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Evolving Therapeutic Paradigms in Bladder Cancer: The Impact of Immunotherapy and Antibody-Drug Conjugates

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Abstract

Bladder cancer is a significant global health challenge. Despite advances in surgery and platinum-based chemotherapy over the decades, limited improvements in clinical outcomes have been observed. However, recent years have witnessed the development of immune checkpoint inhibitors (ICIs) and antibody-drug conjugates (ADCs) that has transformed the therapeutic landscape of bladder cancer across different disease stages. ICIs block inhibitory pathways including PD-1/PD-L1 and CTLA-4 and reawake antitumor immunity, whereas ADCs, the combination of tumor-selective antibodies with potent cytotoxic payloads, ensure targeted cancer cell death with less systemic toxicity. Both therapies have exhibited clinical benefit in bladder cancer individually and in combination. Clinical trials including NIAGARA, CheckMate-274, and EV-302, have defined new perioperative and first-line standards based on ICIs and ADCs. Ongoing advancements in HER2-, Trop-2-, and Nectin-4-directed ADCs, bispecific and small-molecule conjugates, and combination with ICIs are revolutionizing the therapeutic options for bladder cancer. Of note, the combination of an ADC, enfortumab vedotin, with ICI, pembrolizumab, has improved survival in advanced disease scenarios in bladder cancer. Resistance against ICIs and ADCs remains a significant challenge, but identifying predictive biomarkers, integrating molecular profiling with these therapies, and developing effective combination strategies hold strong potential to achieve durable, precise, and personalized treatment outcomes for bladder cancer.

Key words bladder cancer, immunotherapy, immune checkpoint inhibitors, antibody-drug conjugate, combination therapy

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Introduction

Bladder cancer is among common malignancies worldwide, accounting for nearly 600,000 diagnoses annually and about 200,000 deaths each year [1, 2]. Bladder cancer primarily affects older adults, with a median age at diagnosis of 73, and exhibits well-established associations with cigarette smoking, chronic bladder irritation, and occupational exposures [3]. With population aging and continued exposure to carcinogens such as industrial chemicals, the global incidence is projected to approach one million new cases per year by 2040 [4]. Urothelial carcinoma constitutes about 90% of all bladder cancers. These tumors are classified based on the depth of invasion into non-muscle-invasive, muscle-invasive, or metastatic categories [5]. The remaining subtypes of bladder cancer include histologic variants such as squamous cell carcinoma, adenocarcinoma, and small-cell carcinoma [6]. The prognosis of bladder cancer is closely tied to tumor stage. Non-muscle-invasive bladder cancer is typically managed with transurethral resection followed by intravesical therapy. Muscle-invasive disease or the presence of distant metastases is associated with significantly poorer clinical outcomes [7]. Conventional regimens, such as gemcitabine with cisplatin (GC) or methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), typically achieve median overall survival of 14-15 months [8]. Platinum-based chemotherapy has been the cornerstone of treatment for advanced disease for decades [8]. Up to 30-50% of patients are not eligible for cisplatin-based treatment due to renal impairment or poor performance status, limiting access to these therapies and underscoring the need for novel therapeutic strategies [9, 10].

Over the past decade, the therapeutic management of bladder cancer has transformed by the introduction of immune checkpoint inhibitors (ICIs). Leveraging the intrinsic immunogenicity, ICIs restore antitumor immune responses and have become standard treatments across multiple cancer types including bladder cancer [11]. Antibody-drug conjugates (ADCs) have entered clinical practice as well, offering a targeted cytotoxic approach that links tumor-specific antibodies with potent chemotherapeutic payloads to induce cancer cell apoptosis while minimizing systemic toxicity [12]. Together, ICIs and ADCs are redefining the bladder cancer management strategies. Combination regimens such as enfortumab vedotin (an ADC) plus pembrolizumab (an ICI) have demonstrated remarkable efficacy in advanced bladder cancer, achieving response rates of approximately 68% and one-year survival near 79%, exceeding traditional chemotherapy outcomes substantially [13]. Thus, immunotherapy and ADCs represent highly promising therapeutic approaches for patients with bladder cancer.

In this review, we discuss the evolving therapeutic landscape of bladder cancer, emphasizing the integration of both immunotherapy and ADCs into current clinical treatment paradigms. Furthermore, we explore the combination strategies that merge the two modalities, highlighting their potential to define the next generation of personalized therapy for bladder cancer.

Mechanistic basis of immunotherapy and ADCs

Human immune system is primed to recognize and eradicate cancer cells. However, tumors often evade this surveillance by activating inhibitory immune checkpoints. ICIs counteract these mechanisms by restoring cytotoxic immune activity in the tumor microenvironment. The cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and programmed death-1/programmed death-ligand 1 (PD-1/PD-L1) axes are the two crucial pathways mainly involved and therapeutically targeted in this regard [14]. The CTLA-4 pathway play crucial role in T-cell activation during their priming within the lymphoid tissues. CTLA-4 competes with CD28 for B7 ligands on antigen-presenting cells, thereby leading to limited immune activation. Antibodies such as ipilimumab and tremelimumab inhibit this interaction, promoting T-cell expansion and enhanced antitumor activity [15]. PD-1, expressed on activated T cells, binds to its ligands PD-L1 or PD-L2 on tumor or immune cells, leading to T-cell exhaustion and reduced cytokine production [16]. Monoclonal antibodies including avelumab, atezolizumab, and durvalumab (anti-PD-L1) and nivolumab, and pembrolizumab (anti-PD-1) promote tumor cell death by reactivate exhausted T cells [16]. Dual blockade of CTLA-4 and PD-1/PD-L1 has shown additive effect in several cancers, including bladder cancer [17]. Despite this, predictive biomarkers for checkpoint therapy remain imperfect. PD-L1 expression alone is an imperfect biomarker of response due to assay variability, dynamic expression, and intratumoral heterogeneity, warranting further investigation to define the biomarkers of response [18]. Tumor mutational burden, PD-L1 expression, and molecular subtypes such as luminal and basal/squamous provide some insight but lack sufficient reproducibility for clinical decision-making [19, 20]. Alternative indicators, such as tumor-infiltrating lymphocytes, interferon-related gene signatures, and gut microbiome composition are being explored to refine patient selection in bladder cancer [21]. Overall, ICI-based immunotherapies has garnered much appraisal for their efficacy in delivering targeted cancer cell eradication.

ADCs belong to a distinct precision-based strategy for targeted cytotoxic drug delivery. Mechanistically, ADC integrates three components: a monoclonal antibody directed against a tumor-specific antigen, a potent cytotoxic payload, and a linker connecting the two [22]. The antibody component ensures tumor selectivity, while the payload, commonly a microtubule inhibitor such as monomethyl auristatin E (MMAE) or a topoisomerase I inhibitor such as SN-38, provides highly potent cell-killing activity at nanomolar concentrations [23]. Cleavable linkers respond to tumor-specific conditions, such as acidic pH or lysosomal enzymes, while non-cleavable linkers release the payload only after antibody degradation within the cell [24, 25]. Upon antigen binding, the ADC-antigen complex is internalized, and intracellular linker cleavage releases the active drug, which induces apoptotic death primarily through DNA damage or microtubule disruption [26]. Some ADCs also exhibit a "bystander effect," in which membrane-permeable payloads diffuse inside the neighboring tumor cells, eradicating antigen-negative cells as well within the heterogeneous tumors [27]. The antibody moiety can also trigger immune effector functions such as antibody-dependent cellular cytotoxicity, further amplifying the therapeutic response [28]. Overall, ICIs and ADCs employ complementary mechanisms, one reawakening the immune surveillance, and the other delivering precise cytotoxic attack, marking both classes as essential pillars in the field of modern cancer therapeutics (**Figure 1**).

Immunotherapy as an emerging therapeutic strategy in bladder cancer

Immunotherapy has profoundly reshaped the management of bladder cancer over the past few years, extending its impact from metastatic disease into perioperative and organ-preserving settings. The introduction of ICIs has enabled durable disease control for various subsets of patients. NIAGARA phase III trial evaluated perioperative durvalumab combined with standard cisplatin-based chemotherapy in more than 500 patients with resectable, muscle-invasive disease [29]. This regimen improved the event-free survival significantly with a complete pathological response rate of 37% compared with 27% in the chemotherapy-alone arm. Survival at two years reached 82% versus 75% for control, establishing durvalumab as a new benchmark for perioperative integration. A

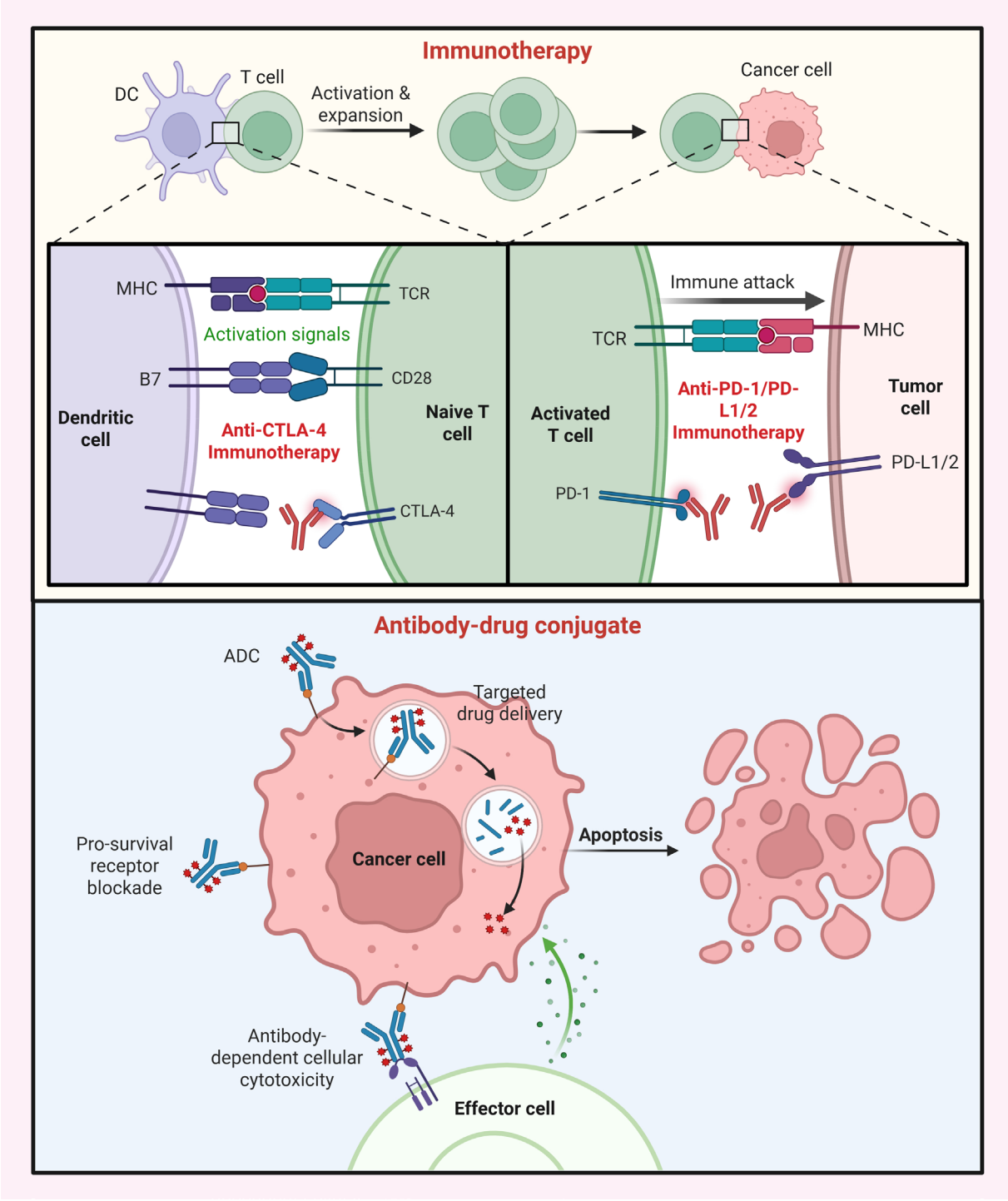

Figure 1. Mechanistic basis of immunotherapy and ADCs. (Top) Immunotherapy (ICIs) restore antitumor T-cell activity by blocking inhibitory pathways exploited by tumors. Anti-CTLA-4 antibodies enhance T-cell priming by preventing CTLA-4-mediated suppression, while anti-PD-1/PD-L1/2 antibodies reinvigorate exhausted T cells in the tumor microenvironment, promoting immune cell-driven tumor cell destruction. (Bottom) ADCs combine a tumor-targeting antibody with a cytotoxic payload linked by a cleavable or non-cleavable linker. Following antigen binding and internalization, the payload is released to induce apoptosis, while additional mechanisms such as antibody-dependent cellular cytotoxicity may further enhance tumor cell killing.

complementary circulating tumor DNA (ctDNA) analysis found that ctDNA clearance was more frequent in the durvalumab arm, and that patients remaining ctDNA-positive before surgery rarely achieved a complete response [30]. These results strongly support combining PD-L1 blockade with neoadjuvant chemotherapy for cisplatin-eligible patients. Several ongoing studies are extending this approach. KEYNOTE-866 is testing pembrolizumab with GC, and ENERGIZE explores nivolumab with linrodostat in the

neoadjuvant phase [31, 32]. For patients unable to tolerate cisplatin, alternative strategies have emerged. The NURE-COMBO trial combined nab-paclitaxel with perioperative nivolumab, achieving a 32% complete response rate and tumor downstaging in over two-thirds of participants, with one-year event-free survival close to 90% [33]. Similarly, the RAD-VACCINE trial is investigating neoadjuvant sasanlimab with stereotactic body radiotherapy, aiming to elicit immune priming in cisplatin-ineligible patients [34]. Overall, these studies will eventually help to establish the effective neoadjuvant programs for patients ineligible for standard cisplatin-based regimens.

On the adjuvant therapy frontier, CheckMate-274 established nivolumab as key option for high-risk muscle-invasive bladder cancer following cystectomy [35]. Pateints on adjuvant nivolumab exhibited almost double median disease-free survival time compared with those on placebo, and updated results reported a median overall survival of nearly 70 months in the treatment arm versus around 50 months in controls [36]. The benefit was observed across subgroups, regardless of nodal involvement or prior chemotherapy. In the CheckMate-032 trial, the nivolumab-ipilimumab combination has been shown to yield higher response rates than nivolumab monotherapy, particularly with optimized dosing schedules [37]. Building on these, the MODERN trial employs ctDNA-guided escalation with nivolumab plus relatlimab for ctDNA-positive cases, while ctDNA-negative patients undergo immunotherapy or surveillance depending on biomarker status [38]. Retrospective analyses of IMvigor010 trial of adjuvant atezolizumab suggested survival improvement in patients with detectable ctDNA, prompting the IMvigor011 study to prospectively evaluate adjuvant atezolizumab in this biomarker-defined population [39, 40]. This evolving ctDNA-based framework may aid in personalizing adjuvant immunotherapy by distinguishing patients who need additional systemic treatment from those who do not.

Intravesical and vaccine-based immunotherapies are also being explored. The SunRISe-4 trial examined TAR-200, a gemcitabine-releasing intravesical device, combined with the PD-1 inhibitor cetrelimab in cisplatin-ineligible patients. The combination produced a 42% complete pathological response rate compared with 23% with cetrelimab alone [41]. On the same lines, the CORE-002 trial investigated the oncolytic adenovirus CG0070 (armed with GM-CSF) plus nivolumab, achieving a 42% complete response rate and one-year recurrence-free survival exceeding 70% [42]. Another line of investigation involves cytokine modulation: the phase III PIVOT IO 009 trial evaluates nivolumab with bempegaldesleukin (an IL-2 agonist) as neoadjuvant and adjuvant therapy for cisplatin-ineligible patients [43]. For advanced disease, the CheckMate-901 trial confirmed that adding nivolumab to first-line gemcitabine-cisplatin improved both progression-free and overall survival compared with chemotherapy alone, reinforcing the role of chemo-immunotherapy in cisplatin-eligible patients [44]. Meanwhile, the KEYMAKER-U04 platform study is examining pembrolizumab with the LAG-3 inhibitor favezelimab in previously untreated metastatic disease. Personalized vaccine strategies are also emerging. In a pilot study, a neoantigen-based mRNA vaccine (PGV001) given with atezolizumab prevented metastatic recurrence in three of four treated patients with high-risk disease [45]. The V940 (mRNA-4157) vaccine encoding patient-specific neoantigens is being tested with pembrolizumab ± enfortumab vedotin in the perioperative setting [46]. Another personalized mRNA construct, autogene cevumeran, is under evaluation alone or with nivolumab for high-risk adjuvant therapy in resected disease.

Beyond systemic treatment, bladder-preserving approaches incorporating immunotherapy are gaining attention. A multicenter phase II study combining gemcitabine, pembrolizumab, and hypofractionated radiotherapy achieved a two-year bladder-intact disease-free survival of 71% and overall survival of 83% [47]. The IMMUNOPRESERVE trial tested durvalumab plus tremelimumab with radiotherapy in patients unwilling or ineligible for cystectomy, resulting in an 81% complete response rate and 2-year survival above 80% [48]. Similarly, interim analysis from another phase II study combining chemoradiation with nivolumab showed superior two-year relapse-free survival compared to chemoradiation alone [49]. Phase III programs, INTACT (atezolizumab with chemoradiation) and KEYNOTE-992 (pembrolizumab with chemoradiation), have both completed accrual, with results anticipated soon [50, 51]. Collectively, immunotherapy has evolved from a salvage option to a foundation of multimodal bladder cancer management (**Table 1**). It now spans neoadjuvant, adjuvant, intravesical, and organ-sparing applications. Integration with ctDNA monitoring, radiotherapy, and novel agents continues to expand its utility, bringing the field closer to individualized, biomarker-guided immuno-oncology for bladder cancer.

ADCs in the treatment landscape of bladder cancer

ADCs have rapidly become a cornerstone in the modern treatment of bladder cancer, expanding therapeutic possibilities beyond chemotherapy and immunotherapy. By coupling tumor-specific antibodies with potent cytotoxic payloads, ADCs achieve targeted tumor cell destruction while limiting systemic toxicity [52]. Several ADCs directed against HER2, Nectin-4, and Trop-2 have now demonstrated meaningful efficacy in both pretreated and treatment-naïve settings, and are being tested to redefine therapeutic regimens in bladder cancer (**Table 2**) [53]. Among HER2-directed agents, trastuzumab deruxtecan (T-DXd) has emerged as a pivotal molecule, earning tumor-agnostic approval following the DESTINY-PanTumor02 trial [54]. In patients with HER2 over-expression, T-DXd monotherapy after prior systemic therapy achieved 39% objective response rate and a median progression-free survival of 7 months [55]. Leveraging a high drug-to-antibody ratio and a topoisomerase-I payload, T-DXd offers potent cytotoxicity even in tumors with heterogeneous HER2 expression [55]. HER2-targeting ADC, disitamab vedotin, has also shown consistent benefit across multiple trials [56]. Pooled results from the RC48-C005 and RC48-C009 studies reported an overall response rate of about 50%, median progression-free survival of 6 months, and overall survival near 14 months in previously treated HER2-positive disease [57]. Toxicities, including neuropathy, alopecia, and cytopenias, were common but manageable with supportive care. Combination regimens have proven particularly promising. In the RC48-C014 trial, disitamab vedotin plus the PD-1 inhibitor toripalimab produced a 75% response rate and extended overall survival to over 33 months in cisplatin-ineligible patients [58]. Data from RC48-G001 has also shown that disitamab vedotin with pembrolizumab achieves response rates exceeding 60% in treatment-naïve HER2-expressing disease, with even higher activity among HER2-low subgroups [59]. Two pivotal phase III trials, DV-001 and RC48-C016, are now comparing disitamab vedotin -based combinations to platinum chemotherapy in the first-line setting and have reported positive survival outcomes in preliminary analyses, suggesting disitamab vedotin could become a front-line competitor to enfortumab vedotin-based regimens.

ADC named enfortumab vedotin, which targets Nectin-4, has exhibited another transformative finding in advanced bladder cancer. In the phase III EV-302 trial, the combination of enfortumab vedotin and pembrolizumab nearly doubled both progression-free and overall survival compared with standard chemotherapy, with median overall survival extending beyond

Table 1. List of clinical trials testing immunotherapy in bladder cancer.

Trial No.	Regimen	Settings	Mechanism	Phase
NCT03359239	Atezolizumab + PGV001	Adjuvant	Neoantigen vaccine; Anti-PD-1	1
NCT03740256	CAdVEC + HER2 CAR-T	Refractory	Oncolytic adenovirus; CAR-T	1
NCT04601857	Pembrolizumab + Fudibatinib	First-line	Pan-FGFR inhibitor; Anti-PD-1	2
NCT04919512	Cetrelimab ± TAR-200 (gemcitabine)	Neoadjuvant	Anti-PD-1; intravesical gemcitabine device	2
NCT06534983	Nivolumab + Autogene cevumeran	Adjuvant	mRNA vaccine; Anti-PD-1	2
NCT04601857	Pembrolizumab + Fudibatinib	First-line	Pan-FGFR inhibitor; Anti-PD-1	2
NCT04919512	Cetrelimab ± TAR-200 (gemcitabine)	Neoadjuvant	Anti-PD-1; intravesical gemcitabine device	2
NCT02632409	Nivolumab	Adjuvant	Anti-PD-1	3
NCT03036098	Ipilimumab/Nivolumab; GC ± NIVOLUMAB	First-line	Anti-CTLA-4; Anti-PD-1	3
NCT03661320	Nivolumab ± Linrodostat	Perioperative	Anti-PD-1; IDO1 inhibitor	3
NCT03732677	Durvalumab	Perioperative	Anti-PD-L1	3
NCT03924856	Pembrolizumab	Perioperative	Anti-PD-1	3
NCT04209114	Nivolumab ± Bempeg (NKTR-214)	Perioperative	Anti-PD-1; IL-2 prodrug	3

30 months [60, 61]. This regimen has now been established as the new global first-line standard for locally advanced or metastatic bladder cancer, applicable to both cisplatin-eligible and -ineligible populations. Common toxicities included neuropathy, rash, and alopecia, reflecting ADC-specific rather than chemotherapy-related profiles [60, 61]. Several next-generation Nectin-4 ADCs are under development. 9MW2821, which employs a site-specific linker to ensure a consistent drug-to-antibody ratio, showed an objective response rate of 62% and median progression-free survival of nearly 9 months in early-phase studies [62]. Large-scale trials are ongoing to evaluate it both as monotherapy and in combination with immune checkpoint inhibitors [62, 63]. Similarly, SHR-A2102, a topoisomerase-I payload-based ADC targeting Nectin-4, produced an objective response rate of 38% in heavily pretreated patients, with higher activity observed at increased dosing levels [64], offering alternatives for patients who develop resistance or intolerance to enfortumab vedotin.

Datopotamab deruxtecan (Dato-DXd), a Trop-2-directed ADCs, has shown early promise in patients previously treated with chemotherapy and immunotherapy, achieving a 25% overall response rate and a median progression-free survival of about 7 months [65]. The TROPION series of trials is aimed at optimizing the dosage to clarify the impact of Trop-2 expression on response [66]. While sacituzumab govitecan demonstrated encouraging early data in the TROPHY-U-01 trial, its confirmatory phase III study (TROPiCS-04) did not meet its survival endpoint, leading to withdrawal of its indication in bladder cancer [67]. A newer Trop-2 ADC, sacituzumab tirumotecan, links the antibody to a novel topoisomerase-I payload with enhanced stability. In the MK-2870-001 trial, response rates reached 46% in second-line and 26% in later-line therapy, with median progression-free survival extending several months [68]. Trials combining sacituzumab tirumotecan with enfortumab vedotin and pembrolizumab are now underway, potentially enabling dual antigen targeting with immune activation.

Beyond single-agent ADCs, dual-ADC regimens have entered exploration. The DAD study tested sacituzumab govitecan with enfortumab vedotin in metastatic bladder cancer refractory to prior therapies, achieving a 70% response rate with durable responses in several patients [69]. Toxicities were frequent but consistent with known class effects. A subsequent cohort (DAD-IO) is evaluating the addition of pembrolizumab, reflecting a growing interest in multi-target ADC and checkpoint inhibitor combinations. Innovative constructs such as BL-B01D1, a bispecific EGFR-HER3 ADC carrying a topoisomerase-I payload, have also shown early efficacy. In a phase Ib/II trial, the objective response rate approached 44%, with manageable hematologic toxicities [70]. Multiple phase II and III trials are ongoing to determine whether bispecific targeting can overcome antigen heterogeneity and resistance mechanisms in advanced disease. Smaller conjugate designs, small-molecule drug conjugates (SMDCs), are also entering clinical testing. Zelenectide pevedotin (BT8009), a Nectin-4-directed bicyclic peptide conjugate, has been shown to achieve a 45% response rate in patients previously treated with checkpoint inhibitors and platinum therapy [71]. The Duravelo-2 study is now evaluating BT8009 alone and with pembrolizumab as a first-line option in bladder cancer [72]. BT7480, combines Nectin-4 and CD137 (4-1BB) targeting in a single bicyclic construct to stimulate both tumor and immune cells, while BT5528, directed at EphA2, has demonstrated promising activity with confirmed responses in 45% of the bladder cancer patients [73, 74]. Therefore, bicyclic conjugates may offer a next generation of ADC-like precision therapies with improved pharmacokinetics. ADCs within bladder-preserving protocols are also being explored. The RAD-SG study is evaluating concurrent delivery of sacituzumab govitecan with adaptive radiotherapy following maximal transurethral resection, testing whether localized ADC exposure can enhance tumor control while preserving organ

Table 2. List of clinical trials testing antibody-drug conjugates in bladder cancer.

Trial No.	Regimen	Settings	Mechanism	Phase
NCT03401385	Datopotamab deruxtecan	Refractory	Trop-2 ADC	1
NCT05735275	SHR-A2102	Unspecified	Nectin-4 ADC	1
NCT06238479	LY4101174	Refractory	Nectin-4 ADC	1
NCT04152499	Sacituzumab tirumotecan	Refractory	Trop-2 ADC	1/2
NCT05460273	Datopotamab deruxtecan	Unspecified	Trop-2 ADC	1/2
NCT03288545	Enfortumab vedotin	Perioperative	Nectin-4 ADC	1b/2
NCT05216965	9MW2821	Unspecified	Nectin-4 ADC	1a/2
NCT04482309	Trastuzumab deruxtecan	Refractory	HER2 ADC	2
NCT05785039	BL-B01D1	Refractory	EGFR-HER3 ADC (bispecific)	2
NCT06857175	BL-B01D1	Refractory	EGFR-HER3 ADC (bispecific)	3

*ADC: antibody-drug conjugate.

function [75].

ADCs have now transitioned from experimental tools to clinically viable therapeutic options in bladder cancer. Refining antigen selection, linker chemistry, and payload design are expected to yield more effective results, and position ADCs as a core pillar of personalized therapy in bladder cancer.

Therapeutic synergy: Combination approaches with immunotherapy and ADCs in bladder cancer

Combining ADCs with ICIs represent a major therapeutic breakthrough in the treatment of bladder cancer. By uniting two complementary mechanisms where ADCs induce targeted cytotoxicity and immunogenic cell death by releasing tumor antigens and inflammatory signals, and ICIs relieve inhibitory checkpoints and sustain cytotoxic T-cell activity, this combination strategy present a promising therapeutic option [76, 77]. Mechanistically, this approach can convert immunologically "cold" tumors into "hot" lesions, deepen responses, and delay or prevent resistance [78, 79]. EV-103 trial tested the combination of enfortumab vedotin and pembrolizumab in patients who were not eligible for cisplatin therapy, achieved an 65% objective response rate, which is substantially higher than 45% objective response rate achieved with enfortumab vedotin alone in a comparable subset of patients [79]. A pooled meta-analysis has also confirmed simmilar activity, with overall response rates of about 68% and 85% disease control rate across early-phase cohorts of bladder cancer patients [13]. These results led to the EV-302/KEYNOTE-A39 trial, which established the combination of enfortumab vedotin and pembrolizumab superior to platinum-based chemotherapy. In this trial, the combination of enfortumab vedotin plus pembrolizumab almost doubled the median overall survival (31.5 vs 16.1 months) and median progression-free survival (12.5 vs 6.3 months). It also achieved a higher overall response rate of 68% compared to 44% with chemotherapy [60]. These advances have offered an option that is more effective in both cisplatin-eligible and -ineligible patients, thereby facilitating the clinical decision-making in bladder cancer. In addition, the toxicity profile of combining enfortumab vedotin and pembrolizumab as a treatment is also tolerable, with primary adverse events being limited to rash and neuropathy rather than hematologic suppression. Reduced incidence of anemia and neutropenia compared to standard platinum regimens was also observed with this combination, which makes it particularly suitable for older adults or patients with marginal performance status [13, 60].

Other combination treatments entailing ICIs and ADCs are also actively being explored in bladder cancer. For instance, TROPHY-U-01 trial encompassing patients who had progressed after platinum chemotherapy but had not received checkpoint-inhibitor treatment evaluated the sacituzumab govitecan plus pembrolizumab regimen. The combination produced an objective response rate of 41%, and 20% patients achieved complete responses. The median duration of response was 11 months with median overall survival of 13 months [80]. Adverse events were consistent with known drug profiles, primarily including neutropenia, leukopenia, and diarrhea. As enfortumab vedotin plus pembrolizumab now anchors first-line management, sacituzumab govitecan-based combinations may have future roles in post-platinum or post-ADC settings, particularly in biomarker-defined patient subgroups [60]. This affirms that ADC-ICI synergy extends beyond a single drug pair and may serve as a broader therapeutic option across multiple tumor targets in bladder cancer.

Combining ADCs with immunotherapy has rapidly evolved from a conceptual rationale to a clinically tested reality in bladder cancer (**Table 3**). Ongoing studies involving HER2-, Trop-2-, and Nectin-4-directed ADCs, as well as dual ADC or bispecific constructs, are expected to extend these benefits further in the realm of bladder cancer treatment [60, 80]. Identification of biomarkers that predict synergy, optimization of sequence and dosing, and management of overlapping toxicities is warranted to sustain durable immune-cytotoxic synergy of combining ICIs and ADCs in bladder cancer.

Conclusion and future perspectives

Table 3. List of clinical trials testing combinations of immunotherapy and antibody-drug conjugates in bladder cancer.

Trial No.	Regimen	Settings	Mechanism	Phase
NCT04606472	SI-B003	Refractory	PD-1/CTLA-4 (bispecific)	1
NCT05297552	Disitamab vedotin + Toripalimab	Neoadjuvant	HER2 ADC; Anti-PD-1	2
NCT05535218	Sacituzumab govitecan + Pembrolizumab	Neoadjuvant/ Periop	Trop-2 ADC; Anti-PD-1	2
NCT06405425	BL-B01D1 + Anti-PD-1 (unspecified)	First-line	EGFR-HER3 ADC (bispecific); Anti-PD-1	2
NCT06823427	9MW2821 ± Toripalimab	First-line	Nectin-4 ADC; Anti-PD-1	2
NCT03924895	Enfortumab vedotin ± Pembrolizumab	Perioperative	Nectin-4 ADC; Anti-PD-1	3
NCT04223856	Enfortumab vedotin + Pembrolizumab	First-line	Nectin-4 ADC; Anti-PD-1	3
NCT04700124	Enfortumab vedotin + Pembrolizumab	Perioperative	Nectin-4 ADC; Anti-PD-1	3
NCT04960709	Enfortumab vedotin + Durvalumab ± Tremelimumab	Neoadjuvant	Nectin-4 ADC; Anti-PD-L1; Anti-CTLA-4	3
NCT05302284	Disitamab vedotin + Toripalimab	First-line	HER2 ADC; Anti-PD-1	3
NCT05911295	Disitamab vedotin + Pembrolizumab	First-line	HER2 ADC; Anti-PD-1	3
NCT06196736	9MW2821 + Toripalimab	Refractory	Nectin-4 ADC; Anti-PD-1	3
NCT06592326	9MW2821 + Toripalimab	First-line	Nectin-4 ADC; Anti-PD-1	3

*ADC: antibody-drug conjugate.

Therapeutic progress in bladder cancer research has accelerated dramatically over the past few years. With a substantial number of bladder cancer patients unsuitable for cisplatin-based therapy always present, the need for validated alternative treatment strategies has been fulfilled by incorporating immunotherapy and ADCs to achieve curative outcomes. The integration of ICIs and ADCs has redefined standards across the disease spectrum, from neoadjuvant and adjuvant settings to metastatic therapy. Perioperative immunotherapy strategy in muscle-invasive bladder cancer has demonstrated that combining cisplatin-based chemotherapy with checkpoint blockade can significantly improve pathological response and survival among eligible patients [29]. Immunomodulators, including anti-LAG-3 antibodies, are combined with checkpoint inhibitor, while next-generation ADCs are expanding the spectrum of treatment. ADCs with bispecific antigens like EGFR-HER3 and those targeting HER2, Trop-2, and Nectin-4, have demonstrated promising results in clinical trials [59, 70]. Small-molecule and bicyclic conjugates have also significantly improved tissue penetration and pharmacologic precision, marking a new phase in targeted drug delivery.

Treatment planning equipped with molecular diagnostics and ctDNA analyses is also a big-step forward. ctDNA has emerged as a robust biomarker for detecting minimal residual disease and assessing relapse risk, enabling adjuvant therapies to be guided by molecular evidence rather than clinical suspicion [38, 40]. Genomic profiling is aiding by precise and accurate patient selection for treatment with ADCs and targeted agents, which is eventually bringing precision oncology into everyday clinical decision-making. Multimodal approaches that combine maximal transurethral resection, chemoradiation, and immunotherapy have demonstrated promising results, particularly with respect to bladder preservation. Several phase II trials have reported two-year bladder-intact survival rates exceeding 70% [47, 48]. T Enfortumab vedotin plus pembrolizumab has been established as the recommended first-line regimen for both cisplatin-eligible and -ineligible populations in the metastatic setting [60], as it doubled overall survival compared with chemotherapy and offered a more manageable toxicity profile with reduction in hematologic suppression. For patients who are unable to tolerate ADC-based therapy due to neuropathy, autoimmune conditions, or dermatologic toxicity, platinum-based chemotherapy is unfortunately still a valuable alternative. Resistance to both ICIs and ADCs remains a major obstacle. Immune evasion mechanisms, such as loss of antigen presentation, exclusion of T cells, or activation of alternative checkpoints, can limit immunotherapy efficacy, while ADC resistance often results from target downregulation, defective internalization, or enhanced drug efflux [81, 82]. Dissecting these adaptive processes will be essential for achieving durable responses and long-term disease control.

Key priorities that are essential to elevate the next phase of progress in bladder cancer therapy include: 1) Refinement of biomarker-guided patient selection to personalize therapy and predict benefit; 2) Expansion of ADC target repertoires beyond Nectin-4 and Trop-2 to address tumor heterogeneity; and 3) Designing of rational multi-agent combinations that integrate ICIs, ADCs, and molecularly targeted drugs to delay resistance. These priorities signify a pivotal transition from traditional, stage-based management to a precision-oriented, mechanism-informed treatment paradigm. Through continued integration of immunotherapy, ADCs, and molecular profiling, the field is progressing toward better therapeutic management in bladder cancer.

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Availability of data and materials

All data generated or analysed during this study are included in this publication.

Author contributions

Ahmed Helmy Abdelhaseb contributed to design of the work, data collection, and drafting the article; Shahd Mustafa Ibrahim draw the figure and checked the tables; Ahmed Attia Ahmed Abdelmoaty revised the final manuscript.

Competing interests

The author declares no competing interests.

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