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Role of immunotherapy in bladder cancer

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ABSTRACT

The role of immunotherapy in bladder urothelial cancers is rapidly expanding. Since the initial second-line therapy approval for patients who fail prior platinum-based chemotherapy, the use of immunotherapy with checkpoint inhibitors has been rapidly evolving. There are approved indications for first-line metastatic disease in the platinum-ineligible patients or the cisplatin-ineligible PD-L1 positive patients, and there is a label for high-risk non-muscle-invasive bladder cancer who are BCG-refractory. In addition, a trial on maintenance immunotherapy with avelumab showed positive findings with improvement in overall survival that has also changed standard of care for these patients. There are ongoing clinical trials evaluating its use in the neoadjuvant and adjuvant perioperative muscle-invasive bladder cancer setting. The pivotal trials that led to these FDA approvals and promising and ongoing trials are discussed herein.

1. Introduction

Bladder cancer is the most common malignancy of the urinary tract, and will occur in about 81,400 patients in the United States in 2020, the majority of whom would be men (about 62,100) [1,2]. The vast majority of histology would be urothelial (formerly transitional cell) in origin, [3] accounting for approximately 90% of all bladder cancers in the United States and Europe [4]. In other parts of the world, non-urothelial forms of bladder cancer have an increased incidence, primarily due to endemic schistosomiasis. In recent years, the five-year survival rate in the United States has increased to approximately 80 percent, since majority of urothelial cancers also remain to be superficial. However, treatment for locally advanced or metastatic urothelial cancer remains challenging with cisplatin-based regimens given the generally elderly population of patients [5], and the outcomes remain guarded with a median survival of only around 14–15 months despite cisplatin-based chemotherapy combinations [6,7]. Therefore, treatment for metastatic urothelial cancers has been an important area of increased unmet need. Recent drug approvals of checkpoint inhibitors have revolutionized the treatment of patients with metastatic urothelial cancers, with improvement in survival, progression-free survival, as well as durability of responses seen with these agents. This review will address the different stages of bladder cancer and application of checkpoint inhibitors in the varying phases of the disease.

2. Bladder cancer staging and treatment

Bladder urothelial carcinoma has been classified historically as low or high grade urothelial cancers based upon the degree of nuclear anaplasia and architectural abnormalities [8]. Pathologic tumor staging is primarily based upon the extent of invasion into the deeper layers of the bladder and divided accordingly to superficial or muscle-invasive bladder cancers (MIBC). Patients who are defined to have non-muscle invasive bladder cancer (nMIBC) would have risks for recurrence and disseminated disease after initial treatment that dictates need for further therapy. The 2016 European Association of Urologists (EAU) guidelines defines different risks of progression based on the tumor grade, invasion into lamina propria, tumor size, and whether the tumor is recurrent or multifocal [9]. Conservative management is favored to potentially allow for the preservation of a functional bladder based upon transurethral resection of bladder tumor (TURBT), potentially combined with adjuvant intravesical therapy. Patients classified to have low-risk disease are typically managed by TURBT alone, plus single perioperative dose of intravesical chemotherapy with mitomycin [9,10], Intermediate- or

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high-risk nMIBC are generally treated with further intravesical therapy to decrease the risk of recurrence or progression, typically with Bacillus Calmette-Guerin (BCG) therapy, though with alternatives offered due to existing BCG shortages [10]. An estimated 40 to 80 percent of nMIBC patients will recur within 6 to 12 months when managed with TURBT alone, and approximately 10 to 25 percent will progress to muscle invasive or metastatic disease [11]. For those who are deemed high-grade or who meet an indication for primary cystectomy (including lymphovascular invasion, variant histologies, incomplete resections), the reported cancer-specific survival with cystectomy ranges from 85 to 90 percent [12,13]. Following initial TURBT, with or without intravesical therapy, surveillance is required for all patients for both recurrence and secondary malignancy for the genitourinary tract with cystoscopy and urine cytology [14].

Radical cystectomy is the recommended and preferred treatment for MIBC [15],though multimodality therapy is also considered a viable alternative option [16]. Neoadjuvant cisplatin-based chemotherapy has been shown to lower the risk of recurrence and improve overall survival compared to surgery alone [17,18]. Compared to local therapy alone, neoadjuvant cisplatin-based combination chemotherapy resulted in an improvement in five-year overall survival (OS) of 50 versus 45 percent, hazard ratio [HR] 0.87, 95% CI 0.78–0.98) [17,19]. While there is no established ideal regimen, cisplatin-based therapy is generally composed of two regimens: MVAC (methotrexate, vinblastine, doxorubicin, and cisplatin) typically given in a dose-dense schedule for better tolerance [20], and gemcitabine plus cisplatin (GC). A randomized phase III trial directly comparing dose-dense MVAC and GC has not yet resulted [21]. Cisplatin ineligibility is primarily driven by renal insufficiency limiting the administration for standard doses of cisplatin [22], in these cases carboplatin has been considered, however data has suggested overall inferiority as compared to cisplatin-based regimens [23,24]. Up to this point, there have not been adequate studies to compare adjuvant to neoadjuvant chemotherapy. For those who are not candidates for radical cystectomy, or those who desire to preserve their native bladder, a combined-modality approach including maximal TURBT, radiation therapy and concurrent chemotherapy has classically been considered an alternative option.

3. History of immunotherapy use in bladder cancer

Intravesical therapy has long been standard for adjuvant treatment for high-risk nMIBC following TURBT, to prevent recurrence of the cancer [25]. Intravesical therapy may also be given to treat residual disease following TURBT, though mostly in isolated cases of diffuse carcinoma in situ. The most common form of intravesical therapy is the use of Bacillus Calmette–Guérin (BCG), a live attenuated form of Mycobacterium bovis. The intravesical administration of BCG is thought to trigger local immune response, through a variety of mechanisms, including: increased expression of interferon gamma, elevated urinary cytokine levels and direct suppression of tumor growth [26,27].

Early studies evaluating the mutational signatures of varying types of cancers revealed high overall mutation rates for bladder cancer, 3rd only to melanoma and lung cancers [28]. This signifies potential value of targeting the immune system as a way of resulting in favorable effects against bladder carcinoma. Following the development and relative effectiveness of checkpoint inhibitor therapy, primarily targeting programmed cell death-1 protein (PD-1) or its ligand (PD-L1), for various forms of cancer, especially those with high mutational burdens, it was only a matter of time before these agents were tested within the realm of bladder cancer.

4. Role of checkpoint inhibitors (PD-1/PD-L1 inhibitors) in metastatic bladder cancer second-line therapy

Five immunotherapy agents targeting the PD-1 or PD-L1 pathway have been approved by the US Food and Drug Administration (FDA) for patients who have progressed during or after platinum-based therapy and have not received prior immunotherapy: atezolizumab, pembrolizumab, avelumab, nivolumab, and durvalumab (see summary in Table 1), and will be discussed herein.

TABLE. 1
Second-line therapy Immune Checkpoint Inhibitors approved by FDA for metastatic urothelial cancers.

Trial	Mechanism of Action	Experimental Arms	Outcome(s)	Phase of Trial
IMvigor210	PD-L1 Inhibitor	Atezolizumab 1200 mg IV every 3 weeks (n = 310)	ORR: 15.0% (11–20%) mPFS 2.1 mos (2.1–2.1 mos)	II
Keynote 045	PD-L1 Inhibitor	Pembrolizumab 200 mg IV every 3 weeks (n = 266)	ORR: 21.1% (16.4–26.5%) mPFS 2.1 mos (2.0–2.2 mos)	III
JAVELIN Solid Tumor	PD-L1 Inhibitor	Avelumab 10 mg/kg IV every 2 weeks (n = 44)	ORR: 18.2% (8.2–32.7%) mPFS 11.6 wks (6.1–17.4 wks)	Ib
Checkmate 275	PD-1 Inhibitor	Nivolumab 240 mg IV every 2 weeks (n = 270)	ORR: 19.6% (15.1–24.9%) mPFS 2 mos (1.87–2.63 mos)	II
Study 1108	PD-1 Inhibitor	Durvalumab 10 mg/kg IV every 2 weeks (n = 182)	mPFS 2.2 mos (1.4–2.7 mos)	I/II

4.1. *Atezolizumab*

The effect of atezolizumab, a monoclonal antibody of the IgG1 isotype that inhibits its interactions with the PD-1 and B7.1 receptors, in patients with locally advanced or metastatic urothelial bladder cancer was initially approved based on results from the phase II, single-arm IMvigor210 clinical trial [29]. The trial included two cohorts, the first cohort (n = 119 patients) was reported as part of a different study (NCT02951767) consisted of treatment-naïve, cisplatin-ineligible patients [30]. The second, larger cohort 2 (n = 310) consisted of patients who progressed during and/or following a prior platinum-based chemotherapy regimen. Atezolizumab was the first PD-L1 inhibitor found active in bladder cancer [31].

In the study, atezolizumab was given at a dose of 1200 mg IV every 3 weeks, and continued until disease progression, loss of clinical benefit or unmanageable toxicity. The co-primary endpoints for this cohort was objective response rate (ORR) assessed by independent review and investigator-assessed ORR according to immune-modified RECIST, analyzed by intention to treat. PD-L1 expression on tumor-infiltrating immune cells (ICs) was prospectively determined by immunohistochemistry, and analyzed in three different categories based on percentage of PD-L1-positive immune cells: IC0 (<1 percent expression), IC1 (≥1 percent, but ≤5 percent expression), and IC2/3 (≥5 percent expression). When compared to a historical control overall response rate of 10 percent, treatment with atezolizumab resulted in significantly improved ORR of 15% for all patients, ([95% CI 11–20], p = 0.0058), with the most robust response in the IC2/3 group, which had a 27 percent ORR ([95% CI 19–37], p<0.0001). The most common adverse event associated with the treatment was fatigue, occurring in 31 percent of patients including a grade 3/4 reaction in 2 percent. The overall occurrence of grade 3/4 adverse events was 16 percent, and immune-related events including pneumonitis, elevated liver enzymes and rash occurred in 5 percent of patients. There were no treatment-related deaths reported with the study, and the rate of discontinuation due to adverse events was low. [32]

A larger, phase III trial IMvigor211 provided additional data to support atezolizumab's role in previously treated urothelial cancers

[33]. 931 patients with metastatic urothelial carcinoma who have previously failed platinum-based chemotherapy were enrolled and were randomly assigned to either atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel). While there was no significant improvement for overall survival (OS) or ORR, which the former served as the primary endpoint, the median duration of response was longer with atezolizumab compared with chemotherapy (15.9 versus 8.3 months). An exploratory analysis of the intention-to-treat population showed no difference in ORR (equal at 13.4 percent), but the duration of response was much longer with atezolizumab (21.7 versus 7.4 months) and at the data cutoff of median follow-up of 17.3 months, 13.1 percent of patients assigned to atezolizumab remained on treatment, compared to 1.9 percent assigned to chemotherapy. The study also showed higher response rates with atezolizumab in patients with increased PD-L1 expression, compared to those with lower levels of PD-L1 expression, though this was also noted for chemotherapy response rates. Safety analysis also favored atezolizumab with lower high-grade toxicities (20 versus 43 percent) and lower incidence of treatment discontinuation (7 versus 18 percent).

Given this data, and overall tolerability of the drug, atezolizumab was approved for patients with locally advanced or metastatic urothelial carcinoma who progressed on or after platinum-based chemotherapy. This study was also the first to show an association of The Cancer Genome Atlas (TCGA) subtype with response to immune checkpoint inhibition, along with the importance of mutation load as a predictive measure for response in advanced urothelial carcinoma [32].

4.2. Pembrolizumab

Pembrolizumab, the monoclonal antibody that targets the PD-1 receptor initially approved for advanced melanoma, was found to prolong OS with less toxicity and improved quality of life compared to additional lines of chemotherapy. This was studied in the randomized phase III KEYNOTE-045 trial [34,35]. 542 participants who had metastatic, locally advanced or unresectable urothelial cancer that recurred or progressed on a platinum-based regimen were randomized to receive pembrolizumab 200 mg IV every three weeks or chemotherapy (paclitaxel, docetaxel, or vinflunine). The primary outcome for the trial included overall survival (OS) and progression-free survival (PFS), which were both superior in the pembrolizumab arm. Median overall survival was 10.1 months with pembrolizumab, compared to 7.3 months in the chemotherapy arm. Hazard ratio for death was 0.70 (95% CI 0.57–0.85; $p = 0.002$). The percentage of PD-L1-expressing tumor and infiltrating immune cells was measured compared to overall total number of tumor cells, and those whose combined score was $\geq$10 percent had a higher median overall survival (8.0 months, 95% CI, 5.0–12.3) with pembrolizumab compared to the chemotherapy group (5.2 months, 95% CI, 4.0–7.4). There was no significant difference between the two groups in respect to progression-free survival, regardless of PD-L1 combined positive scoring. Pembrolizumab was also associated with fewer total treatment-related adverse events, and less frequent grade 3 or higher adverse effects (17 versus 50 percent).

Given this longer overall survival and lower incidence of treatment-related adverse events, pembrolizumab emerged as an option for second-line therapy for platinum-refractory urothelial carcinoma. Additional follow-up analyses at two years were consistent with initial data, reinforcing survival benefit.

4.3. Avelumab

Avelumab, another anti-PD-L1 monoclonal antibody, was studied in the JAVELIN Solid Tumor (NCT01772004) phase I dose-expansion clinical trial in which consecutive parallel group expansions for various cancer-subtype cohorts occurred [36]. Both secondary expansion and efficacy expansion cohorts were studied for patients with metastatic urothelial carcinoma that progressed after at least one previous attempt of treatment with platinum-based chemotherapy [37]. Patients were given avelumab 10 mg/kg IV every 2 weeks until progression, unacceptable toxicity or withdrawal from trial. The combined analysis of the two studies was performed on 161 patients. The ORR was 17 percent, including 6 percent with complete response, 11 percent with a partial response and 23 percent with stable disease. ORR rates were much more robust in patients with PD-L1 positivity, noted to be 24 percent versus 14 percent for those found to be PD-L1 negative [38]. The most frequent treatment-related adverse events of any grade were infusion-related reactions in 29 percent (all grade 1–2) and fatigue in 16 percent. Grade 3 or worse events occurred in 8 percent the most common being fatigue (2 percent). There was one treatment related death from pneumonitis that occurred with avelumab treatment.

Overall avelumab showed strong antitumor activity with an acceptable safety profile in patients with platinum-refractory metastatic urothelial carcinoma, with greater activity noted in PD-L1 positive tumors. These results led to accelerated FDA approval for this indication. Phase III study data to confirm these findings remains to be needed.

4.4. Nivolumab

Nivolumab, another monoclonal antibody directed against PD-1, and its effect on the reduction in tumor size in patients with metastatic or unresectable locally advanced bladder cancer was studied in a phase II, single-arm, open-label CheckMate 275 study (NCT02387996) [39]. The study found that nivolumab as a single agent had significant activity in patients who progressed after previous platinum-based therapy. The 270 enrolled patients received nivolumab 3 mg/kg IV every 2 weeks until measured disease progression, clinical deterioration, or unacceptable toxicity. Tumor PD-L1 expression was also quantified as $\geq$5 percent or $\geq$1 percent. The ORR was 19.6 percent, and responses were noted at all levels of PD-L1 expression. At seven months follow-up, the median OS for the entire cohort was 8.7 months, with OS longer for those with higher PD-L1 expression (11.3 months for $\geq$1 percent and 6.0 months for $<$1 percent), with greater response in patients with higher PD-L1 expression (28 percent for those greater than 5 percent, and 23.8 percent for those between 5 and 1 percent). A total of 18 percent of patients experienced grade 3–4 treatment related adverse events; most commonly grade 3 fatigue and diarrhea. There were three treatment related deaths including pneumonitis, acute respiratory failure and cardiovascular failure. Nivolumab proved to provide a significant clinical benefit with satisfactory safety profile, regardless of tumor PD-L1 expression, and was approved in February of 2017.

Combination immunotherapy with nivolumab and ipilimumab, a monoclonal antibody targeting cytotoxic T lymphocyte antigen-4 (CTLA-4), for locally advanced or metastatic urothelial carcinoma is an active area of investigation. This regimen has proven to be effective in other forms of malignancy with potentiated cancer immune response with the dual-agent approach, followed by nivolumab maintenance therapy. CheckMate 032 [40], an open-label phase II study of 274 patients with advanced or metastatic urothelial carcinoma previously treated with platinum-based chemotherapy investigated this regimen. Patients were randomly assigned to receive single-agent nivolumab 3 mg/kg or nivolumab 3 mg/kg plus ipilimumab 1 mg/kg or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, with the combinations followed by nivolumab 3 mg/kg maintenance therapy. After a follow-up of eight months, the combination of nivolumab 1 mg/kg plus ipilimumab 3 mg/kg demonstrated the strongest response, with a response rate of 38 percent compared to 26 percent for nivolumab alone and 27 percent with the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg combination, responses occurring regardless of PD-L1 expression. There was no statistically significant improvement in PFS or OS between groups, though data favored the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg arm. Grade 3 or higher adverse events occurred more frequently in the combination arms [41].

TABLE. 2
First-line Phase III Metastatic Urothelial Cancer Trials.

Trial	Regimen	Outcome(s)
IMvigor 130	Gemcitabine/Platinum	Improvement in PFS 8.2 vs 6.3 months
	Atezolizumab	HR 0.82; $p = 0.007$
	Gemcitabine/Platinum + Atezolizumab	OS 16 vs 13.4 months
		HR 0.83; $p = 0.027$
Javelin Bladder 100	Gemcitabine/Platinum → Avelumab	Improvement in OS 21.4 vs 14.3
	Gemcitabine/Platinum → BSC	HR 0.69; $p = 0.001$
Keynote 361	Gemcitabine/Platinum	Did not meet dual primary endpoints of OS and PFS
	Pembrolizumab	
	Gemcitabine/Platinum + Pembrolizumab	
DANUBE	Gemcitabine/Platinum	Failed to improve OS
	Durvalumab	
	Gemcitabine/Platinum + Durvalumab	
Checkmate 901	Gemcitabine/Platinum	Ongoing
	Gemcitabine/Platinum + Nivolumab	
	Nivolumab + Ipilimumab	
EV302	Enfortumab + Pembrolizumab	Ongoing
	Gemcitabine/Platinum	
	Enfortumab + Pembrolizumab + Gemcitabine/platinum (discontinued)	

4.5. Durvalumab

Durvalumab is another PD-L1 inhibitor that has been approved for treatment of advanced urothelial carcinoma that progressed during or after previous platinum-based chemotherapy. A total of 61 patients, 40 of whom were considered to have PD-L1 positive tumors (≥25 percent of tumor cells or tumor-infiltrating immune cells expressing PD-L1), were treated with durvalumab 10 mg/kg every 2 weeks. Of these patients, 93.4 percent had received one or more lines of previously therapy for advanced disease. The ORR was 31 percent in the overall population, and 46.4 percent of the PD-L1 positive vs 0 percent in the PD-L1 negative subgroup. Treatment related adverse events were mostly mild, with no grade 4 or 5 events occurring. Fatigue and diarrhea were most common (13.1 percent and 9.8 percent, respectively), and grade 3 events occurred in only three (4.9 percent) patients [42].

In a phase 1/2 study (NCT01693562) of durvalumab, patients with various solid tumor types were studied for exposure-safety analysis [43]. This study included 191 patients who were also given durvalumab 10 mg/kg IV every 2 weeks. Objective responses were noted in 17.8 percent of patients, including complete response in 7 patients. Response was higher in those who had greater rates of PD-L1 expression (28 percent versus 5 percent in low-or-negative PD-L1 expression). Median PFS and OS were 1.5 and 18.2 months, respectively, with the 1-year OS rate at 55 percent. High grade (grades 3 or 4) treatment-related adverse events were noted in 7 percent of patients, and there were two treatment related deaths noted from autoimmune hepatitis and pneumonitis.

5. First-line therapy

Systemic immunotherapy can be appropriate first line therapy for patients with advanced urothelial carcinoma who are ineligible for any platinum-based chemotherapy regimen, regardless of PD-L1 expression status. Immunotherapy can also be considered as a first line approach for patients who are simply not cisplatin-eligible but in those who have PD-L1 high expression [44].

It should be noted that although clinical trials for respective immunotherapy agents, against a variety of tumor types, have shown that efficacy often correlates with PD-L1 expression, responses have also been noted in patients whose tumors have low-to-negative PD-L1 expression. While the presence of PD-L1 can be predictive of an expected response, the lack of expression should also not preclude the use of these agents. Testing for PD-L1 expression is not yet standardized, and various institutions utilize different methods, and it is unknown whether different tests can be readily interchanged with different treatments or across indications [45]. Additionally, PD-L1 expression is heterogeneous within tumors, between the primary tumor and metastasis, and may appear and disappear over time. While PD-L1 expression testing becomes more widely available, it is opening conversations regarding treatment options between providers and patients. This field of first-line therapy is rapidly evolving with different agents mainly in combination with chemotherapy or other novel agents such as antibody drug conjugates being studied in combination with immune checkpoint inhibitors (see Table 2).

5.1. Atezolizumab

Atezolizumab was granted conditional approval as monotherapy by the FDA as initial therapy for patients who are not candidates for platinum-based chemotherapy as studied in the phase II IMvigor210 and phase III IMvigor130 trials. In the former, 119 patients with advanced or metastatic urothelial carcinoma who were not eligible for cisplatin-based treatment were treated with atezolizumab 1200 mg every three weeks. At the median follow-up of 17 months, objective responses were noted in 23 percent of patients, including 9 percent with a complete response. The median OS for the entire cohort was 16 months [30].

In the IMvigor130 phase III trial (NCT02807638) [46], atezolizumab was given 1200 mg IV every three weeks as monotherapy or with chemotherapy, which included the regimen of gemcitabine plus either carboplatin or cisplatin in 21-day cycles. A total of 1213 treatment-naive patients were randomly assigned to three different groups. Group A consisted of 451 (37 percent) patients who received atezolizumab with chemotherapy, group B included 362 (30 percent) patients who received atezolizumab monotherapy, and group C consisted of 400 (33 percent) patients treated with placebo and chemotherapy. The addition of atezolizumab to the chemotherapy groups improved the median PFS to 8.2 months in group A compared to 6.3 months in group C. Median overall survival was similar between the two groups, 16.0 months in group A and 13.4 months in group C. The chemotherapy arms had similar and increased adverse-event rates, affecting 34 percent of patients in both groups A and C, while the atezolizumab monotherapy arm had a lower incidence at 6 percent. In group A, 11% of patients that were withdrawn were due to atezolizumab-related adverse events. The addition of atezolizumab to platinum-based chemotherapy as first-line treatment led to prolonged progression-free and overall survival, with similar safety profiles for the combination compared to that of individual chemotherapy agents.

5.2. Pembrolizumab

The phase II KEYNOTE-052 study treated 370 patients with advanced urothelial carcinoma who were not eligible for cisplatin-based treatment with pembrolizumab at 200 mg every three weeks for up to two years [47]. At a minimum follow-up of two tears, the ORR was 29 percent for the entire cohort, which included 9 percent complete response and 20 percent partial response. The ORR was higher in patients with PD-L1 expression >10 percent, but observed in all populations. The median duration of response was 30 months, with a median OS of 11.3 months [47,48]. Combination of pembrolizumab with another agent with antibody drug conjugate (ADC) enfortumab vedotin in a study called EV-103 showed promising overall results in the first-line cisplatin-ineligible cohort of 45 patients [49]. The investigator-assessed ORR was 73.3% (95% CI, 58.1, 85.4) and even patients with liver metastasis had a response rate of 53.3%, showing this

potent combination. A phase III trial of EV-302 NCT04223856 seeks to establish the benefit of enfortumab vedotin and pembrolizumab with the initial intent to evaluate its benefit with or without chemotherapy versus chemotherapy alone in approximately 760 patients However, given the promising results of the EV-103 trial and lack of seeming benefit from triplet therapy with checkpoint inhibitor plus platinum-based chemotherapy seen in the therapeutic arms of the Imvigor130 trial and the KEYNOTE 361 trials, this combination arm was discontinued in EV-302.

Pembrolizumab was also studied in a large phase III trial as a monotherapy arm versus chemotherapy alone with gemcitabine and cisplatin or carboplatin versus chemotherapy with pembrolizumab followed by maintenance pembrolizumab in patients with advanced urothelial cancer in the KEYNOTE 361 trial (NCT02853305) [50]. Approximately 1010 patients were randomized in 1:1:1 fashion and results recently reported showing failure to improve PFS or OS though ORR was better in the combination pembrolizumab and chemotherapy arm of 54.7% compared to chemotherapy only at 44.9% and only 30.3% for the pembrolizumab monotherapy arm. Median PFS for combination pembrolizumab and chemotherapy was 8.3 months compared to 3.9 months for pembrolizumab monotherapy, and 7.1 months for the chemotherapy only arm while median OS was 17.0 months for the pembrolizumab and chemotherapy arm compared to 15.6 months for the pembrolizumab monotherapy arm and 14.3 months for the chemotherapy arm, respectively; HR 0.86 (0.72–1.02, $P = 0.0407$) for OS.

The results of KEYNOTE 361 has dampened the enthusiasm regarding combination chemotherapy with pembrolizumab although further studies exploring biomarkers or trial design would be helpful in further defining the reason for the negative findings.

5.3. Durvalumab

Durvalumab was combined with tremelimumab, an anti-CTLA4 agent, in a phase III trial called DANUBE (NCT02516241), as a first-line treatment for metastatic urothelial cancer patients [51]. Patients were randomized in a 1:1:1 fashion to durvalumab monotherapy at 1.5 g IV every 4 weeks or durvalumab with tremelimumab at 75 mg IV every 4 weeks induction as 4 doses followed by maintenance durvalumab at 1.5 g IV every 4 weeks versus chemotherapy with gemcitabine and cisplatin or carboplatin for up to 6 cycles, until disease progression or unacceptable toxicity. The dual primary endpoints were overall survival between the durvalumab and chemotherapy arms in patients with high PD-L1 expression and durvalumab and tremelimumab versus chemotherapy in the intention to treat population. A total of 1032 pts were randomized. Median OS was not significantly different between D and CT among pts with high PD-L1 expression, nor between $D + T$ and CT in the ITT population. Results showed durvalumab yielded a median OS of 14.4 months (10.4 – 17.3) in the durvalumab arm compared to 12.1 months (10.4 – 15 months) in the chemotherapy arm, HR (95% CI) of 0.89 (0.71–1.11) P value of 0.3039. The ITT population of combination durvalumab and tremelimumab ($n = 342$) median OS of 15.1 months (13.1 – 18 months) verus the chemotherapy arm ($n = 344$) of 12.1 months (10.9 – 14 months); HR (95% CI) = 0.85 (0.72 – 1.02); P value = 0.0751. The overall results of DANUBE was therefore considered negative for its primary endpoint.

6. Maintenance therapy

Previously, standard of care following platinum-based chemotherapy was observation and best supportive care (BSC). While several maintenance trials have been attempted in bladder cancer [52,53], none have been found to be unanimously beneficial. Pembrolizumab was evaluated in a phase II trial HCRN GU14–184 with a switch maintenance approach with 108 patients randomized 1:1 to either pembrolizumab ($n = 55$) or placebo ($n = 53$) [54]. The primary endpoint was progression-free survival which was met and longer with maintenance pembrolizumab at 5.4 months versus placebo at 3 months; HR, 0.65; log-rank $P = 0.04$. Objective response rates of 23% was observed in the pembrolizumab arm compared to 10% in the placebo arm. Median OS was 22 months for those who received pembrolizumab and 18.7 months for those who received placebo. Avelumab as maintenance therapy has recently been tested in the phase III JAVELIN Bladder 100 trial, which enrolled 700 patients with locally advanced, unresectable or metastatic urothelial bladder cancer [55]. These patients were initially treated with gemcitabine plus platinum-based chemotherapy and experienced either an objective response or stable disease after four to six cycles, then were randomized to receive either maintenance avelumab 10 mg/kg every two weeks with BSC or BSC alone. Approximately 51 percent of the study population had PD-L1 positive tumors. At a median follow-up of approximately 19 months, the addition of avelumab improved OS in the entire study population (median 21 months versus 14 months of BSC alone, HR 0.69, 95% CI 0.56–0.86), with a more robust response noted with PD-L1 positive tumors (median not reached versus 17 months, HR 0.56; 95% CI 0.40–0.79). Avelumab also improved median PFS in both groups (5.7 months with PD-L1 expression, 3.7 months without PD-L1 expression compared to approximately 2.0 months with BSC alone) and the ORR for maintenance avelumab was 14 percent in PD-L1 positive patients and 10 percent of the entire treated population. Treatment with maintenance avelumab was overall well tolerated. Grade 3 or higher toxicity rates were notably greater in the avelumab population compared to BSC (47 versus 25 percent), most commonly urinary tract infection and anemia (4% each). The immune-related adverse event rate with those treated with avelumab was 7%. Two patients died from toxicity attributed to avelumab, caused by sepsis and ischemic stroke. However, given promising data based on survival, the FDA approved avelumab for maintenance therapy for patients with locally advanced or metastatic urothelial carcinoma that had not progressed on initial platinum-based chemotherapy. Further analyses looking at biomarkers of response [56], as well as patient reported outcomes [57], have also been reported at this time.

7. Role of checkpoint inhibitors in muscle-invasive bladder cancers (MIBC)

Given the overall positive activity of checkpoint inhibitor immunotherapy in treating metastatic urothelial cancer, there has been consideration of its use as neoadjuvant or adjuvant therapy in muscle-invasive disease. Results from phase I/II studies using atezolizumab and pembrolizumab, along with the combination of durvalumab and tremelimumab have reported complete pathologic responses in approximately one-third of patients [58,59].

The ABACUS phase II trial (NCT02662309) enrolled 95 patients with MIBC, who were treated with atezolizumab for two cycles prior to cystectomy. The primary endpoint of pathological complete response (pCR) was observed in 91% of patients. An additional component of this study was testing biomarkers which may identify tumors more likely to respond to neoadjuvant atezolizumab therapy. Baseline biomarker analysis revealed that the presence of preexisting activated T cells was correlated with outcomes, while other established biomarkers, such as tumor mutational burden, did not predict outcomes [58].

The PURE-01 phase II study (NCT02736266) enrolled 50 patients who were given pembrolizumab 200 mg every 3 weeks for three cycles prior to radical cystectomy [59]. The primary endpoint was pathologic complete response, which 42 percent of patients achieved. A secondary outcome of down staging of tumor to less than pT2 was achieved in 54 percent of patients. Those with higher PD-L1 CPS scores of $\geq$10 percent had much higher incidences of complete response (54.3 percent), compared to those with CPS $<$10% (13.3 percent). Additionally a significant nonlinear association between tumor mutational burden (TMB) and complete response was noted. These findings indicate that pembrolizumab may be an effective neoadjuvant therapy for the treatment of MIBC when limited to patients with PD-L1 positive or high TMB tumors.

The utility of neoadjuvant cisplatin-based chemotherapy and immunotherapy combinations for MIBC is also being studied in multiple ongoing phase III clinical trials. The ENERGIZE trial (NCT03661320) is investigating the use of neoadjuvant chemotherapy alone or with nivolumab, additionally with or without linrodostat mesylate [60]. The NIAGARA trial (NCT03732677) tests durvalumab with gemcitabine and cisplatin versus chemotherapy alone in the neoadjuvant, followed by durvalumab versus placebo in the adjuvant setting [61]. Finally the KEYNOTE-866 trial (NCT03924856) seeks to assess the efficacy and safety of chemotherapy with perioperative pembrolizumab versus chemotherapy with perioperative placebo [62]. In addition, a perioperative pembrolizumab monotherapy trial that was recently amended with or without enfortumab vedotin for cisplatin-ineligible patients was also launched for KEYNOTE 905/EV-303, NCT03924895 [63].

Adjuvant immunotherapy is also being explored in the clinical trial setting. Preliminary results from the phase III IMvigor010 trial (NCT02450331) have not shown that adjuvant atezolizumab improves disease-free survival compared to observation [64]. Additional trials evaluating immunotherapy are also in progress, including nivolumab versus placebo (CheckMate-274, NCT02632409) and pembrolizumab versus placebo (NCT03244384). Preliminary results released via press for CheckMate-274, a phase III trial evaluating nivolumab after surgery in patients with high-risk, muscle invasive urothelial carcinoma, found improved disease-free survival (DFS) versus placebo in all patients, as well as those with PD-L1 expression $\geq$1%.

8. Role of checkpoint inhibitors in non-muscle-invasive bladder cancers (nMIBC)

Given challenges of treatment and risks for recurrence and progression in patients who are deemed to have BCG-refractory disease, the FDA in January of 2020 approved pembrolizumab for the treatment of BCG-refractory, high-risk nMIBC with CIS with or without papillary tumors who are either ineligible for or have declined cystectomy [65]. The basis for this approval was the clinical trial, KEYNOTE-057 (NCT02625961) which enrolled 148 patients for its single-arm trial of which 96 patients had BCG-refractory CIS. Among the 96 patients, 41 percent had a 3-month complete response (negative cystoscopy, urine cytology, and CTU) with a median response duration of 16.2 months.[56] A subsequent ongoing phase III trial, KEYNOTE-676 (NCT03711032), is evaluating pembrolizumab in addition to BCG-therapy in patients with high-risk NMIBC that is persistent or recurrent after BCG induction therapy [66]. The goal is to determine the efficacy and safety of this combination treatment.

Pembrolizumab was previously only indicated for locally advanced or metastatic disease [67]. It is currently considered second-line therapy for those who fail or are intolerant to first-line platinum-based chemotherapy [68]. As multiple trials continue, this exciting breakthrough in the field of immunotherapy may allow for additional treatment options for those who previously failed other standard treatments.

9. Ongoing studies and future directions

The future of immunotherapy in bladder cancer is promising, encompassing a wide spectrum of disease states from non-muscle invasive to metastatic disease. As our science continues to evolve, the utilization of the unique genetic profiles of individual tumors will continue to lead to more targeted therapies that are better tolerated and potentially more cost effective than traditional chemotherapy. However, the role of targeted therapies at this time is still limited to a minority few of patients. While the role of immunotherapy is strongly established in almost every phase of the disease, current investigations with regard to the best first-line metastatic approach is still evolving. It is increasingly becoming clear that chemotherapy remains the most optimal first-line regimen. Trials comparing immunotherapeutic agents and traditional modalities of chemotherapy treatment are vast and diverse and already underway (see Table 3). Maintenance immunotherapy has been shown to be of benefit after response or stable disease to platinum-based chemotherapy although the upfront management of combination chemotherapy with immunotherapy can not be considered standard of care at this time. The choice of agents and interchangeability from avelumab to pembrolizumab is still a subject of debate since the former was indeed tested in a phase III setting though the latter is more convenient with more protracted dosing [69]. As novel agents continue to be formulated and tested, including the use of antibody drug conjugates with enfortumab vedotin which is a potent new addition to the treatment landscape of urothelial cancers, we expect to see a great deal of investment and research into the ever-expanding field of immunotherapy.

TABLE. 3
Select Ongoing clinical trials using immune checkpoint inhibitors in urothelial cancers.

Trial	Phase	Immunotherapy
NCT03747419	II	Avelumab
NCT03317158	I/II	Durvalumab
NCT04383743	II	Pembrolizumab
NCT03520491	II	Nivolumab, Ipilimumab
NCT04216290	II	Durvalumab
NCT03912818	II	Durvalumab
NCT02621151	II	Pembrolizumab
NCT04165317	III	Sasanlimab (PF-06,801,591)
NCT03775265	III	Atezolizumab
NCT04164082	II	Pembrolizumab
NCT04209114	III	Nivolumab, Bempegaldesleukin (Bempeg/NKTR-214)
NCT03732677	III	Durvalumab
NCT03866382	II	Cabozantinib, Nivolumab, Ipilimumab
NCT03513952	II	Atezolizumab, CYT107
NCT03854474	I/II	Pembrolizumab
NCT03606174	II	Nivolumab, Pembrolizumab, Enfortunmab, Sitravatinib

10. Conclusions

Advances in the management of advanced bladder cancer in recent years have led to beginning changes in survival, and much of these improved outcomes are a reflection of the rise of the use of immunotherapy. While first-line therapy is typically anchored with a cisplatin or platinum-based regimen, immunotherapy is increasingly being used in concert with first-line platinum-based therapy, as maintenance therapy for patients treated with platinum-based therapy, as second-line therapy in those who progressed after platinum-based therapy, as well in first-line settings in those who are not candidates for platinum-based therapy. Across the globe, clinical trials exploring the utility of immunotherapy will continue to shape the future of the treatment of bladder cancer.

11. Authors contributions

JAC and LR responsible for conceptualization, data curation, analyses, initial drafting and writing; LR, SM, DK and JAC all responsible for drafting, writing, review and editing of the manuscript.

Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JBAC is on the Speakers' Bureau of BMS and Astellas/Seattle Genetics; serves on the Advisory Board of Pfizer, Merck, EMD Serono, and Immunomedics. The rest of the authors have no known competing financial interests to declare.

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