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Review

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# Current Status and Future Perspectives of Immunotherapies in Bladder Cancer

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ABSTRACT

Bladder cancer exhibits a broad spectrum of progression, ranging from early stage to metastatic disease. Approximately 75% of newly diagnosed patients present with non-muscle-invasive bladder cancer, while the remaining 25% have muscle-invasive bladder cancer or metastatic disease. The prognosis of advanced urothelial carcinoma is poor, with more than 90% of patients succumbing to metastatic disease within five years of diagnosis. In recent years, the role of immunotherapies, particularly immune checkpoint inhibitors, in the treatment of bladder cancer has become increasingly recognized. This review aims to evaluate the current status of immunotherapies in bladder cancer and their future potential.

**Keywords:** Bladder cancer, checkpoint inhibitors, immunotherapy

## Introduction

According to global data, bladder cancer is one of the most common urological malignancies worldwide [1]. Although most patients are diagnosed with the superficial or non-muscle-invasive form, it can also present as muscle-invasive bladder cancer (MIBC) or metastatic bladder cancer (MBC). Unfortunately, MIBC and metastatic stages are associated with a high risk of mortality. Spanning a broad spectrum from non-invasive bladder cancer to the metastatic stage, this disease necessitates different treatment approaches. While surgical intervention, intravesical therapy, radiotherapy (RT), and chemotherapy (CT) are among the treatment options for bladder cancer, a growing understanding of immunological mechanisms in recent years has positioned immunotherapy as an important treatment alternative. Immunotherapies are utilized both to prevent tumor recurrence in early-stage disease and to control tumor progression in more advanced stages. The primary objective of immunotherapies is to enhance the natural response of the immune system against cancer cells. In particular, immune checkpoint inhibitors (ICIs) offer potential benefits not only in metastatic disease but also in early-stage bladder cancer. Notably, Bacillus Calmette-Guérin (BCG), which has been used in bladder cancer treatment for decades, is considered the gold standard for non-invasive bladder cancer therapy, highlighting the efficacy of immunotherapies. Immunotherapy is employed either as monotherapy or in combination with CT, and its role in intravesical therapies is being investigated, with promising results. This review comprehensively examines the current status of immunotherapies for bladder cancer and their potential future applications based on relevant clinical studies.

### Bladder Cancer Staging

The staging of bladder cancer is crucial for assessing prognosis and determining appropriate treatment strategies. The tumor, node, metastasis classification, recommended by the World Health Organization and the American Joint Committee on Cancer, is considered the gold standard for bladder cancer staging. The T classification of bladder cancer is divided into two main categories: non-invasive and invasive. Non-invasive bladder cancer is typically confined to the superficial

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epithelium and includes a papillary tumor (Ta) and carcinoma *in situ* lesions. Invasive bladder cancer, on the other hand, encompasses stages in which the tumor infiltrates the muscle layer of the bladder wall (T2) and beyond, including perivesical invasion (T3) and spread to adjacent organs (T4). In addition, regional lymph node involvement (N1-3) and distant metastasis (M1) were evaluated. Tumors with muscle invasion exhibit a more aggressive course and generally require multimodal treatment.

**Non-muscle Invasive Bladder Cancer Treatment**

**Bacillus Calmette-Guérin**

BCG therapy is the standard treatment for non-muscle-invasive bladder cancer (NMIBC). BCG is a live-attenuated strain of *Mycobacterium bovis* and is used to reduce the risk of bladder cancer recurrence and its progression to a more invasive disease [2]. BCG is administered following transurethral resection of the tumor and is generally recommended for patients with high-risk NMIBC [2,3]. BCG therapy is rarely associated with significant side effects, such as sepsis and allergic reactions [4]. In the NIMBUS trial, reducing the standard dose and frequency of BCG administration was evaluated and found to be less effective than the standard regimen [4].

BCG resistance poses a significant challenge for the treatment of NMIBC. In BCG resistant cases, radical cystectomy is generally the recommended treatment approach. However, considering the high morbidity associated with this surgical procedure and its impact on patients' quality of life, there is a growing need for alternative treatment strategies. Alternative therapeutic options include intravesical CT, immunotherapy, antibody-drug conjugates, device-assisted therapies, gene therapy, RT [5]. Emerging treatment modalities offer promising outcomes for BCG-resistant patients and enable the development of bladder-sparing strategies. Ongoing research in this field aims to expand the treatment options and improve disease outcomes.

**Immunotherapy Treatment Options in Bacillus Calmette-Guérin-resistant Bladder Cancer Immune Checkpoint Inhibitors**

Various immunotherapy options are available for the treatment of NMIBC in BCG-resistant patients. ICIs play a significant role in the management of bladder cancer [3]. In the KEYNOTE-057 trial, intravenous pembrolizumab demonstrated efficacy with a complete response (CR) rate of 40.6% and a median response duration of 16.2 months, leading to Food and Drug Administration approval [3,6,7]. Common adverse events include pruritus, fatigue, and diarrhea, whereas high-grade adverse effects are rare (12.7%) [8]. In a SWOG S1605 trial, intravenous atezolizumab demonstrated a 6-month response rate of 27%. While its safety profile was similar to that of pembrolizumab, treatment-related serious adverse events were observed in 16% of patients [9]. In a study conducted by Sekino et al. [10], the combination of intravenous atezolizumab and RT was evaluated. Initial results suggest that RT may have a synergistic effect with immunotherapy. In a study conducted by Fragkoulis et al. [11], intravesical durvalumab reduced recurrence rates, and adverse effects generally did not disrupt the treatment process. In the CheckMate 9UT trial, the investigation of nivolumab as monotherapy and in combination with an indoleamine 2,3-dioxygenase (IDO-1) inhibitor is ongoing [12]. Table 1 provides a detailed overview of immunotherapy studies in NMIBC patients.

**Gene Therapies and Oncolytic Viruses**

Gene therapies and oncolytic viruses are being explored as novel approaches in the treatment of NMIBC. Oncolytic viruses such as nadofaragene firadenovec and CG0070 have demonstrated favorable efficacy with no significant adverse effects reported [3]. These therapies offer organ-preserving strategies, potentially improving patients' quality of life [13].

**Interleukins and Other Immune Modulators**

Interleukin-based therapies, particularly interleukin-15 and ALT-803, are currently being investigated for the treatment of NMIBC. These therapies aim to enhance the immune system, promoting a more effective response against tumor cells [3,6].

**Non-metastatic Muscle Invasive Bladder Cancer Neoadjuvant Treatment**

MIBC is an aggressive malignancy often characterized by early and distant recurrences. Cisplatin-based combination regimens are commonly used as neoadjuvant CT before radical cystectomy, providing overall survival (OS) and disease-free survival (DFS) benefits [14]. However, ICIs have revolutionized the treatment of metastatic urothelial carcinoma (mUC) and are now being investigated in the neoadjuvant setting [14,15].

In the ABACUS phase 2 trial, atezolizumab was administered as neoadjuvant therapy in cisplatin-ineligible patients with MIBC. A pathological CR (pCR), was observed in 31% of the patients, and the analysis of 2-year survival revealed a DFS of 68% and an OS of 77% [16]. In another study, atezolizumab combined with CT was tested in cT2-4aN0M0 patients who received neoadjuvant gemcitabine, cisplatin, and atezolizumab. With the combination treatment, 69% of patients achieved NMIBC (<pT2N0) and 41% achieved pCR. In the same study, the low rate of PD-L1 positive tumors limited the use of PD-L1 as a predictive marker [17].

The PURE-01 phase 2 trial is an open-label study evaluating the efficacy of neoadjuvant pembrolizumab in MIBC. The study included clinical stage T2-4aN0M0 patients and investigated the administration of three cycles of 200 mg pembrolizumab before radical cystectomy. A pCR rate of 42% was achieved, and PD-L1 expression and high tumor mutation burden were found to be strongly associated with treatment response [18,19]. Three-year OS rate was 83.8%, while the event-free survival (EFS) rate was 74.4% [20]. The results of the KEYNOTE-905/EV-303 phase 3 trial, which is investigating the efficacy and safety of perioperative pembrolizumab alone or in combination with enfortumab vedotin (EV) in MIBC patients who are ineligible for or decline cisplatin-based therapy, have not yet been reported [21].

**Table 1. NMIBC studies and patient characteristics**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| NIMBUS | 2013-2019 | Randomized phase 3 clinical trial | Ta/T1 | Arm A: Standard BCG schedule (15 instillations)<br>Arm B: Reduced frequency BCG schedule (9 instillations) | The reduced frequency schedule was found to be inferior to the standard schedule for recurrence prevention.<br>- Hazard ratio: 0.40 (with an upper 97.5% confidence interval of 0.68)<br>Due to these findings, further recruitment into the reduced frequency group was stopped early to prevent harm. |
| KEYNOTE-057 (NCT02625961) | 2015-2018 | Open-label, single-arm, multicenter, phase 2 study | CIS | Pembrolizumab | Primary result:<br>- cCR ratio (40.6%; 95% CI: 30.7-51.1)<br>- Thirty-nine (41%) of 96 BCG-resistant CIS patients showed onse at 3 months of treatment.<br>Secondary results:<br>- Rate of serious treatment-related side effects: 8%<br>- Grade 3 or 4 side effects: 12.7% (most common: arthralgia 2%, hyponatremia 3%) |
| SWOG S1605 (NCT02844816) | 2016-2023 | Single-arm, phase 2 clinical trial | CIS/Ta/T1 | Atezolizumab | Primary result:<br>- pCR rate at 6 months in CIS patients: 27% (20/74 patients)<br>Secondary results:<br>- Median response time: 17 month<br>- In 56% of responding patients (95% CI: 34-77), the response was sustained through 12 months<br>- 18-month event-free survival rate in Ta/T1 patients: 49% (95% CI: 38-60)<br>- Twelve of 129 patients progressed to intramuscular invasive or metastatic disease<br>- TRAEs, grade 3-5: 16% (26 patients)<br>- Treatment-related deaths: 3 patients |
| BPT-ART (RCT2031180060) | 2019-Ongoing | Open-label, phase 2, multicenter clinical study | T1-3 | Atezolizumab+radiotherapy | Initial results suggest that radiotherapy may have a synergistic effect with immunotherapy.<br>The study is ongoing. |
| NCT03759496 | 2018-2024 | Single-arm, phase 2 clinical trial | High-risk NMIBC patients who fail BCG therapy | Intravesical durvalumab | Primary result:<br>- 1-year HGR-free survival rate: 39% (95% CI: 18-59)<br>Secondary results:<br>- 1st, 3rd, and 6th month HGR-free survival rate:<br>- 70% (95% CI: 45-85) - 1. months<br>- 55% (95% CI: 31-74) - 3. months<br>- 39% (95% CI: 18-59) - 6. months<br>- 1-year bladder integrity preservation rate: 78% (95% CI, 57-89)<br>- Treatment-related adverse events: Only grade 1 hematuria (in 5 patients-17%) |
| CheckMate 9UT | 2019-ongoing | Multi-arm, phase 2 clinical trial | High-risk NMIBC unresponsive to BCG | Arm A: nivolumab monotherapy<br>Arm B: nivolumab+intravesical BCG combination<br>Arm C: nivolumab in combination with other mesylate-based agents | Initial results show that nivolumab is well tolerated and safe.<br>The study is ongoing. |

cTNM: Clinical tumor, node, metastasis, BCG: Bacillus Calmette-Guérin, CIS: Carcinoma *in situ*, cCR: Clinical complete response, CI: Confidence interval, HGR: High-grade relapse, BPT-ART: Bladder preservation therapy-accelerated radiotherapy, SWOG: Southwest Oncology Group, NCT: National clinical trial (number), NMIBC: Non-muscle-invasive bladder cancer

The Oncodistinct 004-AURA phase 2 trial (NCT03674424) investigated the impact of neoadjuvant perioperative avelumab, in cisplatin-eligible and ineligible bladder cancer patients. In the cisplatin-eligible cohort, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (ddMVAC) and CG (cisplatin+gemcitabine), regimens combined with avelumab demonstrated high DFS and OS rates at 12 and 36 months, with the ddMVAC-A combination showing particularly strong efficacy (36-month DFS and OS rates of 77% and 87%, respectively). Patients who achieved a pCR maintained high DFS rates up to 36 months. In the cisplatin-ineligible cohort, avelumab monotherapy yielded promising results, while the PG (paclitaxel+gemcitabine) combination did not provide additional benefit. Overall, neoadjuvant avelumab combinations significantly improved survival outcomes in cisplatin-eligible patients, whereas lower efficacy was observed in cisplatin-ineligible patients [22].

The NABUCCO trial is a phase 1b, single-arm clinical study evaluating the efficacy and feasibility of preoperative ipilimumab and nivolumab combination therapy in patients with locally advanced urinary tract cancer (stage 3). The study included 24 patients who were ineligible for or declined cisplatin-based treatment, and received ipilimumab plus nivolumab over 12 weeks before surgery. The pCR rate was 46%, reaching 50% in lymph node-negative patients. The treatment was found to be effective regardless of preoperative CD8+ T-cell density, with higher response rates observed in patients with high PD-L1 expression [23]. In a phase 2 study conducted by Kim et al. [24] in 2023, the efficacy and safety of neoadjuvant nivolumab combined with gemcitabine/cisplatin (N+GC) were evaluated in patients with MIBC. A total of 51 patients received 3-4 cycles of nivolumab (3 mg/kg) along with gemcitabine/cisplatin. The clinical CR rate was 59%, while the pCR rate was 24% in the overall cohort and 35% in patients who underwent radical cystectomy. Median DFS was not reached, with 12- and 24-month DFS rates of 90% and 73%, respectively. The treatment was generally well tolerated, and subgroup analyses showed that PD-L1 positivity (CPS >1%) was not associated with pCR. The results of the ENERGIZE trial (NCT03661320), which investigates the use of nivolumab and linrodostat mesylate, have not yet been reported [25].

The phase 3 NIAGARA trial, which evaluates the efficacy and safety of perioperative durvalumab, enrolled 1.063 patients who were randomized in a 1:1 ratio [26]. One group received durvalumab combined with gemcitabine and cisplatin, while the control group received standard gemcitabine-cisplatin CT. OS was 82.2% in the durvalumab arm compared to 75.2% in the standard CT arm [hazard ratio (HR): 0.68, p<0.001]. The addition of perioperative durvalumab to standard CT resulted in a statistically significant improvement in EFS and OS. Treatment-related serious adverse events were observed at similar rates in both groups (~40%) [26]. Additionally, the NEMIO trial (NCT03549715), which is evaluating the neoadjuvant effects of durvalumab and tremelimumab in MIBC, is ongoing and its results await publication [27]. Table 2 provides a detailed overview of the study characteristics and outcomes.

**Adjuvant Treatment**

Adjuvant therapy in MIBC is recommended by guidelines for patients with high pathological risk [28]. The use of adjuvant ICIs is being considered as an alternative approach to standard CT regimens due to their tolerability advantages. This treatment modality has the potential to provide an additional therapeutic option, particularly for cisplatin-ineligible patients. Moreover, adjuvant immunotherapy may be beneficial for patient groups with poor prognosis following neoadjuvant CT and radical cystectomy, where standard treatment protocols have not yet been clearly established [29].

The phase 3 IMvigor010 trial compared adjuvant atezolizumab monotherapy with observation in patients with muscle-invasive urothelial carcinoma (MIUC) who were at high risk after radical surgery. This included patients with ypT2-4a or ypN+ disease following neoadjuvant CT, as well as those who had not received neoadjuvant CT but had pT3-4a or pN+ disease [30]. In the IMvigor010 trial, circulating tumor DNA (ctDNA) status was assessed in 581 enrolled patients. In ctDNA-positive patients, atezolizumab provided a significant OS benefit compared to observation [HR: 0.59, 95% confidence interval (CI): 0.42-0.83; median OS: 29.8 months vs. 14.1 months]. However, in ctDNA-negative patients, atezolizumab did not demonstrate an improvement in OS (HR: 1.38, 95% CI: 0.93-2.05). These findings highlight ctDNA status as a critical biomarker for identifying patients who may benefit from adjuvant immunotherapy. Although atezolizumab was associated with increased adverse event rates, its efficacy in ctDNA-positive patients is clinically significant.

The phase 3 AMBASSADOR trial evaluated adjuvant pembrolizumab in high-risk MIUC patients, similar in intent to the IMvigor010 study [31]. A total of 702 patients were randomized to receive pembrolizumab (200 mg every three weeks for one year) or observation after radical surgery. Median DFS was significantly improved with pembrolizumab (29.6 months) compared to observation (14.2 months) (HR=0.73, p=0.003). while no significant difference was observed in OS (HR=0.98). Although grade 3 adverse events were more frequent in the pembrolizumab arm (50.6% vs. 31.6%), disease recurrence was significantly reduced.

Similar to other immunotherapy studies, the phase 3 CheckMate 274 trial evaluated the efficacy and safety of adjuvant nivolumab in high-risk MIUC patients following radical surgery [32]. Nivolumab significantly prolonged DFS compared with placebo (20.8 months vs. 10.8 months; HR: 0.70; p<0.001), and this effect was more pronounced in patients with PD-L1 expression ≥1% (HR: 0.55; p<0.001). The safety profile was tolerable, similar to previous studies, and no significant deterioration in quality of life was observed.

**Table 2. Non-metastatic MIBC neoadjuvant therapy studies and patient characteristics**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| ABACUS (NCT02662309) | 2016-2022 | Multicenter, single-arm, phase 2 clinical trial | T2-4aN0M0 | Atezolizumab | Primary result:<br>- pCR: 31% (in 27 of 88 patients)<br>Secondary results:<br>- 2 year DFS: 68%<br>- 2 year OS: 77%<br>- ctDNA positivity is associated with worse prognosis<br>- Side effects were generally mild and manageable (grade 3-4 side effects: 12%) |
| NCT02989584 | 2016-Ongoing | Multicenter, single-arm, phase 2 clinical trial | cT2-4aN0MO | Atezolizumab+gemcitabine+cisplatin | Primary result:<br>- pCR (<pT2N0): 69% (27/39 patients)<br>- pCR rate: 41% (16/39 patients)<br>Secondary results:<br>- Patients with PD-L1 positive tumors: 100% showed <pT2N0 response.<br>- In patients with low or negative PD-L1: 68% <pT2N0, 32% ≥pT2N0 |
| PURE-01 (NCT02736266) | 2017-2021 | Open-label, single-arm, phase 2 clinical study | cT2-T4aN0M0 | Pembrolizumab | Primary result:<br>- 3 years EFS: 74.4% (95% CI: 67.8-81.7)<br>- 3 years OS: 83.8% (95% CI: 77.8-90.2) |
| KEYNOTE-905/ EV-303 (NCT03924895) | 2023-Ongoing | Open-label, multicenter, randomized phase 2 clinical trial | T2-4aN0M0<br>Veya<br>T1-4aN1M0 | Arm A: pembrolizumab<br>Arm B: standard surgery<br>Arm C: enfortumab vedotin+pembrolizumab | The study is still ongoing. |
| AURA (Oncodistinct 004) (NCT03674424) | 2018-2024 | Multicenter, randomized, phase 2 clinical trial | T2-4aN0M0<br>Veya<br>T1-4aN1M0 | <u>Cohort 1: (*cisplatin eligible*)</u><br>Arm A: ddMVAC+avelumab<br>Arm B: cisplatin-gemcitabine+avelumab<br><u>Cohort 2: *sisplatin inegible*</u><br>Arm C: paclitaxel-gemcitabine+avelumab<br>Arm D: avelumab monotherapy | ddMVAC + avelumab (ddMVAC-A):<br>- 12 months DFS: 97% (95% CI: 83-100)<br>- 36 months DFS: 77% (95% CI: 55-89)<br>- 12 months OS: 95% (95% CI: 81-99)<br>- 36 months OS: 87% (95% CI: 68-95)<br>Cisplatin-gemcitabine+avelumab (CG-A):<br>- 12 months DFS: 86% (95% CI: 70-94)<br>- 36 months DFS: 68% (95% CI: 46-82)<br>- 12 months OS: 84% (95% CI: 67-92)<br>- 36 months OS: 61% (95% CI: 40-76)<br>Paclitaxel-gemcitabin+avelumab (PG-A) (<u>*sisplatin inegible*</u>):<br>- 12 months DFS: 52% (95% CI: 32-69)<br>- 36 months DFS: data is not yet mature<br>- 12 months OS: 67% (95% CI: 46-81)<br>- 36 months OS: data is not yet mature<br>Avelumab monotherapy (A) (<u>*sisplatin inegible*</u>):<br>- 12 months DFS: 68% (95% CI: 47-82)<br>- 36 months DFS: data is not yet mature<br>- 12 months OS: 75% (95% CI: 55-87)<br>- 36 months OS: data is not yet mature |

**Table 2. Continued**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| ENERGIZE (NCT03661320) | 2018-ongoing | Multicenter, randomized, phase 3 clinical trial | T2-4aN0M0 | Arm A: standard neoadjuvant chemotherapy (NAC)<br>Arm B: NAC+nivolumab<br>Arm C: NAC+nivolumab+BMS-986205 | The study is still ongoing. |
| NABUCCO (NCT03387761) | 2018-2023 | Open-label, single-arm, phase Ib clinical study | T3-T4aN0M0 veya T1-4a, N1-2, M0 | Nivolumab+Ipilimumab | Primary result:<br>- pCR rate: 46% (11/24 patients)<br>Secondary results:<br>- pCR rate in PD-L1 positive patients: 67%<br>- pCR rate in PD-L1 negative patients: 17%<br>- After treatment, CD8+ T cell infiltration increased in the tumor microenvironment in 88% of patients.<br>- irAE's: 30% grade 3-4 side effect<br>- Rate of patients who could not complete treatment due to side effects: 21% (5/24 patients) |
| ONO-4538-X41 (KCT0003804) | 2019-2020 | Single-arm, phase 2 clinical trial | cT2-4aN0M0 | Nivolumab+gemcitabine+cisplatin | Primary result:<br>- pCR rate:<br>- ITT population: 24% (12/49 patients)<br>- In patients undergoing radical cystectomy: 35% (12/34 patients)<br>Secondary results:<br>- cCR rate: 59% (clinical response was seen in 29 of 49 patients)<br>- PD-L1 expression did not appear to be a factor determining pathological response rates. |
| NIAGARA (NCT03732677) | 2018-2024 | Multicenter, randomized, phase 3 clinical trial | cT2-4a, N0-1, M0 | Arm A: gemcitabine+cisplatin+durvalumab<br>Arm B: gemcitabine+cisplatin | Primary result:<br>- pCR rate: 34% (Arm A) vs. 20% (Arm B)<br>- EFS (36 months): EFS 68% (Arm A) vs. 54% (Arm B)<br>Secondary results:<br>- OS: 72% (Arm A) vs. 60% (Arm B)<br>- TRAEs: grade 3-4 side effect rate 28%<br>- In the durvalumab group, treatment was discontinued in 10 patients due to immune-mediated side effects.<br>- No strong correlation was found between PD-L1 expression and treatment response. |
| NEMIO (NCT03549715) | 2018-2021 | Open-label, randomized, phase 2 clinical trial | T2-4, N0-1, M0 | Arm A: ddMVAC<br>Arm B: ddMVAC+durvalumab<br>Arm C: ddMVAC+durvalumab+tremelimumab | Primary result:<br>- pCR rate:<br>- ddMVAC (control groups): 30%<br>- ddMVAC+durvalumab (ddMVAC+D): 45%<br>- ddMVAC+durvalumab+tremelimumab (ddMVAC+D+T): 50%<br>Secondary results:<br>- DFS and OS results are monitored.<br>- TRAEs (grade 3-4 side effect rate):<br>- ddMVAC group: 22%<br>- ddMVAC+Durvalumab group: 30%<br>- ddMVAC+Durvalumab+tremelimumab group: 36% |

MIBC: Muscle-invasive bladder cancer, pCR: Pathological complete response, DFS: Disease-free survival, OS: Overall survival, PD-L1: Programmed death-ligand 1, EFS: Event-free survival, NAC: Neoadjuvant chemotherapy, TRAEs: Treatment-related adverse events, ddMVAC: Dose-dense methotrexate, vinblastine, doxorubicin (adriamycin), and cisplatin, ITT: Intention-to-treat, cTNM: Clinical tumor, node, metastasis

The extended follow-up analysis of the CheckMate 274 study (median follow-up of 36.1 months) demonstrated a stronger DFS advantage with nivolumab in both the intention-to-treat (ITT) (HR: 0.71; 95% CI: 0.58-0.86) and PD-L1 ≥1% (HR: 0.52; 95% CI: 0.37-0.72) populations and presented OS data for the first time [33]. Nivolumab reduced the risk of death by 24% (HR: 0.76; 95% CI: 0.61-0.96) in the ITT population and by 44% (HR: 0.56; 95% CI: 0.36-0.86) in the PD-L1 ≥1% population. Efficacy was also confirmed in the MIBC subgroup, regardless of PD-L1 status.

The use of adjuvant immunotherapy may be an effective option for preventing relapse, especially in high-risk MIUC patients. The characteristics and results of the studies are presented in detail in Table 3.

**Table 3. Non-metastatic MIBC adjuvant therapy studies and patient characteristics**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| IMvigor010 (NCT02450331) | 2015-2024 | Open-label, randomized, double-arm phase 3 clinical trial | T2-4, N0-1, M0 | Arm A: atezolizumab<br>Arm B: placebo | ctDNA positive patients OS:<br>- Atezolizumab vs. observation group: HR: 0.59 (95% CI: 0.42-0.83)<br>ctDNA negative patients OS:<br>HR: 1.05 (95% CI: 0.78-1.40) |
| AMBASSADOR (NCT03244384) | 2017-2024 | Open-label, randomized, phase 3 clinical trial | T2-4a, N0-1, M0 | Arm A: pembrolizumab<br>Arm B: placebo | DFS: pembrolizumab vs. observation group:<br>- HR: 0.73 (95% CI: 0.59-0.90), p=0.003<br>- Median DFS: pembrolizumab 29.6 months (95% CI: 20.0-40.7) vs. observation 14.2 months (95% CI: 11.0-20.2)<br>- OS:<br>- Pembrolizumab vs. observation group:<br>- HR: 0.98 (95% CI: 0.76-1.26)<br>3 years OS rate: pembrolizumab 60.8% (95% CI: 55.3-66.9) vs. observation 61.9% (95% CI: 56.5-67.9)<br>DFS results according to PD-L1 expression:<br>- PD-L1 positive patients: median DFS: 36.9 months vs. 21.0 months (HR: 0.81, 95% CI: 0.61-1.08)<br>- PD-L1 negative patients: median DFS: 17.3 months vs. 9.0 months (HR: 0.71, 95% CI: 0.53-0.95) |
| CheckMate 274 (NCT02632409) | 2016-2021 | Multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial | T2-4a, N0-1, M0 | Arm A: nivolumab<br>Arm B: placebo | DFS<br>- Median DFS in the nivolumab arm: 20.8 months<br>- Median DFS in placebo arm: 10.8 months<br>- (HR: 0.70, p<0.001)<br>DFS in PD-L1 positive patients:<br>- Median DFS in the nivolumab arm: 22.0 months<br>- Median DFS in placebo arm: 10.7 months<br>- (HR: 0.55, p<0.001).<br>Adverse effects:<br>- Grade 3-4 adverse event rate in the nivolumab arm was 17.9%<br>- The rate of grade 3-4 adverse events in the placebo arm was 7.2%<br>- Treatment-related deaths: 3 patients in the nivolumab arm (pneumonitis and bowel perforation). |

MIBC: Muscle-invasive bladder cancer, cTNM: Clinical tumor, node, metastasis, DFS: Disease-free survival, OS: Overall survival, HR: Hazard ratio, PD-L1: Programmed death-ligand 1, CI: Confidence interval, ctDNA: circulating tumor deoxyribonucleic acid

**Metastatic Bladder Cancer**

MBC is associated with limited systemic treatment options and generally poor prognosis. Recently, immunotherapy, targeted therapies, and antibody-drug conjugates have emerged as promising treatment options in this setting [7].

The IMvigor130 trial is a randomized, controlled phase 3 study comparing first-line atezolizumab monotherapy with platinum-based CT in locally advanced or mUC [34]. In the overall population, atezolizumab did not significantly improve median OS (15.2 months vs. 13.3 months; HR: 0.98, 95% CI: 0.82-1.16). However, in patients with high PD-L1 expression, particularly those ineligible for cisplatin, potential survival benefits were observed (median OS: 18.6 months vs. 10.0 months; HR: 0.56, 95% CI: 0.34-0.91). Atezolizumab demonstrated a better safety profile with fewer severe adverse events (16% vs. 80% in the control group). These findings support atezolizumab as a treatment alternative in patients with PD-L1-positive tumors or those ineligible for cisplatin.

Similarly, the phase 3 IMvigor211 trial investigated the efficacy of atezolizumab in mUC patients who had progressed after platinum-based CT. Patients received either atezolizumab (1200 mg) or investigator's choice of CT (vinflunine, paclitaxel, or docetaxel). In the atezolizumab group, the 24-month survival rate was 23% compared to 13% in the CT group, while the 30-month survival rates were 18% and 10%, respectively (HR: 0.82; 95% CI: 0.71-0.94). Atezolizumab was associated with a lower incidence of severe adverse events (22% vs. 43%) [35]. These results demonstrate that atezolizumab is an effective and safe treatment option for patients with advanced urothelial carcinoma following platinum-based therapy, regardless of PD-L1 status.

In 2023, Balar et al. [36] evaluated the efficacy and safety profile of pembrolizumab in mUC patients with up to five years of follow-up data from the KEYNOTE-045 and KEYNOTE-052 trials. In the KEYNOTE-045 trial, pembrolizumab demonstrated a significant OS benefit compared to CT in platinum-resistant mUC patients (48-month OS: 16.7% vs. 10.1%) and a longer median duration of response (29.7 months vs. 4.4 months). In the KEYNOTE-052 trial, pembrolizumab emerged as a strong first-line option for cisplatin-ineligible patients, with an objective response rate (ORR) of 28.9% and a median duration of response of 33.4 months. Pembrolizumab was found to be effective and had a manageable safety profile, making it a reliable treatment option for both second-line therapy and cisplatin-ineligible patients. The KEYNOTE-361 trial evaluated the efficacy of pembrolizumab monotherapy or its combination with CT in advanced urothelial carcinoma. The findings indicated that pembrolizumab, whether as monotherapy or in combination with CT, did not provide a significant benefit as a first-line treatment. Instead, the results suggest that immunotherapy may be more effective when used as maintenance therapy [37]. The EV-302 trial is a randomized clinical study comparing the efficacy and safety of the EV-pembrolizumab combination with platinum-based CT as a first-line treatment for locally advanced or mUC. The combination therapy significantly improved progression-free survival (PFS) (12.5 months vs. 6.3 months; HR: 0.45, p<0.001) and OS (31.5 months vs. 16.1 months; HR: 0.47, p<0.001). Additionally, the combination demonstrated superiority in ORR (67.7% vs. 44.4%) and CR rate (29.1% vs. 12.5%). Treatment-related adverse events were less frequent in the combination group (55.9% vs. 69.5%), with the most common adverse effects being peripheral neuropathy and pruritus [38]. With this study, the EV and pembrolizumab combination has become the treatment option providing the longest survival benefit in metastatic urothelial cancer to date and has been integrated into routine clinical practice. In a study comparing erdafitinib and pembrolizumab in patients with fibroblast growth factor receptor mutations who progressed after platinum-based CT, erdafitinib demonstrated a higher ORR and PFS advantage. However, OS was similar between the two treatments (10.9 months vs. 11.1 months) [39].

The multicenter ARIES phase 2 trial evaluated the efficacy and safety of avelumab as a first-line treatment in PD-L1-positive patients with metastatic or locally advanced urothelial cancer who were ineligible for cisplatin-based therapy. The study reported a median OS of 10 months and a one-year survival rate of 43%, with an ORR of 24% [40]. The phase 3 JAVELIN Bladder 100 trial investigated the efficacy of avelumab maintenance in patients with advanced urothelial cancer who did not experience progression following platinum-based CT. Maintenance with avelumab significantly improved OS (23.8 months vs. 15.0 months; HR: 0.76, p=0.0036) and PFS (5.5 months vs. 2.1 months; HR: 0.54, p<0.0001) compared to best supportive care. Long-term follow-up (>2 years) confirmed the treatment's efficacy and manageable safety profile. Avelumab has now been established as a standard maintenance therapy option for advanced urothelial cancer following first-line treatment [41].

The CheckMate 901 trial demonstrated that the combination of nivolumab with gemcitabine-cisplatin significantly improved OS (21.7 months vs. 18.9 months; HR: 0.78, p=0.02) and PFS (7.9 months vs. 7.6 months; HR: 0.72, p=0.001) compared to gemcitabine-cisplatin alone in advanced urothelial carcinoma. Additionally, the CR rate was doubled in the combination group (21.7% vs. 11.8%), while the rate of treatment-related adverse events was reported as 61.8%. These findings suggest that concurrent nivolumab and CT could be an effective treatment strategy [42].

The multicenter randomized DANUBE trial compared durvalumab monotherapy and durvalumab plus tremelimumab combination therapy with standard platinum-based CT in patients with locally advanced or mUC. The study did not meet its primary endpoint of OS [43]. Table 4 provides a detailed overview of the study characteristics and outcomes.

**Table 4. Metastatic MIBC treatment studies and patient characteristics**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| IMvigor130 (NCT02807636) | 2016-2018 | Randomized, controlled, phase 2 clinical trial | Locally advanced or mUC | Arm A: atezolizumab+platinum-based chemotherapy<br>Arm B: atezolizumab monotherapy<br>Arm C: platinum-based chemotherapy | mOS:<br>- Atezolizumab+chemotherapy group: 16.0 months (95% CI: 13.9-18.0)<br>- Chemotherapy alone group: 13.4 months (95% CI: 12.0-15.3)<br>- HR=0.85 (95% CI: 0.72-1.02, p=0.04)<br>- Atezolizumab monotherapy: 15.7 months<br>- HR=1.02 (95% CI: 0.83-1.24, p=0.82) |
| IMvigor211 (NCT02302807) | 2015-2016 | Randomized, open-label, phase 3 clinical trial | Locally advanced or mUC | Arm A: atezolizumab<br>Arm B: chemotherapy (vinflunine or paclitaxel or docetaxel) | mOS:<br>- Atezolizumab group: 11.1 months (95% CI: 9.1-13.1)<br>- Chemotherapy group: 10.6 months (95% CI: 8.4-11.8)<br>- HR=0.87 (95% CI: 0.73-1.02, p=0.07)<br>In patients with high PD-L1 expression (IC2/3):<br>- Atezolizumab: 11.1 months<br>- Chemotherapy: 10.6 months<br>- HR=0.95 (95% CI: 0.74-1.24)<br>Treatment-related adverse events (TRAEs):<br>- Any grade adverse event rate:<br>- Atezolizumab: 60.9%<br>- Chemotherapy: 90.2%<br>Grade 3-4 adverse event rate:<br>- Atezolizumab: 20.9%<br>- Chemotherapy: 43.2% |
| SAUL (NCT02928406) | 2016-2018 | Single-arm, phase 3b, clinical trial | Locally advanced or mUC | Atezolizumab | - In patients with high PD-L1 (IC2/3), OS was longer (11.6 months vs. 7.75 months, p=0.002).<br>- Patients who received treatment 6 months before the last chemotherapy (TFLC >6 months) had a better advantage in terms of OS (11.63 months vs. 6.97 months, p<0.001).<br>- Bellmunt risk factors (0, 1, 2-3) have a strong prognostic impact on survival.<br>- The type of prior chemotherapy regimen (cisplatin/carboplatin) and the number of prior lines of therapy were not associated with survival outcomes. |
| KEYNOTE-045 (NCT02256436) | 2015-2020 | Phase 3, randomized controlled trial | mUC | Arm A: pembrolizumab<br>Arm B: chemotherapy | - 48$^{th}$ month OS rate:<br>Pembrolizumab 16.7%,<br>Chemotherapy 10.1%<br>- 48$^{th}$ months PFS rate:<br>Pembrolizumab 9.5%,<br>Chemotherapy 2.7%<br>-DOR:<br>Pembrolizumab 29.7 months,<br>Chemotherapy 4.4 months<br>- 36$^{th}$ months DOR rate:<br>Pembrolizumab 44.4%,<br>Chemotherapy 28.3% |
| KEYNOTE-052 (NCT02335424) | 2015-2020 | Phase 2, single-arm study | Cisplatin inegible mUC | Pembrolizumab | - ORR: 28.9% (95% CI: 24.3-33.8)<br>- DOR: 33.4 months<br>- 36$^{th}$ month DOR rate: 44.8% |

**Table 4. Continued**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| KEYNOTE-361 (NCT02853305) | 2016-2021 | Phase 3, open label, randomized controlled trial | mUC | Arm A: pembrolizumab<br>Arm B: pembrolizumab+chemotherapy<br>Arm C: chemotherapy | OS:<br>- No statistically significant difference was observed between the pembrolizumab+chemotherapy arm and the chemotherapy alone arm (HR: 0.86; 95% CI: 0.72-1.02; p=0.0407; statistical significance threshold was set at p<0.0242).<br>- No significant difference was detected between pembrolizumab monotherapy and chemotherapy arms (HR: 0.91; 95% CI: 0.77-1.08).<br>PFS:<br>- The pembrolizumab+chemotherapy arm did not provide a statistically significant improvement compared to chemotherapy alone (HR: 0.78; 95% CI: 0.65-0.93; p=0.0033; statistical significance threshold set at p<0.0019).<br>- Pembrolizumab monotherapy has shown inferior PFS results compared to chemotherapy |
| EV-302/ KEYNOTE-A39 (NCT04223856) | 2020-2024 | Phase 3, open label, randomized controlled trial | mUC | Arm A: enfortumab vedotin+pembrolizumab<br>Arm B: platinum based chemotherapy | OS:<br>- EV+P group: 31.5 months (95% CI: 25.3-not reached)<br>- Chemotherapy group: 16.1 months (95% CI: 13.9-18.8)<br>- HR=0.47 (95% CI: 0.38-0.58, p<0.0001)<br>PFS<br>- EV+P group: 12.5 months (95% CI: 10.4-15.0)<br>- Chemotherapy group: 6.3 months (95% CI: 6.2-6.4)<br>- HR=0.51 (95% CI: 0.41-0.62, p<0.0001)<br>ORR<br>- EV+P group: 67.9% (complete response: 29.1%, partial response: 38.8%)<br>- Chemotherapy group: 44.9% (complete response: 12.4%, partial response: 32.5%)<br>- p<0.0001 |
| THOR (NCT03390504) | 2018-2024 | Phase 3, open-label, randomized controlled trial | mUC | Arm A: erdafitinib<br>Arm B: pembrolizumab | OS:<br>- Erdafitinib: 10.9 months (95% CI: 9.2-13.4)<br>- Pembrolizumab: 11.1 months (95% CI: 8.9-14.3)<br>- HR=1.18 (95% CI: 0.92-1.51, p=0.18)<br>PFS<br>- Erdafitinib: 4.4 months (95% CI: 3.6-5.3)<br>- Pembrolizumab: 2.7 months (95% CI: 2.0-3.4)<br>- HR=0.88 (95% CI: 0.70-1.10)<br>ORR:<br>- Erdafitinib: 40.0% (complete response: 7.5%, partial response: 32.5%)<br>- Pembrolizumab: 21.6% (complete response: 5.7%, partial response: 15.9%)<br>- Relative risk =1.85 (95% CI: 1.32-2.59) |

**Table 4. Continued**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| ARIES (NCT03869190) | 2020-2022 | Phase 2, open-label, single-arm study | mUC | Avelumab | mOS: 10.0 months (95% CI: 5.5-14.5 months)<br>- 1-year survival rate: 43%<br>ORR<br>- Complete response: 8.5%<br>- Partial response: 15.5%<br>- Overal response rate (ORR): 24.0 |
| JAVELIN Bladder 100 (NCT02603432) | 2016-2024 | Phase 3, open label, randomized controlled trial | mUC | Arm A: avelumab maintenance<br>Arm B: BSC | OS:<br>- Avelumab group: 23.8 months (95% CI: 19.9-27.7)<br>- BSC group: 15.0 months (95% CI: 13.0-17.4)<br>- HR=0.69 (95% CI: 0.56-0.85, p<0.001)<br>- 2 years OS:<br>- Avelumab group: 54.3%<br>- BSC group: 39.8%<br>mPFS:<br>- Avelumab group: 5.5 months (95% CI: 4.6-6.2)<br>- BSC group: 2.2 months (95% CI: 2.1-3.2)<br>- HR=0.62 (95% CI: 0.52-0.75, p<0.0001)<br>ORR:<br>- Avelumab group: 25.6%<br>- BSC group: 10.3%<br>- p<0.001<br>DOR:<br>- Avelumab group: 20.2 months<br>- BSC group: 8.5 months<br>TRAEs:<br>- 47.4% of patients receiving avelumab experienced adverse events of any grade. Grade 3-4 adverse event rate: 12.9%<br>- Grade 3-4 adverse event rate in the BSC group: 6.3% |
| CheckMate 901 (NCT03036098) | 2017-2024 | Phase 3, open label, randomized controlled trial | mUC | Arm A: nivolumab+gemcitabine-cisplatin<br>Arm B: gemcitabine-cisplatin | OS:<br>- Nivolumab+gemcitabine-cisplatin arm: 21.7 months (95% CI: 18.6-26.4)<br>- Gemcitabine-cisplatin arm: 18.9 months (95% CI: 14.7-22.4)<br>- HR=0.78 (95% CI: 0.63-0.96, p=0.02)<br>PFS:<br>- Nivolumab+gemcitabin-sisplatin arm: 7.9 months (95% CI: 7.6-9.5)<br>- Gemcitabin-sisplatin arm: 7.6 months (95% CI: 6.1-7.8)<br>- HR=0.72 (95% CI: 0.59-0.88, p=0.001)<br>ORR:<br>- Nivolumab+gemcitabine-cisplatin arm: 57.6% (complete response: 21.7%, partial response: 35.9%)<br>- Gemcitabine-cisplatin arm: 43.1% (complete response: 11.8%, partial response: 31.2%)<br>- p<0.001<br>Grade 3-4 adverse event rate:<br>- Nivolumab+gemcitabine-cisplatin: 61.8%<br>- Gemcitabine-cisplatin: 51.7% |

**Table 4. Continued**

| Trial ID/name | Study period | Study design | cTNM | Study arm | Oncological outcomes |
|---|---|---|---|---|---|
| DANUBE (NCT02516241 | 2015-2020 | Phase 3, open label, randomized controlled trial | Unresectable, locally advanced or muc | Arm A: durvalumab monotherapy<br>Arm B: durvalumab+tremelimumab<br>arm c: standard chemotherapy | OS:<br>- Durvalumab monotherapy (patients with high PD-L1 expression): 14.4 months (95% CI: 10.4-17.3)<br>- Chemotherapy arm: 12.1 months (95% CI: 10.4-15.0)<br>- HR 0.89 (95% CI: 0.71-1.11, p=0.30)<br>- Durvalumab+tremelimumab arm: 15.1 months (95% CI: 13.1-18.0)<br>- Chemotherapy arm (all patients): 12.1 months (95% CI: 10.9-14.0)<br>- HR=0.85 (95% CI: 0.72-1.02, p=0.075)<br>PFS:<br>- Durvalumab monotherapy: 2.1 months<br>- Durvalumab+tremelimumab: 3.6 months<br>- Chemotherapy: 6.1months<br>ORR:<br>- Durvalumab monotherapy: 23.5%<br>- Durvalumab+tremelimumab: 31.5%<br>- Chemotherapy: 40.2%<br>Grade 3-4 adverse events rate:<br>- Durvalumab monotherapy: 14%<br>- Durvalumab+tremelimumab: 27%<br>- Chemotherapy: 60% |

MIBC: Muscle-invasive bladder cancer, mOS: Median overall survival, HR: Hazard ratio, TRAEs: Treatment-related adverse events, PD-L1: Programmed death-ligand 1, OS: Overall survival, TFLC: Total free light chains, DOR: Duration of response, ORR: Objective response rate, PFS: Progression-free survival, EV: enfortumab vedotin, BSC: Best supportive care

## Conclusion

Immunotherapy has become a key treatment option across the entire spectrum of bladder cancer, from non-invasive disease to metastatic stages. In particular, ICIs have demonstrated significant efficacy in both neoadjuvant and adjuvant settings, as well as in metastatic disease, either as monotherapy or in combination with CT and targeted therapies. However, critical challenges remain, including patient selection, biomarker-driven treatment strategies, resistance mechanisms, and immune-related adverse events. The integration of novel agents such as antibody-drug conjugates and oncolytic viruses into treatment protocols offers promising advancements in cancer therapy.

The integration of personalized immunotherapies into treatment algorithms will further refine therapeutic approaches. Future studies should focus on optimizing combination therapies, improving the identification of predictive biomarkers, and clarifying treatment sequencing. As the role of immunotherapy in bladder cancer continues to expand, a multidisciplinary approach is crucial for enhancing long-term patient outcomes.

### Ethics

### Footnotes

### Authorship Contributions

Surgical and Medical Practices: G.Ç., B.D., Concept: B.D., Design: G.Ç., Data Collection or Processing: G.Ç., Analysis or Interpretation: B.D., Literature Search: G.Ç., Writing: G.Ç., B.D.

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