had strong rationale, initially as monotherapy for neoadjuvant therapy and also as adjuvant treatment although more contemporary trials are now exploring more combination treatments with other agents such as chemotherapy. Preliminary results from phase I/II studies using atezolizumab and pembrolizumab, along with the combination of durvalumab and tremelimumab have reported CRs in approximately one-third of patients.[48,49]

The use of neoadjuvant atezolizumab in MIBC was explored in the phase II ABACUS trial (NCT02662309) which treated 95 patients with MIBC with atezolizumab for 3 cycles prior to cystectomy. A pathologic CR (considered the primary endpoint) was observed in 91% of patients. In addition, this study sought to identify biomarkers which could allow for the testing of tumors to determine the likelihood of response to neoadjuvant atezolizumab. An analysis of baseline biomarkers found that the presence of activated T cells prior to treatment was able to be correlated with outcomes, while other established biomarkers, such as tumor mutational burden (TMB), did not predict outcomes.[48]

The beneficial role of pembrolizumab was explored in the phase II PURE-01 trial (NCT02736266) which enrolled 50 patients and treated them with pembrolizumab 200 mg intravenously every 3 weeks for 3 cycles prior to radical cystectomy.[49] This study also considered a pathologic CR as the primary endpoint, and was achieved in 42% of patients. Down-staging of tumor at the time of surgery to less than pT2 was an additional secondary endpoint and was achieved in 54% of patients. Similar to the earlier trials, patients whose tumors express higher PD-L1 CPS of $\geq$10% had higher incidences of CR (54.3%) compared with those with CPS $<$ 10% (13.3%), suggesting a bigger role for the use of checkpoint inhibitors in patients who overexpress PD-L1. Similarly, there was a significant nonlinear association between patients with high TMB and CR. Given these findings, pembrolizumab may be an effective neoadjuvant treatment for MIBC, especially when considered for patients with PD-L1 positive or high TMB tumors.

Therefore, the role of neoadjuvant immune checkpoint inhibitors has been found to be promising although the endpoints of pathologic CR would have to be determined as adequate surrogate for survival in the MIBC population. Hence, multiple other trials exploring neoadjuvant immunotherapy combined with chemotherapy are currently ongoing.

Adjuvant immunotherapy also has been explored with some controversial findings (see Table 3), which provides a data summary from landmark trials that used immune checkpoint inhibitor therapy in the adjuvant setting, including their arms, eligibility, primary endpoints, and available/preliminary findings. There are 3 randomized trials using nivolumab (CheckMate 274), atezolizumab (IMvigor010),[50] and pembrolizumab (AMBASSADOR), the former 2 being reported whereas the adjuvant pembrolizumab continues to accrue patients at this time. CheckMate 274, a phase III trial of adjuvant nivolumab versus placebo in patients who have undergone radical surgery for high-risk muscle-invasive urothelial carcinoma, with or without neoadjuvant chemotherapy, recently reported its findings that ultimately led to accelerated approval granted by the FDA for adjuvant nivolumab in patients with high-risk MIBC after surgery.[51] The study found that adjuvant treatment with nivolumab led to improved disease-free survival (mean of 20.8 months compared with 10.8 months with placebo) in all patients, with a more pronounced effect noted in the PD-L1 $\geq$ 1% population (median not reached compared with 10.8 months with placebo). The safety profile of nivolumab was consistent with previous studies, and health-related quality of life scores were not significantly changed with treatment.

**Table 3.** Select phase III trials using immune checkpoint inhibitors as adjuvant therapy for MIBC.

| TRIAL NAME | PHASE OF TRIAL | EXPERIMENTAL ARMS N; ELIGIBILITY | PRIMARY ENDPOINTS | FINDINGS | COMMENTS |
|---|---|---|---|---|---|
| IMvigor010 | III | Atezolizumab vs Observation (N = 809) ypT2–4a or ypN+ tumors following neoadjuvant chemotherapy or pT3–4a or pN+ tumors if no neoadjuvant chemotherapy was received. | DFS | Atezolizumab Median DFS = 19.4 mo (95% CI, 15.9-24.8) vs Observation = 16.6 mo (11.2-24.8) (stratified HR 0.89 [95% CI, 0.74-1.08]; $P = .24$). | Did not meet primary endpoint |
| CheckMate 274 | III | Nivolumab vs Placebo (N = 353 pts to Nivo; PD-L1 ⩾ 1%, n = 140 and 356 pts to Placebo (PD-L1 ⩾ 1%, n = 142); s/p radical surgery within 120 days ± NAC cisplatin or were ineligible/declined cisplatin-based chemo; evidence of UC at high risk of recurrence per pathologic staging, disease-free by imaging, ECOG PS ⩽ 1. | DFS in all randomized pts (ITT population) and in pts with tumor PD-L1 expression ⩾ 1%. | Median DFS ITT: Nivo = 20.8 (16.5-27.6) vs Placebo = 10.8 mo (8.3-13.9); HR = 0.70 (0.55-0.90); $P < 0.001$; PD-L1 ⩾ 1%: Nivo = 74.5% vs Placebo = 55.7%; HR = 0.55; 98.72% CI, 0.35 to 0.85; $P < 0.001$ | Met primary endpoint; FDA approval 2021 |
| AMBASSADOR (A031501) | III | Pembrolizumab vs Observation (N = 739) +NAC = >/= pT2 and/or N+ or Cis-ineligible or cis-refusal –NAC = >/= pT3 or pN+ | Co-primary endpoint: DFS and OS | Enrollment ongoing | Not yet reported |

Abbreviations: CI, confidence interval; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; ITT, intention-to-treat; MIBC, muscle-invasive bladder cancer; N+, node-positive; NAC, neoadjuvant chemotherapy; OS, overall survival; PD-L1, programmed death-ligand 1; PS, Performance Status; pts, patients; UC, urothelial cancer; NR, not reached.

However, results from the phase III IMvigor010 trial (NCT02450331)[50,52] of adjuvant atezolizumab did not meet the primary endpoint of disease-free survival compared with observation, and no pre-specified subgroups, including higher PD-L1 status, showed treatment benefit with atezolizumab. Additional phase II trials evaluating immunotherapy are also in progress, including nivolumab versus placebo (NCT02632409) and pembrolizumab versus placebo (NCT03244384). There are also ongoing studies using chemotherapy with gemcitabine and cisplatin with or without pembrolizumab for cisplatin-eligible patients (KEYNOTE-866; NCT03924856) or perioperative pembrolizumab followed by cystectomy or perioperative pembrolizumab with enfortumab vedotin with cystectomy versus cystectomy alone in the cisplatin-ineligible population (MK-3475-905/KEYNOTE-905/EV-303; NCT03924895). It remains to be seen whether adjuvant nivolumab would garner FDA approval in the MIBC setting, which has not yet achieved approval as of this writing.

## Non-Muscle-Invasive Bladder Cancers: Role of Checkpoint Inhibitors

Pembrolizumab monotherapy was approved by the US FDA in January 2020 for the treatment of BCG-refractory, high-risk non-muscle-invasive bladder cancers (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors who either are ineligible for or have declined cystectomy based on the promising results of the KEYNOTE-057. The KEYNOTE-057 (NCT02625961) was a phase II single-arm trial[53] that studied 148 patients, including 96 patients who had BCG-refractory CIS. Pembrolizumab was given at 200 mg IV every 3 weeks for up to 2 years, in the absence of disease progression, recurrence, or treatment-related toxicity. Among those 96 patients with BCG-refractory disease, 41% had a 3-month CR with a median duration of response of 16.2 months, with 19% achieving durable responses at 12 months. Pembrolizumab yielded no new safety concerns with grade 3 or higher toxicity rate noted at 29% which was mainly diarrhea, fatigue, and hematuria. There is an ongoing phase III trial, KEYNOTE-676 (NCT03711032),[54] which explores pembrolizumab in addition to BCG-therapy, being evaluated for safety and efficacy in patients with high-risk NMIBC that is persistent or recurrent after BCG induction therapy. In addition, there are multiple trials that includes the use of not just pembrolizumab but other agents that includes durvalumab (NCT03528694), nivolumab (CheckMate 7G8; NCT04149574), atezolizumab (BladderGATE; NCT04134000), the recombinant IL-15 complex ALT-803 (NCT02138734), with routes including intravenous for the checkpoint inhibitors but also intravesical route with additional BCG (see Table 4; selected phase III trials that includes checkpoint inhibitors with or in comparison with BCG).

## Ongoing Studies, Controversies, and Future Directions

The use of immune checkpoint inhibitors has changed the landscape of treatment for various stages of bladder cancer,

**Table 4.** Select phase III clinical trials for high-risk NMIBC.

| CLINICALTRIALS.GOV | PHASE OF TRIAL | NAME OF TRIAL | EXPERIMENTAL ARMS | PRIMARY ENDPOINTS | N |
|---|---|---|---|---|---|
| NCT03528694 | III | Assessment of Efficacy and Safety of Durvalumab Plus BCG Compared to the Standard Therapy With BCG in Non-muscle Invasive Bladder Cancer (POTOMAC) | Durvalumab + BCG (induction and maintenance) vs induction vs BCG | DFS | N = 1019 pts |
| NCT04149574 | III | A Study Comparing the Efficacy and Safety of Nivolumab in Combination With Bacillus Calmette-Guerin (BCG) Versus BCG Alone in Participants With High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) (CheckMate 7G8) | Nivolumab + BCG vs Placebo + BCG | Event-free survival | N = 700 pts |
| NCT03711032 | III | Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Bacillus Calmette-Guerin (BCG) in High-Risk Non-Muscle Invasive Bladder Cancer (HR NMIBC) (MK-3475-676/KEYNOTE-676) | Pembrolizumab + BCG post-induction, reduced/full maintenance vs BCG alone | Complete response rates and Event-free survival | N = 1525 pts |
| NCT03799835 | III | Atezolizumab Plus One-year BCG Bladder Instillation in BCG-Naive High-Risk Non-muscle Invasive Bladder Cancer Patients (ALBAN) | Atezolizumab + BCG vs Placebo + BCG | Recurrence-free survival | N = 516 pts |

Abbreviations: BCG, Bacillus Calmette-Guerin; DFS, disease-free survival; HR, hazard ratio; NMIBC, non-muscle-invasive bladder cancer; pts, patients.

encompassing a broad spectrum of disease states and various clinical settings. There are many ongoing clinical trials that has already allowed for additional treatment options in both first and subsequent line settings. Ongoing trials that compare a variety of immunotherapeutic agents with more traditional modalities of treatment are plentiful and will continue to offer insight into the broad indications of these treatments. While treatment in general, with the use of immune checkpoint inhibitors yields favorable responses, responses are still seen in only a minority of patients and many still have progressive disease as their best response.

Therefore, a multitude of complex issues with regard to the right population of patients who are deemed to benefit from immunotherapy approaches are still unknown, especially with regard to adequate biomarkers. While the initial accelerated approval for the use the checkpoint inhibitors were based on early phase I/II trials that have shown promising results, confirmatory trials have not always proven continued response. Two relevant drugs that have seen recent voluntary withdrawals are durvalumab and atezolizumab, based on the negative confirmatory trials for DANUBE and IMvigor211, respectively. The inherent question is whether there are true different biologic effects rendered from each different drug versus a measure of different clinical trial design, geographic differences, or statistical results that drove the differences in outcomes. Questions abound as to the impact of using immunotherapy drugs in an earlier state of disease, for instance, in the neoadjuvant or adjuvant setting. It is also unclear why the results of certain drugs would be different such as the positive findings seen with the use of adjuvant nivolumab in MIBC as compared with the negative results with adjuvant atezolizumab. Perhaps the differences in results can be explained in part by the differences in trial design. For instance, IMvigor010 which is considered the negative trial, had observation as the comparator arm compared with a placebo-controlled arm with the CheckMate 274 trial, leading to 10% higher rate of drop-out in the observation arm for the IMvigor010 trial. Changes in the landscape of treatment will also be brought on by earlier potential use of immunotherapy drugs in an earlier disease state. Patients who are already receiving immune checkpoint inhibitors as maintenance therapy would unlikely switch over to other second-line immune checkpoint inhibitor drugs on failure, unless a prolonged time has transpired from the time of failure, and would likely transition to use of enfortumab vedotin, sacituzumab govitecan or rarely, erdafitinib for those who have fibroblast growth factor receptor (FGFR) alterations.

Finding the most appropriate biomarker remains elusive as well. While the initial first-line indication for metastatic urothelial cancers over-expressing PD-L1 was the basis of both pembrolizumab and atezolizumab approval, results of confirmatory trials KEYNOTE-361 and IMvigor130, respectively, were mixed. A recent US FDA ODAC meeting upheld the decision to retain the current first-line label for PD-L1 high expressing cisplatin-ineligible patients or platinum-ineligible patients; with regular FDA approval granted to pembrolizumab in those patients who are platinum-ineligible. The assay used for either drug is different with the FDA-approved test for use of atezolizumab using the Ventana PD-L1 (SP142) Assay (Ventana Medical Systems, Inc.) for PD-L1 expression in $\geqslant$5% IC in

urothelial carcinoma tissue and for pembrolizumab, the use of PD-L1 IHC (22C3) pharmDx assay to detect tumors that express PD-L1 (CPS ⩾ 10), therefore subjecting wide variability in the use or interpretation of PD-L1 positivity.

## Conclusions

Advances in the management of advanced bladder cancer in recent years have led to improved overall outcomes and survival which has revolutionized the treatment of bladder cancer and can certainly be attributed in large part to the increasing use of immunotherapy. While first-line therapy remains centered on cisplatin or platinum-based regimens for metastatic urothelial cancers, immunotherapy continues to establish a role, especially in those who are truly platinum-ineligible. It is also well understood that maintenance therapy with avelumab following platinum-based therapy in those who have achieved any response or even SD after induction chemotherapy improves survival and is now considered a new standard of care. Further expected regulatory approval of immune checkpoint inhibitors in different disease states including the NMIBC space, as well as in the adjuvant setting, will further shape the landscape of treatment as more patients would be exposed earlier to the use of these agents. Novel clinical trials continue to explore the use of immunotherapy, monotherapy, and in combination with other agents that will continue to shape the treatment landscape of bladder cancer.

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JBAC provided conceptual design, LPR and JBAC drafted, reviewed, and edited final manuscript.

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