

Current Status and Future Perspectives of Immunotherapies in Bladder Cancer

İD Gökhan Çolak, İD Bilgin Demir

Aydın Adnan Menderes University Faculty of Medicine, Department of Medical Oncology, Aydın, Türkiye

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

Address for Correspondence: Gökhan Çolak MD, PhD, Aydın Adnan Menderes University Faculty of Medicine, Department of Medical Oncology, Aydın, Türkiye

E-mail: drgokhancolak@gmail.com **ORCID ID:** orcid.org/0000-0002-3802-461X

Received: 05.03.2025 **Accepted:** 13.06.2025 **Epub:** 04.08.2025

Cite this article as: Çolak G, Demir B. Current status and future perspectives of immunotherapies in bladder cancer. Acta Haematol Oncol Turc. [Epub Ahead of Print]



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) Arm B: Reduced frequency BCG schedule (9 instillations)	The reduced frequency schedule was found to be inferior to the standard schedule for recurrence prevention. - Hazard ratio: 0.40 (with an upper 97.5% confidence interval of 0.68) 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: - cCR ratio (40.6%; 95% CI: 30.7-51.1) - Thirty-nine (41%) of 96 BCG-resistant CIS patients showed onset at 3 months of treatment. Secondary results: - Rate of serious treatment-related side effects: 8% - 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: - pCR rate at 6 months in CIS patients: 27% (20/74 patients) Secondary results: - Median response time: 17 month - In 56% of responding patients (95% CI: 34-77), the response was sustained through 12 months - 18-month event-free survival rate in Ta/T1 patients: 49% (95% CI: 38-60) - Twelve of 129 patients progressed to intramuscular invasive or metastatic disease - TRAEs, grade 3-5: 16% (26 patients) - 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. 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: - 1-year HGR-free survival rate: 39% (95% CI: 18-59) Secondary results: - 1 st , 3 rd , and 6 th month HGR-free survival rate: - 70% (95% CI: 45-85) - 1. months - 55% (95% CI: 31-74) - 3. months - 39% (95% CI: 18-59) - 6. months - 1-year bladder integrity preservation rate: 78% (95% CI, 57-89) - 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 Arm B: nivolumab+intravesical BCG combination Arm C: nivolumab in combination with other mesylate-based agents	Initial results show that nivolumab is well tolerated and safe. 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

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 $\geq 1\%$ (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: - pCR: 31% (in 27 of 88 patients) Secondary results: - 2 year DFS: 68% - 2 year OS: 77% - ctDNA positivity is associated with worse prognosis - Side effects were generally mild and manageable (grade 3-4 side effects: 12%)
NCT02989584	2016-Ongoing	Multicenter, single-arm, phase 2 clinical trial	cT2-4aN0M0	Atezolizumab+gemcitabine+cisplatin	Primary result: - pCR (<pT2N0): 69% (27/39 patients) - pCR rate: 41% (16/39 patients) Secondary results: - Patients with PD-L1 positive tumors: 100% showed <pT2N0 response. - 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: - 3 years EFS: 74.4% (95% CI: 67.8-81.7) - 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 Veya T1-4aN1M0	Arm A: pembrolizumab Arm B: standard surgery Arm C: enfortumab vedotin+pembrolizumab	The study is still ongoing.
AURA (Oncodistinct 004) (NCT03674424)	2018-2024	Multicenter, randomized, phase 2 clinical trial	T2-4aN0M0 Veya T1-4aN1M0	<u>Cohort 1: (cisplatin eligible)</u> Arm A: ddMVAC+avelumab Arm B: cisplatin-gemcitabine+avelumab <u>Cohort 2: (sispaltin ineligible)</u> Arm C: paclitaxel-gemcitabine+avelumab Arm D: avelumab monotherapy	ddMVAC + avelumab (ddMVAC-A): - 12 months DFS: 97% (95% CI: 83-100) - 36 months DFS: 77% (95% CI: 55-89) - 12 months OS: 95% (95% CI: 81-99) - 36 months OS: 87% (95% CI: 68-95) Cisplatin-gemcitabine+avelumab (CG-A): - 12 months DFS: 86% (95% CI: 70-94) - 36 months DFS: 68% (95% CI: 46-82) - 12 months OS: 84% (95% CI: 67-92) - 36 months OS: 61% (95% CI: 40-76) Paclitaxel-gemcitabine+avelumab (PG-A) (<u>sispaltin ineligible</u>): - 12 months DFS: 52% (95% CI: 32-69) - 36 months DFS: data is not yet mature - 12 months OS: 67% (95% CI: 46-81) - 36 months OS: data is not yet mature Avelumab monotherapy (A) (<u>sispaltin ineligible</u>): - 12 months DFS: 68% (95% CI: 47-82) - 36 months DFS: data is not yet mature - 12 months OS: 75% (95% CI: 55-87) - 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) Arm B: NAC+nivolumab 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: - pCR rate: 46% (11/24 patients) Secondary results: - pCR rate in PD-L1 positive patients: 67% - pCR rate in PD-L1 negative patients: 17% - After treatment, CD8+ T cell infiltration increased in the tumor microenvironment in 88% of patients. - irAEs: 30% grade 3-4 side effect - 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: - pCR rate: - ITT population: 24% (12/49 patients) - In patients undergoing radical cystectomy: 35% (12/34 patients) Secondary results: - cCR rate: 59% (clinical response was seen in 29 of 49 patients) - 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 Arm B: gemcitabine+cisplatin	Primary result: - pCR rate: 34% (Arm A) vs. 20% (Arm B) - EFS (36 months): EFS 68% (Arm A) vs. 54% (Arm B) Secondary results: - OS: 72% (Arm A) vs. 60% (Arm B) - TRAEs: grade 3-4 side effect rate 28% - In the durvalumab group, treatment was discontinued in 10 patients due to immune-mediated side effects. - 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 Arm B: ddMVAC+durvalumab Arm C: ddMVAC+durvalumab+tremelimumab	Primary result: - pCR rate: - ddMVAC (control groups): 30% - ddMVAC+durvalumab (ddMVAC+D): 45% - ddMVAC+durvalumab+tremelimumab (ddMVAC+D+T): 50% Secondary results: - DFS and OS results are monitored. - TRAEs (grade 3-4 side effect rate): - ddMVAC group: 22% - ddMVAC+Durvalumab group: 30% - 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 $\geq 1\%$ (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 $\geq 1\%$ 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 Arm B: placebo	ctDNA positive patients OS: - Atezolizumab vs. observation group: HR: 0.59 (95% CI: 0.42-0.83) ctDNA negative patients OS: 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 Arm B: placebo	DFS: pembrolizumab vs. observation group: - HR: 0.73 (95% CI: 0.59-0.90), $p=0.003$ - Median DFS: pembrolizumab 29.6 months (95% CI: 20.0-40.7) vs. observation 14.2 months (95% CI: 11.0-20.2) - OS: - Pembrolizumab vs. observation group: - HR: 0.98 (95% CI: 0.76-1.26) 3 years OS rate: pembrolizumab 60.8% (95% CI: 55.3-66.9) vs. observation 61.9% (95% CI: 56.5-67.9) DFS results according to PD-L1 expression: - PD-L1 positive patients: median DFS: 36.9 months vs. 21.0 months (HR: 0.81, 95% CI: 0.61-1.08) - 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 Arm B: placebo	DFS - Median DFS in the nivolumab arm: 20.8 months - Median DFS in placebo arm: 10.8 months - (HR: 0.70, $p<0.001$) DFS in PD-L1 positive patients: - Median DFS in the nivolumab arm: 22.0 months - Median DFS in placebo arm: 10.7 months - (HR: 0.55, $p<0.001$). Adverse effects: - Grade 3-4 adverse event rate in the nivolumab arm was 17.9% - The rate of grade 3-4 adverse events in the placebo arm was 7.2% - 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

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 Arm B: atezolizumab monotherapy Arm C: platinum-based chemotherapy	mOS: - Atezolizumab+chemotherapy group: 16.0 months (95% CI: 13.9-18.0) - Chemotherapy alone group: 13.4 months (95% CI: 12.0-15.3) - HR=0.85 (95% CI: 0.72-1.02, p=0.04) - Atezolizumab monotherapy: 15.7 months - 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 Arm B: chemotherapy (vinflunine or paclitaxel or docetaxel)	mOS: - Atezolizumab group: 11.1 months (95% CI: 9.1-13.1) - Chemotherapy group: 10.6 months (95% CI: 8.4-11.8) - HR=0.87 (95% CI: 0.73-1.02, p=0.07) In patients with high PD-L1 expression (IC2/3): - Atezolizumab: 11.1 months - Chemotherapy: 10.6 months - HR=0.95 (95% CI: 0.74-1.24) Treatment-related adverse events (TRAEs): - Any grade adverse event rate: - Atezolizumab: 60.9% - Chemotherapy: 90.2% Grade 3-4 adverse event rate: - Atezolizumab: 20.9% - 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). - 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). - Bellmunt risk factors (0, 1, 2-3) have a strong prognostic impact on survival. - 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 Arm B: chemotherapy	- 48 th month OS rate: Pembrolizumab 16.7%, Chemotherapy 10.1% - 48 th months PFS rate: Pembrolizumab 9.5%, Chemotherapy 2.7% -DOR: Pembrolizumab 29.7 months, Chemotherapy 4.4 months - 36 th months DOR rate: Pembrolizumab 44.4%, Chemotherapy 28.3%
KEYNOTE-052 (NCT02335424)	2015-2020	Phase 2, single-arm study	Cisplatin ineligible mUC	Pembrolizumab	- ORR: 28.9% (95% CI: 24.3-33.8) - DOR: 33.4 months - 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 Arm B: pembrolizumab+chemotherapy Arm C: chemotherapy	OS: - 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). - No significant difference was detected between pembrolizumab monotherapy and chemotherapy arms (HR: 0.91; 95% CI: 0.77-1.08). PFS: - 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). - 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 Arm B: platinum based chemotherapy	OS: - EV+P group: 31.5 months (95% CI: 25.3-not reached) - Chemotherapy group: 16.1 months (95% CI: 13.9-18.8) - HR=0.47 (95% CI: 0.38-0.58, p<0.0001) PFS - EV+P group: 12.5 months (95% CI: 10.4-15.0) - Chemotherapy group: 6.3 months (95% CI: 6.2-6.4) - HR=0.51 (95% CI: 0.41-0.62, p<0.0001) ORR - EV+P group: 67.9% (complete response: 29.1%, partial response: 38.8%) - Chemotherapy group: 44.9% (complete response: 12.4%, partial response: 32.5%) - p<0.0001
THOR (NCT03390504)	2018-2024	Phase 3, open-label, randomized controlled trial	mUC	Arm A: erdafitinib Arm B: pembrolizumab	OS: - Erdafitinib: 10.9 months (95% CI: 9.2-13.4) - Pembrolizumab: 11.1 months (95% CI: 8.9-14.3) - HR=1.18 (95% CI: 0.92-1.51, p=0.18) PFS - Erdafitinib: 4.4 months (95% CI: 3.6-5.3) - Pembrolizumab: 2.7 months (95% CI: 2.0-3.4) - HR=0.88 (95% CI: 0.70-1.10) ORR: - Erdafitinib: 40.0% (complete response: 7.5%, partial response: 32.5%) - Pembrolizumab: 21.6% (complete response: 5.7%, partial response: 15.9%) - 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) - 1-year survival rate: 43% ORR - Complete response: 8.5% - Partial response: 15.5% - Overall response rate (ORR): 24.0	
JAVELIN Bladder 100 (NCT02603432)	2016-2024	Phase 3, open label, randomized controlled trial	mUC	Arm A: avelumab maintenance Arm B: BSC	OS: - Avelumab group: 23.8 months (95% CI: 19.9-27.7) - BSC group: 15.0 months (95% CI: 13.0-17.4) - HR=0.69 (95% CI: 0.56-0.85, p<0.001) - 2 years OS: - Avelumab group: 54.3% - BSC group: 39.8% mPFS: - Avelumab group: 5.5 months (95% CI: 4.6-6.2) - BSC group: 2.2 months (95% CI: 2.1-3.2) - HR=0.62 (95% CI: 0.52-0.75, p<0.0001) ORR: - Avelumab group: 25.6% - BSC group: 10.3% - p<0.001 DOR: - Avelumab group: 20.2 months - BSC group: 8.5 months TRAEs: - 47.4% of patients receiving avelumab experienced adverse events of any grade. Grade 3-4 adverse event rate: 12.9% - 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 Arm B: gemcitabine-cisplatin	OS: - Nivolumab+gemcitabine-cisplatin arm: 21.7 months (95% CI: 18.6-26.4) - Gemcitabine-cisplatin arm: 18.9 months (95% CI: 14.7-22.4) - HR=0.78 (95% CI: 0.63-0.96, p=0.02) PFS: - Nivolumab+gemcitabine-cisplatin arm: 7.9 months (95% CI: 7.6-9.5) - Gemcitabine-cisplatin arm: 7.6 months (95% CI: 6.1-7.8) - HR=0.72 (95% CI: 0.59-0.88, p=0.001) ORR: - Nivolumab+gemcitabine-cisplatin arm: 57.6% (complete response: 21.7%, partial response: 35.9%) - Gemcitabine-cisplatin arm: 43.1% (complete response: 11.8%, partial response: 31.2%) - p<0.001 Grade 3-4 adverse event rate: - Nivolumab+gemcitabine-cisplatin: 61.8% - 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 Arm B: durvalumab+tremelimumab arm c: standard chemotherapy	OS: - Durvalumab monotherapy (patients with high PD-L1 expression): 14.4 months (95% CI: 10.4-17.3) - Chemotherapy arm: 12.1 months (95% CI: 10.4-15.0) - HR 0.89 (95% CI: 0.71-1.11, p=0.30) - Durvalumab+tremelimumab arm: 15.1 months (95% CI: 13.1-18.0) - Chemotherapy arm (all patients): 12.1 months (95% CI: 10.9-14.0) - HR=0.85 (95% CI: 0.72-1.02, p=0.075) PFS: - Durvalumab monotherapy: 2.1 months - Durvalumab+tremelimumab: 3.6 months - Chemotherapy: 6.1months ORR: - Durvalumab monotherapy: 23.5% - Durvalumab+tremelimumab: 31.5% - Chemotherapy: 40.2% Grade 3-4 adverse events rate: - Durvalumab monotherapy: 14% - Durvalumab+tremelimumab: 27% - 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.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. National Institutes of Health NCI. Cancer stat facts: bladder cancer [Internet]. 2022 [cited 2025 Mar 5]. Available from: <https://seer.cancer.gov/statfacts/html/urinb.html>
2. Jiang S, Redelman-Sidi G. BCG in bladder cancer immunotherapy. *Cancers (Basel)*. 2022;14:3073.
3. Deininger S, Törzsök P, Mitterberger M, et al. From interferon to checkpoint inhibition therapy-a systematic review of new immune-modulating agents in Bacillus Calmette-Guérin (BCG) refractory non-muscle-invasive bladder cancer (NMIBC). *Cancers (Basel)*. 2022;14:694.
4. Grimm MO, van der Heijden AG, Colombel M, et al. Treatment of high-grade non-muscle-invasive bladder carcinoma by standard number and dose of BCG instillations versus reduced number and standard dose of BCG instillations: results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". *Eur Urol*. 2020;78:690-698.
5. Gupta A, Verma S, Gupta S. Treatment strategies for BCG unresponsive non-muscle invasive bladder cancer. *Ann Urol Oncol*. 2024;7:97-109.

6. Pfai JL, Katims AB, Alerasool P, Sfakianos JP. Immunotherapy in non-muscle-invasive bladder cancer: current status and future directions. *World J Urol.* 2021;39:1319-1329.
7. Roviello G, Catalano M, Santi R, et al. Immune checkpoint inhibitors in urothelial bladder cancer: state of the art and future perspectives. *Cancers (Basel).* 2021;13:4411.
8. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *Lancet Oncol.* 2021;22:919-930.
9. Black PC, Tangen CM, Singh P, et al. Phase 2 trial of atezolizumab in *Bacillus Calmette-Guérin*-unresponsive high-risk non-muscle-invasive bladder cancer: SWOG S1605. *Eur Urol.* 2023;84:536-544.
10. Sekino Y, Ishikawa H, Kimura T, et al. Bladder preservation therapy in combination with atezolizumab and radiation therapy for invasive bladder cancer (BPT-ART) - A study protocol for an open-label, phase II, multicenter study. *Contemp Clin Trials Commun.* 2021;21:100724.
11. Fragkoulis C, Bamias A, Gavalas N, et al. Intravesical administration of durvalumab for high-risk non-muscle-invasive bladder cancer: a phase 2 study by the hellenic GU cancer group. *Eur Urol.* 2025;87:281-284.
12. Albisinni S, Martinez Chanza N, Aoun F, et al. Immune checkpoint inhibitors for BCG-resistant NMIBC: the dawn of a new era. *Minerva Urol Nephrol.* 2021;73:292-298.
13. Hugar LA, Gilbert SM, Sexton WJ, Kamat AM, Li R. Immunotherapy in *Bacillus Calmette-Guerin* (BCG) unresponsive nonmuscle invasive bladder cancer. *Curr Opin Urol.* 2021;31:160-169.
14. Jain RK, Sonpavde G. Neoadjuvant therapy for muscle-invasive bladder cancer. *Expert Rev Anticancer Ther.* 2020;20:603-614.
15. Peyrottes A, Ouzaid I, Califano G, Hermieu JF, Xylinas E. Neoadjuvant immunotherapy for muscle-invasive bladder cancer. *Medicina (Kaunas).* 2021;57:769.
16. Szabados B, Kockx M, Assaf ZJ, et al. Final results of neoadjuvant atezolizumab in cisplatin-ineligible patients with muscle-invasive urothelial cancer of the bladder. *Eur Urol.* 2022;82:212-222.
17. Funt SA, Lattanzi M, Whiting K, et al. Neoadjuvant atezolizumab with gemcitabine and cisplatin in patients with muscle-invasive bladder cancer: a multicenter, single-arm, phase II trial. *J Clin Oncol.* 2022;40:1312-1322.
18. Necchi A, Raggi D, Gallina A, et al. Updated results of PURE-01 with preliminary activity of neoadjuvant pembrolizumab in patients with muscle-invasive bladder carcinoma with variant histologies. *Eur Urol.* 2020;77:439-446.
19. Necchi A, Anichini A, Raggi D, et al. Pembrolizumab as neoadjuvant therapy before radical cystectomy in patients with muscle-invasive urothelial bladder carcinoma (PURE-01): an open-label, single-arm, phase II study. *J Clin Oncol.* 2018;36:3353-3360.
20. Basile G, Bandini M, Gibb EA, et al. Neoadjuvant pembrolizumab and radical cystectomy in patients with muscle-invasive urothelial bladder cancer: 3-year median follow-up update of PURE-01 trial. *Clin Cancer Res.* 2022;28:5107-5114.
21. Necchi A, Bedke J, Galsky MD, et al. Phase 3 KEYNOTE-905/EV-303: perioperative pembrolizumab (pembro) or pembro + enfortumab vedotin (EV) for muscle-invasive bladder cancer (MIBC). *Clin Oncol.* 2023;41(6 Suppl):TP5585-TP5585.
22. Blanc J, Carnot A, Barthelemy P, et al. Avelumab A as neoadjuvant therapy in patients (pts) with muscle-invasive urothelial carcinoma (MIUC): survival data of AURA trial, Oncodistinct 004. *Clin Oncol.* 2024;42(16 Suppl):4516.
23. van Dijk N, Gil-Jimenez A, Silina K, et al. Preoperative ipilimumab plus nivolumab in locoregionally advanced urothelial cancer: the NABUCCO trial. *Nat Med.* 2020;26:1839-1844.
24. Kim H, Jeong BC, Hong J, et al. Neoadjuvant nivolumab plus gemcitabine/cisplatin chemotherapy in muscle-invasive urothelial carcinoma of the bladder. *Cancer Res Treat.* 2023;55:636-642.
25. Sonpavde G, Necchi A, Gupta S, et al. A phase 3 randomized study of neoadjuvant chemotherapy (NAC) alone or in combination with nivolumab (NIVO) ± BMS-986205 in cisplatin-eligible muscle invasive bladder cancer (MIBC). *Clin Oncol.* 2019;37(15 Suppl):TP54587-TP54587.
26. Powles T, Catto JWF, Galsky MD, et al. Perioperative durvalumab with neoadjuvant chemotherapy in operable bladder cancer. *N Engl J Med.* 2024;391:1773-1786.
27. Thibault C, Audenet F, Borchiellini D, et al. NEMIO: a randomized phase II trial evaluating efficacy and safety of dose dense MVAC (ddMVAC) + durvalumab +/- tremelimumab as neoadjuvant treatment in patients with bladder muscle-invasive urothelial carcinoma. *Ann Oncol.* 2019;30:v400-401.
28. Alfred Witjes J, Max Bruins H, Carrión A, et al. European Association of Urology Guidelines on muscle-invasive and metastatic bladder cancer: summary of the 2023 guidelines. *Eur Urol.* 2024;85:17-31.
29. Seisen T, Jamzadeh A, Leow JJ, et al. Adjuvant chemotherapy vs observation for patients with adverse pathologic features at radical cystectomy previously treated with neoadjuvant chemotherapy. *JAMA Oncol.* 2018;4:225-229.
30. Powles T, Assaf ZJ, Degaonkar V, et al. Updated overall survival by circulating tumor DNA status from the phase 3 IMvigor010 trial: adjuvant atezolizumab versus observation in muscle-invasive urothelial carcinoma. *Eur Urol.* 2024;85:114-122.
31. Apolo AB, Ballman KV, Sonpavde G, et al. Adjuvant pembrolizumab versus observation in muscle-invasive urothelial carcinoma. *N Engl J Med.* 2025;392:45-55.
32. Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. *N Engl J Med.* 2021;384:2102-2114.
33. Galsky MD, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab in high-risk muscle-invasive urothelial carcinoma: expanded efficacy from CheckMate 274. *J Clin Oncol.* 2025;43:15-21.
34. Bamias A, Davis ID, Galsky MD, et al. Atezolizumab monotherapy versus chemotherapy in untreated locally advanced or metastatic urothelial carcinoma (IMvigor130): final overall survival analysis from a randomised, controlled, phase 3 study. *Lancet Oncol.* 2024;25:46-61.
35. van der Heijden MS, Loriot Y, Durán I, et al. Atezolizumab versus chemotherapy in patients with platinum-treated locally advanced or metastatic urothelial carcinoma: a long-term overall survival and safety update from the phase 3 IMvigor211 clinical trial. *Eur Urol.* 2021;80:7-11.
36. Balar AV, Castellano DE, Grivas P, et al. Efficacy and safety of pembrolizumab in metastatic urothelial carcinoma: results from KEYNOTE-045 and KEYNOTE-052 after up to 5 years of follow-up. *Ann Oncol.* 2023;34:289-299.
37. Powles T, Csösz T, Özgüroğlu M, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22:931-945.
38. Powles T, Valderrama BP, Gupta S, et al. Enfortumab vedotin and pembrolizumab in untreated advanced urothelial cancer. *N Engl J Med.* 2024;390:875-888.
39. Siefker-Radtke AO, Matsubara N, Park SH, et al. Erdafitinib versus pembrolizumab in pretreated patients with advanced or metastatic urothelial cancer with select FGFR alterations: cohort 2 of the randomized phase III THOR trial. *Ann Oncol.* 2024;35:107-117.
40. Iacovelli R, Ciccarese C, Brunelli M, et al. First-line avelumab for patients with PD-L1-positive metastatic or locally advanced urothelial cancer who are unfit for cisplatin. *Ann Oncol.* 2022;33:1179-1185.
41. Powles T, Park SH, Caserta C, et al. Avelumab first-line maintenance for advanced urothelial carcinoma: results from the JAVELIN bladder 100 trial after ≥2 years of follow-up. *J Clin Oncol.* 2023;41:3486-3492.
42. van der Heijden MS, Sonpavde G, Powles T, et al. Nivolumab plus gemcitabine-cisplatin in advanced urothelial carcinoma. *N Engl J Med.* 2023;389:1778-1789.
43. Powles T, van der Heijden MS, Castellano D, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. *Lancet Oncol.* 2020;21:1574-1588.