SAS Journal of Medicine
Abbreviated Key Title: SAS J Med
ISSN 2454-5112
Journal homepage: https://saspublishers.com

OPEN ACCESS

Urology

Neoadjuvant Immunotherapy in Muscle-Invasive Bladder Cancer: Current Evidence and Future Directions

Mohammed Amine ELAFARI[1*], Ayoub Mamad[1], Mohammed Amine Bibat[1], Amine Slaoui[1], Tariq Karmouni[1], Abdellatif Koutani[1], Khalid Elkadir[1]

[1]Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco

DOI: https://doi.org/10.36347/sasjm.2026.v12i04.015 | **Received:** 12.02.2026 | **Accepted:** 15.04.2026 | **Published:** 21.04.2026

***Corresponding author:** Mohammed Amine Elafari
Urology B Department, IBN SINA Hospital, University Hospital Center IBN SINA, University Mohammed V, Rabat, Morocco

Abstract **Review Article**

Muscle-invasive bladder cancer (MIBC) remains a significant oncological challenge, with approximately 50% of patients experiencing recurrence within 3 years despite standard neoadjuvant cisplatin-based chemotherapy and radical cystectomy. The integration of immune checkpoint inhibitors (ICIs) into the perioperative management of MIBC has transformed the treatment landscape. The landmark phase 3 NIAGARA trial demonstrated that perioperative durvalumab combined with neoadjuvant gemcitabine–cisplatin significantly improves event-free survival (EFS) and overall survival (OS) in cisplatin-eligible patients, leading to FDA approval and NCCN Category 1 preferred status. For cisplatin-ineligible patients, the phase 3 KEYNOTE-905 trial established perioperative enfortumab vedotin plus pembrolizumab as a new standard of care. Multiple phase 2 studies have further explored ICI monotherapy and chemoimmunotherapy combinations, with pooled pathological complete response (pCR) rates ranging from 24% to 43% depending on the strategy employed. Emerging biomarkers, including tumor mutational burden (TMB), PD-L1 expression, molecular subtypes, and circulating tumor DNA (ctDNA), hold promise for patient selection and response monitoring. This mini review synthesizes the current evidence supporting neoadjuvant immunotherapy in MIBC, discusses ongoing challenges, and highlights future directions.

Keywords: muscle-invasive bladder cancer, neoadjuvant immunotherapy, immune checkpoint inhibitors, durvalumab, pembrolizumab, enfortumab vedotin, perioperative therapy, biomarkers.

INTRODUCTION

Bladder cancer is the tenth most common malignancy worldwide, with approximately 25% of patients presenting with muscle-invasive disease (clinical stage ≥T2). The standard of care for operable MIBC has historically consisted of neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy with pelvic lymph node dissection[1-2]. Randomized trials and meta-analyses have demonstrated a survival benefit for cisplatin-based neoadjuvant chemotherapy, with dose-dense MVAC (ddMVAC) and gemcitabine–cisplatin (GC) being the most commonly used regimens [2]. However, despite this approach, recurrence rates remain high, and nearly half of patients with MIBC are ineligible for cisplatin-based chemotherapy due to renal impairment, poor performance status, hearing loss, or cardiac comorbidities [3].

The success of ICIs in metastatic urothelial carcinoma provided the rationale for investigating these agents in the perioperative setting. The hypothesis underlying neoadjuvant immunotherapy is that treatment will activate a systemic T-cell response to tumor antigens, enhancing the detection and elimination of micrometastatic disease beyond the resected primary tumor [4]. Over the past several years, a rapidly evolving body of evidence, from single-arm phase 2 studies to practice-changing phase 3 trials, has established immunotherapy as an integral component of perioperative MIBC management.

Neoadjuvant ICI Monotherapy

PURE-01 Trial (Pembrolizumab)

The PURE-01 study (NCT02736266) was among the first trials to evaluate neoadjuvant ICI monotherapy in MIBC. In this single-arm phase 2 trial, 155 patients with cT2–3bN0M0 MIBC received three cycles of pembrolizumab 200 mg prior to radical

cystectomy [5-6]. The pCR rate (ypT0N0) was 37% in the intention-to-treat population. At a median follow-up exceeding 60 months, the 5-year EFS rate was 68% and the 5-year OS rate was 77% [7]. Pathological response was strongly associated with long-term survival, with a 5-year OS rate of approximately 90% in patients achieving complete or major pathological response [7]. Importantly, PD-L1 combined positive score (CPS) was the strongest predictor of sustained response, with EFS significantly stratified among PD-L1 tertiles (lower: 59.7% vs. medium: 76.7% vs. higher: 89.8%; P = 0.0013) [5]. The claudin-low molecular subtype demonstrated the highest 5-year recurrence-free survival rate (93%) [7].

For cisplatin-ineligible patients within PURE-01, neoadjuvant pembrolizumab was associated with a higher pT0 rate (33% vs. 13%; P = 0.03) and prolonged OS compared with propensity-matched patients undergoing immediate radical cystectomy (HR 2.0 for IRC vs. NAP; 95% CI 1.1–3.89) [8].

ABACUS Trial (Atezolizumab)

The ABACUS trial (NCT02662309) evaluated two cycles of neoadjuvant atezolizumab in 95 cisplatin-ineligible or cisplatin-refusing patients with cT2–4aN0M0 MIBC [9-10]. The pCR rate was 31% (95% CI: 21–41%), with 2-year disease-free survival (DFS) of 68% and 2-year OS of 77% [9]. Notably, baseline PD-L1 and TMB did not correlate with relapse-free survival in this cohort. Instead, high baseline stromal CD8+ T-cell infiltration was significantly associated with improved RFS (HR 0.25; 95% CI: 0.09–0.68; P = 0.007). Serial ctDNA measurements were highly prognostic at all time points, with no relapses observed in patients who were ctDNA-negative at baseline and after neoadjuvant therapy [9].

Neoadjuvant Chemoimmunotherapy

Phase 2 Studies

Several phase 2 trials have evaluated the combination of ICIs with cisplatin-based chemotherapy in the neoadjuvant setting, consistently demonstrating higher pathological response rates compared with either modality alone.

The LCCC1520 trial (NCT02690558) assessed gemcitabine–cisplatin plus pembrolizumab in 39 patients with cT2–4aN0M0 MIBC [11-12]. The pathological downstaging rate was 56% (95% CI: 40–72%), and the pCR rate (pT0N0) was 36% (95% CI: 21–53%) [11]. The regimen was generally well tolerated, with the most common adverse events being cytopenias and hypomagnesemia.

The BLASST-1 trial (NCT03294304) evaluated nivolumab combined with gemcitabine–cisplatin in 41 patients, achieving a pathological downstaging rate of 65.8% and a pCR rate of 49% [13]. Molecular subtyping suggested that basal-type tumors (basal and claudin-low) responded more favorably to chemoimmunotherapy (PaR 73%) compared with luminal-type tumors (PaR 58%), a differential not observed with chemotherapy alone [13].

Neoadjuvant atezolizumab combined with gemcitabine–cisplatin was evaluated in a multicenter phase 2 trial (NCT02989584), demonstrating a downstaging rate of 69% and a pCR rate of 41% (pT0N0) [14].

The HCRN GU14-188 trial (NCT02365766) investigated pembrolizumab with chemotherapy in both cisplatin-eligible and cisplatin-ineligible cohorts. The pathological muscle-invasive response rate (≤ypT1N0) was 54% in cisplatin-eligible and 53% in cisplatin-ineligible patients, with ypT0 rates of 41% in both cohorts [15].

Meta-Analytic Evidence

Multiple systematic reviews and meta-analyses have synthesized the growing body of evidence. A comprehensive meta-analysis of 29 studies (33 treatment arms) reported an overall pooled pCR rate of 32.7% (95% CI: 27.7–37.7%) for neoadjuvant PD-(L)1 inhibitors across all strategies [16]. Subgroup analyses consistently demonstrated that chemoimmunotherapy achieves the highest pCR rates (39.2%; 95% CI: 32.1–46.3%), followed by dual checkpoint inhibition (27.6%; 95% CI: 15.5–39.6%) and ICI monotherapy (24.6%; 95% CI: 16.9–32.3%). The overall pathological partial response (pPR) rate was 45.3% (95% CI: 38.4–52.2%), and the downstaging rate was 62.9% (95% CI: 53.1–72.8%) [16].

A separate meta-analysis comparing neoadjuvant chemotherapy (NAC), neoadjuvant immunotherapy (NAI), and neoadjuvant chemoimmunotherapy (NACI) across 28 trials (2,138 patients) confirmed that NACI achieves significantly higher pCR (42.25%) and pathological downstaging (62.88%) rates compared with NAC (pCR 30.91%; downstaging 40.91%) and NAI alone (pCR 30.92%; downstaging 38.84%; P 0.05 for pCR; P 0.01 for downstaging) [17].

Grade ≥3 immune-related adverse events (irAEs) varied by strategy: 9.4% for ICI monotherapy, 24.9% for dual checkpoint inhibition, and 14.2% for chemoimmunotherapy. These findings indicate that chemoimmunotherapy provides the optimal balance of efficacy and tolerability [16].

Real-world data have corroborated these findings. A comparative study of 100 MIBC patients demonstrated significantly higher pCR rates with chemoimmunotherapy versus chemotherapy alone (48.3% vs. 25.4%; P = 0.034) and higher pathological downstaging rates (75.9% vs. 47.9%; P = 0.014), despite

the chemoimmunotherapy group having more advanced baseline disease [18].

Landmark Phase 3 Trials

NIAGARA Trial (Durvalumab + Gemcitabine–Cisplatin): Cisplatin-Eligible Patients

The NIAGARA trial (NCT03732677) represents the first phase 3 trial to demonstrate a survival benefit for perioperative immunotherapy in MIBC [1]. In this open-label, randomized trial, 1,063 cisplatin-eligible patients with cT2–T4aN0/1M0 MIBC were assigned 1:1 to receive neoadjuvant durvalumab plus gemcitabine–cisplatin for four cycles followed by radical cystectomy and adjuvant durvalumab for eight cycles (durvalumab group) or neoadjuvant gemcitabine–cisplatin followed by radical cystectomy alone (comparison group) [1].

The estimated 24-month EFS was 67.8% (95% CI: 63.6–71.7) in the durvalumab group versus 59.8% (95% CI: 55.4–64.0) in the comparison group (HR 0.68; 95% CI: 0.56–0.82; P 0.001). The estimated 24-month OS was 82.2% versus 75.2% (HR 0.75; 95% CI: 0.59–0.93; P = 0.01) [1]. The EFS benefit was broadly consistent across prespecified subgroups, including different ages, sexes, geographic regions, histologic subtypes, tumor stages, lymph node involvement, renal function levels, and PD-L1 expression levels. Importantly, the addition of neoadjuvant durvalumab did not reduce the proportion of patients undergoing radical cystectomy (88.0% vs. 83.2%). Grade 3–4 treatment-related adverse events were similar between groups (40.6% vs. 40.9%), and treatment-related deaths occurred in 0.6% in each group [1].

Based on these results, durvalumab received FDA approval in March 2025 for MIBC in the perioperative setting, and the NCCN Guidelines (v1.2026) list perioperative cisplatin/gemcitabine plus durvalumab as a Category 1 preferred perioperative/sandwich therapy option [2,19].

KEYNOTE-905 Trial (Enfortumab Vedotin + Pembrolizumab): Cisplatin-Ineligible Patients

The KEYNOTE-905 trial (NCT03924895) addressed the critical unmet need in cisplatin-ineligible patients with MIBC [3,20]. In this phase 3, open-label trial, 344 participants who were ineligible for or declined cisplatin-based chemotherapy were randomized to perioperative enfortumab vedotin (an antibody–drug conjugate targeting nectin-4) plus pembrolizumab with surgery or surgery alone [20].

At a median follow-up of 25.6 months, the estimated 2-year EFS was 74.7% in the enfortumab vedotin–pembrolizumab group versus 39.4% in the control group (HR 0.40; 95% CI: 0.28–0.57; P 0.001) [20]. The estimated 2-year OS was 79.7% versus 63.1% (HR 0.50; 95% CI: 0.33–0.74; P 0.001). The pCR rate was 57.1% versus 8.6% (estimated difference: 48.3 percentage points; 95% CI: 39.5–56.5; P 0.001) [20]. The treatment effect was consistent across most key subgroups, and the proportion of patients undergoing surgery was similar between groups (87.6% vs. 89.7%) [3,20].

Adverse events were more frequent in the enfortumab vedotin–pembrolizumab group (grade ≥3: 71.3%; grade ≥3 drug-related: 45.5%) compared with the control group (grade ≥3: 45.9%), consistent with the known safety profile of this combination [3,20]. Based on these results, the FDA approved neoadjuvant followed by adjuvant enfortumab vedotin plus pembrolizumab for cisplatin-ineligible MIBC, and the NCCN Guidelines (v1.2026) include this regimen as a preferred perioperative option for cisplatin-ineligible bladder cancer [2,3].

The key efficacy and survival data from these landmark studies are summarized in Table 1.

Table 1: Summary of Key Clinical Trials in Neoadjuvant Immunotherapy for MIBC

Trial	Phase	Population	Strategy	Regimen	Key Outcomes (pCR / EFS / OS)
NIAGARA	3	Cis-eligible	Chemo-ICI	Durvalumab + Gem/Cis	pCR: N/A; 24m EFS: 67.8%; 24m OS: 82.2%
KEYNOTE-905	3	Cis-ineligible	ADC + ICI	Enfortumab Vedotin + Pembrolizumab	pCR: 57.1%; 24m EFS: 74.7%; 24m OS: 79.7%
PURE-01	2	All	ICI Mono	Pembrolizumab	pCR: 37%; 5y EFS: 68%; 5y OS: 77%
ABACUS	2	Cis-ineligible	ICI Mono	Atezolizumab	pCR: 31%; 2y DFS: 68%; 2y OS: 77%
BLASST-1	2	Cis-eligible	Chemo-ICI	Nivolumab + Gem/Cis	pCR: 49%; Downstaging: 65.8%
LCCC1520	2	All	Chemo-ICI	Pembrolizumab + Gem/Cis	pCR: 36%; Downstaging: 56%
INDIBLADE	2	Stage II/III	Dual ICI + CRT	Ipilimumab + Nivolumab + Chemoradiotherapy	Bladder-intact EFS (2y): 78%; 2y OS: 96%

Biomarkers of Response

The identification of predictive biomarkers remains a critical area of investigation to optimize patient selection for neoadjuvant immunotherapy.

PD-L1 Expression

PD-L1 expression has shown variable predictive value across studies. In PURE-01, PD-L1 CPS was the strongest predictor of pCR and sustained EFS after neoadjuvant pembrolizumab monotherapy [5-6]. However, in chemoimmunotherapy trials (LCCC1520, GC + atezolizumab), PD-L1 positivity was not predictive of pathological downstaging [11,14,21]. In the NIAGARA trial, the EFS benefit of perioperative durvalumab was observed regardless of PD-L1 expression level [1]. These findings suggest that PD-L1 may be more relevant as a predictive biomarker for ICI monotherapy than for chemoimmunotherapy combinations.

Tumor Mutational Burden

TMB has emerged as a promising biomarker, particularly for ICI-containing regimens. In PURE-01, higher TMB was significantly associated with pCR, and a composite calculator incorporating TMB, CPS, and clinical T stage achieved a C-index of 0.77 for predicting pT0N0 response [22]. In the GC + atezolizumab trial, TMB was significantly higher in responders (median 16 mut/Mb) versus non-responders (median 10 mut/Mb; P 0.01) [21]. Comprehensive genomic profiling confirmed that TMB is the most reliable DNA biomarker for separating responders from non-responders to neoadjuvant pembrolizumab, with a 10 mut/Mb cutoff showing utility for excluding predicted non-responders. Notably, TMB was not predictive of response to neoadjuvant chemotherapy alone [23].

Molecular Subtypes

RNA-based molecular subtyping has revealed differential responses to neoadjuvant immunotherapy. In PURE-01, the claudin-low subtype demonstrated the best outcomes, with no recurrences at 2 years and a 5-year OS of 93% [6-7]. Basal subtypes with higher immune signature scores showed 100% 2-year progression-free survival after pembrolizumab [6]. In BLASST-1, basal-type tumors responded more favorably to chemoimmunotherapy compared with luminal-type tumors, a differential not observed with chemotherapy alone [13]. The Immune190 signature was significantly associated with pCR after pembrolizumab but not after chemotherapy, emphasizing the potential of RNA profiling for personalizing neoadjuvant therapy selection [6].

Circulating Tumor DNA

ctDNA has emerged as a highly promising dynamic biomarker for monitoring treatment response and guiding therapy decisions. In the ABACUS trial, ctDNA status was highly prognostic at all time points (baseline, post-neoadjuvant therapy, and post-surgery), with no relapses observed in ctDNA-negative patients at baseline and after neoadjuvant therapy [9]. In the INDIBLADE trial, absence of detectable ctDNA after induction immunotherapy was associated with bladder-intact EFS (HR 8.3; 95% CI: 1.38–50.36; P = 0.02) [24]. The NIAGARA trial investigators have noted that ctDNA may play a role in assisting treatment decisions in the future, with negative ctDNA status after neoadjuvant treatment appearing to be associated with reduced relapse risk [1].

Immune Microenvironment Features

Beyond individual biomarkers, comprehensive immune profiling has identified additional predictive features. Higher pre-treatment tumor PD-L1 and TIGIT RNA expression were associated with complete response to chemoimmunotherapy [12]. Interferon-γ and interferon-α response hallmark signatures were associated with pCR after pembrolizumab [6]. Conversely, TGF-β signaling and stromal factors have been linked to resistance [10,25]. In the NABUCCO study, high TMB and PD-L1 positivity were associated with response to ipilimumab plus nivolumab, while TGF-β expression was associated with non-response [25]. Plasma IL-9 has been identified as a potential early predictive biomarker of chemoimmunotherapy response [12].

Emerging Approaches and Bladder Preservation
Immunotherapy-Based Bladder Preservation

The high pathological response rates observed with neoadjuvant immunotherapy have raised the possibility of bladder preservation strategies. The INDIBLADE trial (NCT05200988) evaluated induction ipilimumab (3 mg/kg) plus nivolumab followed by chemoradiotherapy in 50 patients with stage II/III MIBC [24]. After a median follow-up of 28.7 months, the 2-year bladder-intact EFS was 78% (95% CI: 0.67–0.9; P 0.001), and the 2-year OS was 96%. Grade 3–4 immune-related adverse events occurred in 24% of patients, and grade 3–4 chemoradiotherapy-related adverse events occurred in 7% [24].

Novel Agents

The SunRISe-4 trial has evaluated TAR-200 (an intravesical gemcitabine-releasing device) plus cetrelimab (anti-PD-1) versus cetrelimab monotherapy as neoadjuvant therapy in cisplatin-ineligible MIBC patients, with interim results showing notable pCR rates [26]. The ongoing KEYNOTE-B15/EV-304 trial (NCT04700124) is evaluating perioperative enfortumab vedotin plus pembrolizumab versus neoadjuvant gemcitabine–cisplatin in cisplatin-eligible patients, which may further reshape the treatment paradigm [27].

Current Treatment Recommendations

While current clinical practice is rapidly evolving, a geographical divergence exists between major international guidelines, primarily reflecting different regulatory approval timelines. The NCCN

Guidelines (v1.2026) have proactively integrated the results of the NIAGARA and KEYNOTE-905 trials, establishing perioperative immunotherapy as a Category 1 preferred standard for both cisplatin-eligible and ineligible patients. In contrast, the EAU Guidelines (2026 update) maintain a more conservative stance; they continue to recommend neoadjuvant cisplatin-based chemotherapy alone as the gold standard (Level of Evidence 1A) for eligible patients, pending full EMA validation of the perioperative durvalumab regimen. For cisplatin-ineligible patients, while the NCCN now prioritizes the EV plus pembrolizumab combination, the EAU considers this an emerging standard, still emphasizing radical cystectomy or bladder-preserving trimodal therapy as the conventional benchmarks in the European setting [28].

Based on the accumulated evidence, the NCCN Guidelines (v1.2026) for MIBC recommend the following perioperative strategies:[2]

For cisplatin-eligible patients (Stage II–IIIA):

- Neoadjuvant cisplatin-based combination chemotherapy or perioperative/sandwich immunotherapy with neoadjuvant cisplatin-based combination chemotherapy followed by radical cystectomy (Category 1)
- Preferred perioperative regimen: Cisplatin/gemcitabine + durvalumab for 4 cycles prior to cystectomy, then durvalumab for 8 cycles after cystectomy (Category 1)

For cisplatin-ineligible patients:

- Perioperative enfortumab vedotin + pembrolizumab for 3 cycles prior to cystectomy, then enfortumab vedotin (6 cycles) + pembrolizumab (14 cycles) after cystectomy (preferred)

Adjuvant therapy following cystectomy:

- If perioperative durvalumab or enfortumab vedotin + pembrolizumab was given preoperatively, the same agent(s) should be continued postoperatively
- For patients with residual high-risk disease after neoadjuvant chemotherapy (ypT2–ypT4a or ypN+): nivolumab (Category 1, preferred) or pembrolizumab

Challenges and Future Directions

Several important questions remain in the field of neoadjuvant immunotherapy for MIBC:

1. Optimal treatment sequencing: The NIAGARA trial was designed to assess perioperative treatment in its totality and was not designed to separately assess the contribution of neoadjuvant versus adjuvant durvalumab. Determining the relative contribution of each phase remains an important research question [1].
2. Biomarker-guided therapy: While TMB, PD-L1, molecular subtypes, and ctDNA show promise, no single biomarker has been validated for routine clinical use in selecting patients for neoadjuvant immunotherapy. Composite biomarker models and ctDNA-guided strategies represent promising approaches for personalized therapy [9,22].
3. De-escalation strategies: The sustained survival outcomes observed with neoadjuvant pembrolizumab monotherapy in PURE-01 (5-year OS 77%) support further investigation of single-agent immunotherapy as a potential de-escalation strategy in selected patients, particularly those with favorable biomarker profiles [7].
4. Cisplatin-ineligible population: The KEYNOTE-905 results have transformed the landscape for cisplatin-ineligible patients, but the higher toxicity profile (grade ≥3: 71.3%) warrants careful patient selection and monitoring [20].
5. Bladder preservation: Immunotherapy-based bladder preservation strategies, as demonstrated in the INDIBLADE trial, offer promising alternatives to radical cystectomy and warrant further investigation in larger randomized trials [24].

CONCLUSION

Neoadjuvant immunotherapy has fundamentally transformed the management of MIBC. The NIAGARA trial has established perioperative durvalumab with neoadjuvant gemcitabine–cisplatin as a new standard of care for cisplatin-eligible patients, while the KEYNOTE-905 trial has provided the first effective perioperative systemic therapy option for cisplatin-ineligible patients. Phase 2 studies have demonstrated that both ICI monotherapy and chemoimmunotherapy achieve meaningful pathological response rates with acceptable safety profiles. The integration of biomarker-guided strategies, including ctDNA monitoring and molecular subtyping, holds promise for further personalizing treatment selection. As ongoing phase 3 trials continue to mature and novel combinations are explored, the perioperative immunotherapy landscape in MIBC will continue to evolve, with the ultimate goal of improving long-term survival while preserving quality of life.

DECLARATION

Conflicts of Interest: The authors declare that they have no competing interests.

Sources of Funding: There are no funding sources to be declared.

Guarantor of Submission: The corresponding author is the guarantor of submission.

Acknowledgements: None.

Availability of Data and Materials: Supporting material is available if further analysis is needed.

Provenance and Peer Review: Not commissioned, externally peer-reviewed.

REFERENCES

1. Powles T, Catto JWF, Galsky MD, *et al.,* Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. N Engl J Med. 2024 ;391(19):1773-1786. doi :10.1056/NEJMoa2408154.
2. National Comprehensive Cancer Network. Bladder Cancer (Version 1.2026). NCCN Guidelines. Updated 2026 Mar 16.
3. Vulsteke C, Adra N, Danchaivijitr P, *et al.,* Perioperative Enfortumab Vedotin and Pembrolizumab in Bladder Cancer. N Engl J Med. 2026 ;394(13):1257-1269. doi :10.1056/NEJMoa2511674.
4. Necchi A, Faltas BM, Slovin SF, *et al.,* Immunotherapy in the Treatment of Localized Genitourinary Cancers. JAMA Oncol. 2023 ;9(10):1447-1454. doi :10.1001/jamaoncol.2023.2174.
5. 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(23):5107-5114. doi: 10.1158/1078-0432.CCR-22-2158.
6. Necchi A, Raggi D, Gallina A, *et al.,* Impact of Molecular Subtyping and Immune Infiltration on Pathological Response and Outcome Following Neoadjuvant Pembrolizumab in Muscle-Invasive Bladder Cancer. Eur Urol. 2020 ;77(6):701-710. doi: 10.1016/j.eururo.2020.02.028.
7. Tateo V, Basile G, Giannatempo P, *et al.,* updated 5-Year Survival Results From PURE-01, a Phase 2 Study of Neoadjuvant Pembrolizumab Followed by Radical Cystectomy in Patients with Muscle-Invasive Bladder Cancer. Eur Urol. 2026 ; S0302-2838(26)00022-9. doi: 10.1016/j.eururo.2026.01.015.
8. Rose K, Bandini M, Huelster H, *et al.,* Neoadjuvant pembrolizumab for cisplatin-ineligible muscle-invasive bladder cancer prior to radical cystectomy. J Clin Oncol. 2023 ;41(Suppl 6):513. doi: 10.1200/JCO.2023.41.6_suppl.513.
9. 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(2):212-222. doi: 10.1016/j.eururo.2022.04.013.
10. Powles T, Kockx M, Rodriguez-Vida A, *et al.,* Clinical Efficacy and Biomarker Analysis of Neoadjuvant Atezolizumab in Operable Urothelial Carcinoma in the ABACUS Trial. Nat Med. 2019 ;25(11):1706-1714. doi :10.1038/s41591-019-0628-7.
11. Rose TL, Harrison MR, Deal AM, *et al.,* Phase II Study of Gemcitabine and Split-Dose Cisplatin Plus Pembrolizumab as Neoadjuvant Therapy Before Radical Cystectomy in Patients with Muscle-Invasive Bladder Cancer. J Clin Oncol. 2021 ;39(28):3140-3148. doi :10.1200/JCO.21.01003.
12. Beckabir W, Zhou M, Lee JS, *et al.,* Immune Features Are Associated with Response to Neoadjuvant Chemo-Immunotherapy for Muscle-Invasive Bladder Cancer. Nat Commun. 2024 ;15(1):4448. doi :10.1038/s41467-024-48480-1.
13. Gupta S, Gibb E, Sonpavde G, *et al.,* Biomarker analysis and updated clinical follow-up from BLASST-1 (Bladder Cancer Signal Seeking Trial) of nivolumab, gemcitabine, and cisplatin in patients with muscle-invasive bladder cancer (MIBC). J Clin Oncol. 2022 ;40(Suppl 6):528. doi: 10.1200/JCO.2022.40.6_suppl.528.
14. 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(12):1312-1322. doi :10.1200/JCO.21.01485.
15. Brown J, Kaimakliotis H, Kelly W, *et al.,* HCRN GU14-188: Phase Ib/II study of neoadjuvant pembrolizumab and chemotherapy for T2-4aN0M0 urothelial cancer. J Clin Oncol. 2023 ;41(Suppl 6):448. doi: 10.1200/JCO.2023.41.6_suppl.448.
16. Hu L, Hu JW, Wang CQ, Li RY, Li S. Neoadjuvant PD-1/PD-L1 Inhibitors for Muscle-Invasive Bladder Cancer: A Meta-Analysis. Clin Genitourin Cancer. 2025 ;23(5):102408. doi: 10.1016/j.clgc.2025.102408.
17. Ayaz A, Naqvi S, Tripathi N, *et al.,* Pathologic response with neoadjuvant chemotherapy, immunotherapy, and chemo-immunotherapy for muscle-invasive bladder cancer (MIBC): A systematic review and meta-analysis. J Clin Oncol. 2023 ;41(Suppl 6):531. doi: 10.1200/JCO.2023.41.6_suppl.531.
18. Ding X, Liu C, Li X, *et al.,* Real-World Comparison of Neoadjuvant Chemoimmunotherapy and Chemotherapy in Muscle-Invasive Bladder Cancer. Sci Rep. 2025 ;15(1):17588. doi :10.1038/s41598-025-99889-7.
19. FDA Orange Book. FDA Orange Book Database. 2025.
20. Vulsteke C, Adra N, Danchaivijitr P, *et al.,* Perioperative Enfortumab Vedotin and Pembrolizumab in Bladder Cancer. N Engl J Med. 2026 ;394(13):1257-1269. doi :10.1056/NEJMoa2511674.
21. Lattanzi M, Solovyov A, Lihm J, *et al.,*Biomarkers of response to neoadjuvant atezolizumab with gemcitabine and cisplatin in muscle-invasive bladder cancer. J Clin Oncol. 2022 ;40(Suppl

16):4584. doi: 10.1200/JCO.2022.40.16_suppl.4584.

22. Bandini M, Ross JS, Raggi D, *et al.,*Predicting the Pathologic Complete Response After Neoadjuvant Pembrolizumab in Muscle-Invasive Bladder Cancer. J Natl Cancer Inst. 2021 ;113(1):48-53. doi :10.1093/jnci/djaa076.
23. Mercinelli C, Raggi D, Cigliola A, *et al.,* Comprehensive genomic profiling (CGP) of clinical T2-4N0M0 muscle-invasive bladder cancer (MIBC) treated with neoadjuvant pembrolizumab or cisplatin-based chemotherapy before radical cystectomy (RC). J Clin Oncol. 2024 ;42(Suppl 4):653. doi: 10.1200/JCO.2024.42.4_suppl.653.
24. Mellema JJ, Stockem CF, Herberts C, *et al.,* Ipilimumab and Nivolumab Followed by Chemoradiotherapy as Bladder-Sparing Treatment in Muscle-Invasive Bladder Cancer : A Phase 2 Trial. Nat Med. 2026. doi:10.1038/s41591-026-04271-3.
25. Stockem CF, Gil-Jimenez A, Ali H, *et al.,* Biomarker Analysis and Treatment Dynamics Following Preoperative Ipilimumab Plus Nivolumab in Locally Advanced Urothelial Cancer from the Phase 1B NABUCCO Study. Clin Cancer Res. 2025. doi: 10.1158/1078-0432.CCR-25-0419.
26. Necchi A, Guerrero-Ramos F, Crispen PL, *et al.,* TAR-200 Plus Cetrelimab Versus Cetrelimab Monotherapy as Neoadjuvant Therapy in Patients with Muscle-Invasive Bladder Cancer Who Are Ineligible for or Decline Neoadjuvant Cisplatin-Based Chemotherapy (SunRISe-4): Interim Analysis of a Randomised, Open-Label Phase 2 Trial. Lancet Oncol. 2025 ;26(10):1312-1322. doi :10.1016/S1470-2045(25)00358-4.
27. Hoimes C, Bedke J, Loriot Y, *et al.,* KEYNOTE-B15/EV-304: Randomized phase 3 study of perioperative enfortumab vedotin plus pembrolizumab versus chemotherapy in cisplatin-eligible patients with muscle-invasive bladder cancer (MIBC). J Clin Oncol. 2021 ;39(Suppl 15): TPS4587. doi: 10.1200/JCO.2021.39.15_suppl.TPS4587.
28. Witjes JA, Bruins HM, Cathomas R, *et al.,* EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. European Association of Urology. Updated 2026 Mar 25. Available from: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer.