Review Article | Oncology: Genitourinary Cancer

Novel immunotherapies and targeted molecular therapies for non-muscle invasive bladder cancer: a literature review

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Contributions: (I) Conception and design: AP Drouaud, MJ Whalen; (II) Administrative support: AP Drouaud, MJ Whalen; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: AP Drouaud, R Antar, B Boyarsky, Y Wang, N Sivanesan, MJ Whalen; (V) Data analysis and interpretation: AP Drouaud, R Antar, B Boyarsky, Y Wang, N Sivanesan, MJ Whalen; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: Bladder cancer (BCa) is the sixth most common malignancy in the United States in 2023. Stratified into non-muscle invasive and muscle-invasive types, non-muscle invasive bladder cancer (NMIBC) comprises 70% of cases. Immune checkpoint inhibitors and targeted molecular therapy agents have shown efficacy in locally advanced and metastatic BCa and may be promising in the localized disease setting, especially for Bacillus Calmette-Guerin (BCG)-unresponsive NMIBC. The present article aims to assess the contemporary status of four therapeutic options [pembrolizumab, atezolizumab, erdafitinib, and enfortumab-vedotin (EV)] for NMIBC as systemic and intravesical therapies.

Methods: We conducted a non-systematic review using PubMed, Google Scholar, ClinicalTrials.gov, and American Society of Clinical Oncology (ASCO) articles published from January 2009 to October 2023. Only articles written in English were considered.

Key Content and Findings: Pembrolizumab, atezolizumab, erdafitinib, and EV offer alternative treatment strategies for BCG-unresponsive high-risk NMIBC. Pembrolizumab is effective as a systemic therapy via level-one evidence as other trials continue to evaluate the safety and immune responses via intravesical delivery. Atezolizumab shows promise in the treatment of NMIBC but its efficacy as a monotherapy is not yet clinically significant with limited follow-up thus far and ongoing studies are exploring combination therapy with BCG to improve outcomes. Erdafitinib has shown its efficacy and safety as ongoing studies explore its role in combination therapies to enhance efficacy and reduce side effects. EV shows significant efficacy and safety in patients with advanced urothelial carcinoma who failed prior therapy, however, the development of pre-treatment biomarkers is essential to optimize its use in NMIBC treatment.

Conclusions: These drugs, with their novel mechanisms of action and targets, offer hope for improved outcomes and may galvanize a paradigm shift for NMIBC treatment in both the BCG-unresponsive and primary settings. Ongoing research and clinical trials are imperative to optimize the utilization of these drugs, define rational combination therapies, identify prognostic biomarkers of treatment efficacy, and thus expand the therapeutic armamentarium.

Keywords: Non-muscle invasive bladder cancer (NMIBC); pembrolizumab; atezolizumab; erdafitinib; enfortumab-vedotin (EV)

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Received: 15 November 2023; Accepted: 24 April 2024; Published online: 06 Jun 2024.
doi: 10.21037/amj-23-222
View this article at: https://dx.doi.org/10.21037/amj-23-222

Introduction

Bladder cancer (BCa) is the sixth most common cancer in the United States (US), with 82,290 new cases estimated in 2023 (1). The categorization of BCa occurs through stratification into two types: non-muscle invasive bladder cancer (NMIBC) and muscle-invasive bladder cancer (MIBC), based on the extent of tumor penetration into the detrusor muscle (2). NMIBC makes up approximately 70% of newly diagnosed cases of BCa, highlighting the importance of treatment in averting progression, an adverse phenomenon observed in roughly 30% of patients (3). Although Bacillus Calmette-Guerin (BCG) is the first-line standard of care for intermediate- and high-risk NMIBC patients, supply shortages have encumbered its routine use, and 30–50% of individuals may not respond to therapy (4). The standard treatment for unresponsive BCG in high-risk BCa involves consideration of early radical cystectomy (RC) when the patient is in good health and has been thoroughly educated about the associated risks, advantages, and impact on their quality of life (5). However, various patients have contraindications that deem them unfit for the procedure. Salvage intravesical therapy is also an option for well-selected patients, however, valrubicin, one of the Food and Drug Administration (FDA)-approved intravesical therapy for BCG-unresponsive NMIBC, demonstrates only a 20% response rate and 8% recurrence-free survival (RFS) at 12 months (6,7). Exciting progress was made with KEYNOTE-057 with the approval of systemic pembrolizumab for BCG-unresponsive NMIBC (8).

The rise of immunotherapy and targeted molecular therapy in the treatment of BCG-unresponsive NIMBC highlights the crossover of therapeutics formerly in the realm of medical oncology into the domain of urologists and urologic oncologists. The paradigm of referral to medical oncology for locally advanced or metastatic disease has significantly evolved. Urologists must now be aware of the increasing complexity of incorporating molecularly targeted agents earlier in the treatment course as part of a personalized and precision-medicine approach. This evolution encompasses a more nuanced understanding of the molecular and genetic characteristics of individual tumors, allowing for targeted therapies that are tailored to a patient's unique cancer profile. Additionally, there's a growing emphasis on immunotherapy, harnessing the body's immune system to recognize and attack cancer cells. The integration of these advancements, along with a focus on combination therapies, aims to improve treatment outcomes while minimizing adverse events.

This review intends to address the contemporary status of novel immune checkpoint inhibitors (ICIs), namely pembrolizumab and atezolizumab, along with the targeted molecular therapy erdafitinib, and antibody-drug conjugate (ADC) enfortumab-vedotin (EV), and outlines the rationale behind their application in BCG-unresponsive NMIBC via systemic and intravesical delivery. Our study stands as the first of its kind, making a valuable contribution to the existing body of knowledge in this field. Furthermore, we provide an overview of ongoing research endeavors investigating the effectiveness of novel immunotherapeutic agents. We present this article in accordance with the Narrative Review reporting checklist (available at https://amj.amegroups.com/article/view/10.21037/amj-23-222/rc).

Methods

Using PubMed and Google Scholar, we performed a non-systematic review of articles published between January 2009 and October 2023. Search terms included combinations of the following terms: "non-muscle invasive bladder cancer", "pembrolizumab", "atezolizumab", "erdafitinib", and "enfortumab-vedotin". MeSH terms included "bladder cancer" and "immuno-oncology". Articles selected were required to be original articles published in English.

Information on clinical trials was collected from www.clinicaltrials.gov. Trials were selected based on the drug of interest and NMIBC. Trials were excluded if they were listed as "terminated" or "withdrawn".

Articles from the American Society of Clinical Oncology (ASCO) were queried with a combination of search terms related to the drugs of interest. We examined major urology journals and NMIBC treatment guidelines. *Table 1* presents a concise summary of past, current, and future pivotal trials, offering key data for an overview of these drugs' clinical development. Our search summary strategy is outlined in *Table 2*. An example of our detailed search strategy for pembrolizumab in PubMed is outlined in Table S1.

Table 1 Summary of non-muscle invasive bladder cancer immunotherapies and targeted molecular therapies

Drug name	Clinical trial	Mode of delivery	Inclusion criteria	Date of first patient enrollment	Estimated completion date	Institution	Phase of study	Outcomes (primary and secondary)	Major findings to date	Principle investigator of findings	Citations
Pembrolizumab	NCT02625961 (KEYNOTE-057)	Intravenous	NMIBC (T1, high grade Ta and/or CIS), TCC	2016-02-10	2030-08-31	54 sites in 14 countries	Phase II	CRR, DFS, DoR	n=96; CRR 41% at 3 mo; 46% responder continued disease free at 12 mo; AE 13% patients (grade 3 and 4)	Balar AV	(8)
	NCT02808143	Intravesical	NMIBC recurrent post TURBT, BCG-refractory, BCG-naive (Ta, Tis, or T1)	2017-02-10	2023-02	Single institution; Northwestern University, USA	Phase I	MTD; DLT; RFS AE	n=9; 6-mo RFS 67%; 12-mo RFS 22%; 1 DLT (grade 2 diarrhea); 1 death (myasthenia gravis)	Meghani K	(9)
	NCT03167151 (PemBla)	Intravenous; Intravesical	NMIBC recurrent post TURBT	2018-03-02	2019-06-26	Single institution; University of Oxford, UK	Phase I/II	DLT	n=6; 0 DLT during dose escalation; AE (dysuria and fatigue); no evidence of systemic absorption or systemic immune effects	Woodcock VK	(10)
	NCT03711032 (KEYNOTE-676)	Intravenous	NMIBC (T1, high grade Ta and/or CIS)	2018-12-24	2028-10-12	203 sites in 30 countries	Phase III	CRR, EFS, RFS, OS, DSS, time to cystectomy, DoR, AE, QoL	Ongoing	Medical Director, Merck Sharp & Dohme LLC	(11)
Atezolizumab	NCT02108652 (IMVigor 210)	Intravenous	MIBC, TCC	2014-05-31	2023-02-28	77 sites, 8 countries	Phase II	CRR, DoR, PFS, OS	n=119; ORR 23%; CRR 9%; median PFS 2.7 mo; median OS 15.9 mo; AE 10% patients (fatigue, diarrhea, pruritis); 1 death (sepsis)	Balar AV	(12)
	NCT02302807 (IMVigor 211)	Intravenous	MIBC, chemotherapy-unresponsive	2015-01-13	2018-11-08	212 sites in 4 countries	Phase III	OS, PFS, DoR, AE	n=931; similar ORR; similar OS; longer DoR atezolizumab (15.9 *vs.* 8.3 mo chemotherapy); fewer AE for atezolizumab	Powles T	(13)
	NCT02792192	Intravenous	NMIBC (CIS), TCC, BCG-unresponsive, high risk NMIBC BCG-naive	2016-06-13	2020-09-29	8 sites in USA	Phase I/II	AE, DLT, CRR, RFS, DFS, PFS, CFS, OS	n=24; CRR 33% at 6 mo (atezolizumab alone); CRR 42% at 6 mo (atezolizumab + BCG)	Inman BA	(14)
	NCT02844816 (SWOG S1605)	Intravenous	NMIBC (T1, CIS and/or Ta), non-papillary	2017-03-13	2024-07-23	272 sites in USA	Phase II	CRR, PFS, CFS, OS, AE	n=166; CRR 43% at 3 mo; CRR 27% at 6 mo; CRR 20% at 12 mo; AE in 23 patients (grade 3 or 4); 3 deaths	Black PC	(15)
	NCT03799835 (ALBAN)	Intravenous	NMIBC (T1, high grade, grade 3 and/or CIS), BCG naive	2019-01-17	2028-02-01	37 sites in 3 countries	Phase III	RFS, PFS, DSS, OS, QoL	Ongoing	Morgan Roupret, Yohann Loriot	(16)
	NCT04134000 (BladderGATE)	Intravenous	NMIBC (T1, high grade Ta, grade 3 and/or CIS), TCC	2020-02-03	2024-02	Single institution: Hospital 12 de Octubre, Spain	Phase I/II	DLT, RFS, AE	n=34; 0 DLT (dose level 0); AE (grade 1–4)	Castellano D	(17)
Erdafitinib	NCT02365597 (BCL-2001)	Oral	MIBC, chemotherapy-unresponsive	2015-04-22	2023-12-29	103 sites in 15 countries	Phase II	DDI, PFS, DoR, OS, AE	n=210; CRR 40%; FGFR-mutated ORR 49%; 12-mo RFS 19%; AE 100% patients; AE 67% patients (grade 3 and 4)	Janssen Research & Development	(18)
	NCT04172675 (THOR/BCL-2003)	Oral	NMIBC recurrent, BCG-unresponsive	2020-02-28	2024-03-29	144 sites in 17 countries	Phase II	RFS, time to progression, OS, AE	Cohort B: 100% CRR at 3 cycles; 75% CRR at 6 cycles Cohort B & C: AE (hyperphosphatemia, diarrhea, dry mouth, dysgeusia)	Catto JWF	(19)
	NCT04917809	Oral	NMIBC, BCG unresponsive, chemotherapy-unresponsive	2022-02-17	2025-08	7 sites in USA	Phase II	ORR	Ongoing	Eugene Pietzak	(20)
	NCT05316155	Intravesical	NMIBC recurrent (papillary), BCG-unresponsive MIBC	2022-04-11	2027-04-14	21 sites in 5 countries	Phase I	AE, DLT, RFS, CRR	Cohort 1: 82% CRR with disease free progression Cohort 3: 87% CRR	Vilaseca A	(21)
	NCT05567185	Intravesical	NMIBC, BCG-unresponsive, chemotherapy-unresponsive	2023-03-03	2026-10-16	4 sites in Japan	Phase I	DLT, AE	Ongoing	Janssen Research & Development	(22)
Enfortin-Vetodin	NCT03219333 (EV-201)	Intravenous	MIBC, TCC, chemotherapy-unresponsive	2017-10-08	2023-07-28	78 sites in 8 countries	Phase II	ORR, DoR, PFS, OS, AE	n=125; ORR 44%; AE (fatigue, peripheral neuropathy, alopecia, rash, decreased appetite, dysgeusia) n=89; ORR 52%	Rosenberg JE, Yu EY	(23,24)
	NCT03474107 (EV-301)	Intravenous	MIBC, chemotherapy-unresponsive, immunotherapy-unresponsive	2018-06-27	2024-02-29	153 sites in 19 countries	Phase III	OS, PFS, ORR, DCR, DoR, AE	n=608; 134 deaths EV; 167 deaths chemotherapy; longer OS EV (12.88 *vs.* 8.97 mo chemotherapy)	Powles T	(25)
	NCT05014139	Intravesical	NMIBC (CIS, papillary, TCC and/or BCG unresponsive)	2021-12-07	2028-05-31	14 sites in 5 countries	Phase I	AE, DLT, CRR, PFS, CFS	n=6; no systemic absorption (125 or 250 mg)	Kamat AM	(26)

NMIBC, non-muscle invasive bladder cancer; CIS, carcinoma in situ; TCC, transitional cell carcinoma; TURBT, trans urethral resection of bladder tumor; BCG, Bacille Calmette-Guerin; MIBC muscle-invasive bladder cancer; CRR, complete response rate; DFS, disease-free survival; DoR, duration of response; MTD, maximum tolerated dose; DLT, dose limiting toxicity; RFS, recurrence-free survival; AE, adverse events; EFS, event-free survival; OS, overall survival; DSS, disease-specific survival; QoL, quality of life; PFS, progression-free survival; CFS, cystectomy-free survival; DDI, drug-drug interaction; ORR, objective response rate; mo, months; DCR, disease control rate; FGFR, fibroblast growth factor.

Table 2 The search strategy summary

Items	Specification
Date of search	28 October 2023
Databases and other sources searched	PubMed, Google Scholar, ClinicalTrials.gov, American Society of Clinical Oncology (ASCO)
Search terms used	Search terms: "non-muscle invasive bladder cancer", "pembrolizumab", "atezolizumab", "erdafitinib", "enfortumab-vedotin"; MeSH terms: "bladder cancer", "immuno-oncology"; filters: publication date, language, study type
Timeframe	January 2009–October 2023
Inclusion criteria	Language: English; study type: not specified
Selection process	Researchers conducted searches based on their assigned drugs (pembrolizumab, atezolizumab, erdafitinib, enfortumab-vedotin). Articles in English were included

Discussion

Managing high-risk, NMIBC typically involves transurethral resection of the bladder tumor (TURBT), followed by intravesical therapy. While this modality appears responsive initially, there is a 20–40% probability of progression to MIBC within 5 years for high-risk patients (27,28). This progression, in turn, poses a 50% risk of culminating in untreatable metastatic disease (29). As the intricate relationship between cancer cells and host immunity has become more apparent, the programmed cell death protein 1/programmed cell death ligand 1 (PD-1/PD-L1) immune checkpoint has emerged as a focal point of this resistance, given its role in tumor immune escape. PD-L1 is also known as cluster of differentiation 274 (CD274), a transmembrane protein that is highly expressed on the surface of tumor cells. PD-L1 plays a significant role in suppressing the adaptive immune system by binding to inhibitory checkpoint molecule PD-1 expressed on activated antigen-specific T cells, subsequently deactivating them and reducing proliferation (30). A study by Fukumoto *et al.* found that PD-1 expression in NMIBC tissues increased with BCG therapy, pinpointing the upregulation of PD-1 as an immune escape mechanism and consequently a predictor of disease recurrence and progression (31).

Pembrolizumab

Pembrolizumab (KEYTRUDA®), a monoclonal antibody targeting PD-1 developed by Merck & Co., has demonstrated efficacy against many solid tumors and remains one of the most widely used immunotherapies (32). In 2020, the FDA approved pembrolizumab for treating BCG-unresponsive NMIBC patients and high-risk patients with carcinoma in situ (CIS), with or without papillary tumors, who are either ineligible for or refuse cystectomy (33). There is no contemporary data on the estimated prevalence of pembrolizumab utilization in NMIBC care, highlighting the need for further investigation to understand trends in treatment since the drug's approval. This approval followed a pivotal phase II clinical trial conducted by Merck at 54 sites in 14 countries between 2015 and 2018. The KEYNOTE-057 (NCT02625961) study was a multicenter, single-arm trial that included 148 high-risk NMIBC patients. Of these, 96 (Cohort A) had BCG-unresponsive CIS with or without papillary tumors. Patients were administered 200 mg intravenously (IV) of pembrolizumab every 3 weeks, continuing until the onset of severe side effects, persistent or recurrent high-risk NMIBC, progressive disease, or up to 24 months without disease progression. The study's median follow-up time was 36.4 months, and the median duration to complete response rate (CRR) for pembrolizumab was 16.2 months. This CRR was achieved in 41% of patients at 3 months with 46% of responders continuing to be disease-free at 12 months. The most common treatment-related adverse events (TRAEs) were diarrhea, fatigue, pruritis, and hypothyroidism (8). These findings display a promising path ahead in NMIBC treatment, serving as a viable therapeutic option for BCG-unresponsive patients who decline or are unfit for surgery.

Role in NMIBC

Following the successful demonstration of pembrolizumab's efficacy in the KEYNOTE-057 trial, another open-label, comparator-controlled, phase III KEYNOTE-676 trial (NCT03711032) is underway until 2024 (11). Patients

(estimated enrollment n=975) will be randomized into three distinct treatment arms: pembrolizumab + BCG with reduced BCG maintenance, pembrolizumab + BCG with complete BCG maintenance, and BCG monotherapy. This trial aims to evaluate the efficacy of combining pembrolizumab with BCG in treating high-risk NMIBC patients, particularly those who are either BCG-naive or have not received BCG treatment in over 2 years. The primary endpoint is event-free survival, measured from random assignment to the first occurrence of high-grade Ta, CIS, T1 disease of the bladder, high-risk disease of the urethra/upper tract, locally advanced/metastatic disease, or death from any cause. Secondary endpoints include CRR, duration of response, disease-specific survival, time to cystectomy, overall survival (OS), and safety.

In addition to the well-established systemic delivery of pembrolizumab, intravesical pembrolizumab is currently under investigation. One such notable endeavor is the ongoing PemBla trial (NCT03167151), a phase I multicenter study in the UK, which focuses on assessing the safety and tolerability of intravesical pembrolizumab in patients with recurrent NMIBC (10). In this trial, which opened for accrual in March 2018, six eligible participants were randomly assigned in a 1:1 ratio to receive either intravesical or intravenous pembrolizumab, allowing for a comprehensive comparative analysis. Notably, the most recent update from the trial reveals that six participants who completed six doses of intravesical pembrolizumab treatment experienced only mild adverse effects, such as dysuria and fatigue, with no evidence of dose-limiting toxicity during dose escalation. Another similar phase I study (NCT02808143) highlighted the safety and efficacy of the strong immune response generated by intravesical pembrolizumab among n=9 BCG-unresponsive NMIBC patients (9). While these phase I studies have firmly established safety and tolerability, future investigations must evaluate oncologic efficacy.

In summary, the future of pembrolizumab in NMIBC is evolving as numerous trials are now ongoing for BCG-naive patients. Exploration of administration routes persists, with intravesical pembrolizumab emerging as a promising option due to its demonstrated safety among recurrent or BCG-unresponsive NMIBC patients following phase I.

Atezolizumab

Atezolizumab (TECENTRIQ®) is a monoclonal antibody against PD-L1 and is under investigation by Genentech/Roche. Initially approved in the US in 2016 for the treatment of metastatic non-small cell lung cancer treatment, the indications of atezolizumab include treating urothelial carcinoma, small cell lung cancer, hepatocellular carcinoma, and melanoma (34). Atezolizumab, similar to pembrolizumab, blocks the immune-dampening effect by inhibiting the interaction between PD-L1 and PD-1, thereby generating an anti-tumor response. Based on the results from IMvigor 210 (NCT02108652) and 211 (NCT02302807) trials, the US and the European Union approved atezolizumab as monotherapy for cisplatin-ineligible patients with locally advanced or metastatic urothelial carcinoma or after prior platinum-based chemotherapy (12,13).

Role in NMIBC

Several studies have investigated atezolizumab for its extended usage in NMIBC patients. The single-arm phase II SWOG S1605 trial (NCT02844816) investigated the effect of systemic atezolizumab on BCG-unresponsive high-grade 3 or 4 TRAEs and three participants died, suggesting a significant adverse risk profile (15). The study enrolled 166 participants who received at least one dose of 1,200 mg atezolizumab IV, of which 23 participants experienced grade 3 or 4 TRAEs, and three participants died. Moreover, the CRR for systemic atezolizumab monotherapy at 3, 6, and 12 months among a subgroup of patients with CIS was 43%, 27%, and 20%, respectively. These results are comparable to the CRR for pembrolizumab monotherapy of 41% at 3 months (8). However, the efficacy of systemic atezolizumab is still lower than the International Bladder Cancer Group's criteria for clinically meaningful outcomes in BCG-unresponsive NMIBC CIS patients (CRR of 50% at 6 months, 30% at 12 months) (35).

The nonoptimal results from systemic atezolizumab monotherapy suggest a combination therapy may be a better alternative. A phase Ib/II trial (NCT02792192) evaluated the safety and clinical activity of atezolizumab with or without BCG in BCG-unresponsive NMIBC patients with CIS (14). Among the 24 patients who participated in the study, the 6-month CRR for those treated with atezolizumab 1,200 mg IV q3w alone was 33%, and 42% for those treated with atezolizumab and BCG (50 mg, six weekly doses for induction and three weekly doses for maintenance). Atezolizumab administration was well-tolerated in this study, and there were no reported treatment-related deaths. An ongoing phase I/II study, BladderGate (NCT04134000),

has a similar study design: investigators are assessing the safety and efficacy of induction BCG and atezolizumab in high-risk NMIBC patients upfront, removing the requirement of prior failed BCG treatment as a criterion for enrollment. The most recent interim report suggested that among the 34 participants enrolled in the study, there were no dose-limiting toxicities reported, and the adverse effects were manageable (17).

ALBAN is an ongoing phase 3 trial (NCT03799835) investigating the safety and efficacy of atezolizumab in combination with BCG *vs.* BCG alone in patients with high-risk NMIBC. The study plans to enroll 516 patients across 45 European centers (16). NMIBC patients with high-risk features such as T1 stage, high grade, or CIS without previous BCG treatment are eligible for this study. Eligible participants will be randomized 1:1 to BCG alone or atezolizumab/BCG combination therapy for 1 year. The study's endpoint includes RFS, OS, progression-free survival (PFS), complete response, disease progression, and quality of life (36).

Overall, atezolizumab is a promising ICI with the application potential to treat NMIBC. Current clinical results suggest that atezolizumab can improve treatment results for NMIBC CIS patients, but to date is still not clinically significant. Multiple studies are currently investigating an alternative approach to combined therapy with BCG on high-risk NMIBC patients. Considering promising results from the intravesical use of other ICIs, evaluating the intravesical application of atezolizumab in the future is crucial.

Erdafitinib

Erdafitinib (BALVERSA®) is a pan-fibroblast growth factor receptor (FGFR) inhibitor discovered by Janssen and Astex in 2008. In April 2019, the FDA granted Janssen accelerated approval for erdafitinib to treat locally advanced and metastatic urothelial carcinoma in adult patients with FGFR2/3 alterations. The FDA also approved Janssen's FGFR reverse transcription-polymerase chain reaction (RT-PCR) (QIAGEN therascreen) to identify candidates for erdafitinib (37).

FGFR alterations are well-studied genetic risk factors of NMIBC and other urothelial carcinomas. The four classes of FGFRs share conserved extracellular, transmembrane, and intracellular domains, which are activated by eighteen ligands (38,39). Ligand-binding activates intracellular pathways via intracellular domain kinases PKC, RAS-MAPK, and PI3K-AKT for motility, mitosis, and proliferation, respectively (38,39). Control of FGFR is essential to prevent unregulated growth and tumorigenesis (38). Non-inflammatory, FGFR3-altered BCa show poor responses to immunotherapies due to local T-cell inactivation (38).

Erdafitinib inhibits all FGFR classes to downregulate intracellular phosphorylation in tumor cells (40). Approximately 50–80% of localized urothelial neoplasms have FGFR3 alterations and 20% of patients with metastatic urothelial cancers possess unfavorable, pathological FGFR3 mutations (41,42). These alterations are more commonly found in low-grade tumors and have been associated with a favorable PFS, but worse RFS (38,43). In a recent systematic review and meta-analysis, 70% of NMIBC patients had FGFR3 alterations compared to 15% of MIBC patients, which consist of FGFR missense mutations and fusion proteins (43,44). However, a 2022 retrospective study indicated that 43% of patients with high-grade NMIBC had FGFR3 alterations (45). Notable mutations include R248C, S249C, and Y375C, which show constitutive activity. FGFR3 fusions are more prevalent in patients with MIBC, with FGFR3-TACC3 and FGFR3-BAIAP2L1 being the most common. The FGFR2-IIIb variant could possess tumor-suppressive properties and FGFR2-IIIc is associated with the mesenchymal-epithelial transition with subsequent metastatic disease (39).

Challenges with erdafitinib and other FGFR inhibitors include resistance via receptor mutations, alternative metabolic pathways, and compensatory mutations in non-FGFR genes (43). Clinical trials of erdafitinib have shown various side effects, including gastrointestinal issues, elevated liver and pancreatic enzymes, thrombocytopenia, and anemia. Erdafitinib is teratogenic and contraindicated in pregnancies. Serious side effects include hyperphosphatemia and retinal detachment. Drug-drug interactions can occur as CYP3A4 and CYP2C9 metabolize erdafitinib in the liver (40).

Trials for MIBC treatment approval

The first trial evaluating erdafitinib usage in BCa began with Janssen's ongoing BCL-2001 clinical trial (NCT02365597) which published interim results and is estimated to conclude in 2023. It includes n=210 patients from 14 countries and 126 testing sites with FGFR3-altered, RECIST-defined, locally advanced, and unresectable or metastatic BCa with FGFR2/3 alterations. The experimental group of 99 patients receiving erdafitinib will be evaluated for the primary endpoint of response rates and the secondary endpoints of safety and efficacy. Initial

findings from 2019 showed median follow-up, OS, and PFS were 11.2, 13.8, and 5.5 months, respectively, with a 40% overall response rate (ORR) and 3% CRR. Adverse events occurred in all treatment group patients, with 46% being treatment-related, primarily hyperphosphatemia, stomatitis, diarrhea, and dry mouth. Thirteen patients (13.1%) in the experimental group discontinued erdafitinib treatment due to adverse events potentially related to treatment while 55 patients (55.6%) needed dose reductions (18).

The BCL-2001 trial confirmed erdafitinib's safety and efficacy, leading to its 2019 FDA approval for FGFR-altered locally advanced or metastatic urothelial carcinoma in the post-chemotherapy or post-immunotherapy setting (37). The initial findings indicate that erdafitinib may outperform other treatments for BCa, surpassing the ORR of other FGFR inhibitors, checkpoint inhibitors, EV and sacituzumab-govitecan, and chemotherapies. Erdafitinib demonstrated a respectable 40% tumor response rate in a heavily pre-treated population of patients who had progressed on one or more prior therapies (18).

Role in NMIBC

Erdafitinib has recently begun investigation for its potential role in patients with NMIBC. THOR/BCL-2003 study (NCT04172675), initiated in 2020, evaluates erdafitinib's efficacy in high-risk, FGFR-altered BCG-unresponsive NMIBC patients. Cohort B received the drug for a median duration of 5.9 months and achieved 100% CRR and 75% CRR in the third and sixth cycles of drug treatment, respectively (9). The September 2022 data cutoff of the second and third cohorts indicated patients experienced TRAEs consistent with those previously known to erdafitinib (19,46). The Memorial Sloan Kettering Cancer Center began a phase II trial (NCT04917809) in February 2022 to determine the ORR of oral erdafitinib as primary chemoablation in patients with FGFR3-altered NMIBC with failure of previous intravesical BCG or chemotherapy treatment. These patients will first receive oral erdafitinib treatment and then proceed to have transurethral resection or biopsy to assess post-treatment tumor burden (20). These trials highlight erdafitinib's potential as a promising treatment option for urothelial carcinomas with FGFR2/3 alterations.

In April 2022, Janssen began a phase I study (NCT05316155) investigating the safety and efficacy of the TAR-210 intravesical delivery system to administer erdafitinib in BCG-resistant NMIBC and MIBC patients with FGFR mutations (47). TAR-210 is a device that is inserted into the bladder and delivers the drug continuously over an extended period. The two-phase study first looks at the dose escalation for intravesical erdafitinib on previously BCG-treated individuals with recurrent papillary NMIBC who either refuse or are ineligible for cystectomy. In the subsequent dose-expansion phase, erdafitinib is given intravesically to either NMIBC or MIBC. Preliminary findings from 43 patients indicate that TAR-210 is well-tolerated, with low-grade TRAE and favorable outcomes in terms of CRR and RFS in NMIBC patients with FGFR alterations (21). Janssen also initiated another phase I study (NCT05567185) in March 2023 to assess the safety of TAR-210 in Japanese recurrent NMIBC patients with FGFR mutations (22). These trials aim to introduce an innovative intravesical erdafitinib delivery approach that could potentially reduce the prevalence of TRAEs. Erdafitinib is currently administered orally, and more direct routes of administration could limit systemic toxicities.

Overall, erdafitinib represents a promising avenue for treating NMIBC, particularly in patients with FGFR2/3 alterations. However, further research and clinical data on erdafitinib in combination therapies are needed to refine its role in NMIBC management.

EV

EV (PADCEV®) is the first ADC approved for patients by the FDA on December 18, 2019, for the treatment of locally advanced or metastatic urothelial carcinoma in adult patients who previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, representing a significant advancement in cancer treatment (48). This drug targets a protein known as nectin-4, which has been strongly detected in bladder and breast tumor specimens (49). A high prevalence of nectin-4 positivity was noted across gross high-grade NMIBC subgroups, as well, in a study including 367 patient samples, with 77% showing moderate/strong expression (50). Another study with 169 patients found 87% (72/83) of NMIBC patients and 68.2% (15/22) of patients with MIBC expressing nectin-4 (51). Extensive research has demonstrated that EV exhibits a high affinity for binding to cell surface-expressed nectin-4 in tumor cells and induces cell death *in vitro* in a dose-dependent manner. For patients who have received platinum or PD-1/PD-L1 therapy, salvage chemotherapy regimens have modest activity and uniformly result in cancer-specific mortality (23). Therefore, patients with urothelial carcinomas require effective and well-tolerated therapies. We acknowledge

other ADCs such as sacituzumab govitecan and trastuzumab emtansine, however, their absence in current NMIBC clinical trials justifies our focused exploration on EV.

Trials for MIBC treatment approval

EV administration in BCa treatment began with the EV-201 trial (NCT03219333), conducted in two phases between 2017 and 2020 encompassing 216 patients with metastatic urothelial carcinoma. In the initial cohort of 125 patients, EV exhibited a clinically meaningful response rate with a confirmed ORR of 44% over a median follow-up of 10.2 months, accompanied by manageable side effects such as fatigue, peripheral neuropathy, alopecia, rash, decreased appetite, and dysgeusia (23). A subsequent trial with 89 patients reported a confirmed ORR of 52% over a median follow-up of 13.4 months, reinforcing EV's tolerability and promise as a treatment option in this patient group previously exposed to platinum and anti-PD-1/PD-L1 therapies (24).

Following the EV-201 trial, a phase III EV-301 trial (NCT03474107) evaluated the drug's efficacy involving 608 patients undergoing randomization, 301 were assigned to receive EV and 307 to receive investigator-chosen chemotherapy (standard docetaxel, paclitaxel, or vinflunine). A total of 301 deaths occurred among 134 in the EV group and 167 in the chemotherapy group. OS was longer in the EV group than in the chemotherapy group. Thus, EV significantly prolonged survival (12.88 *vs.* 8.97 months) as compared with standard chemotherapy in patients with locally advanced or metastatic urothelial carcinoma who previously received platinum and ant-PD-1/PD-L1 therapies (25).

Challenges arise for the treatment of MIBC as nectin-4 expression for EV therapy was found to be clinically beneficial. Given that nectin-4 expression is frequently decreased or absent in metastatic urothelial carcinoma tissue, the efficacy of EV is reduced and may lead to EV resistance. Klümper *et al.* argue for a clinical reconsideration of current practice and recommend the determination of nectin-4 receptor status before treatment with EV (52). Implications for biomarker development, patient selection, and inclusion of molecular subtyping for ongoing and future EV trials need prioritization given the importance of nectin-4 expression in EV sensitivity (53).

Current studies suggest urinary nectin could serve as a potential diagnostic biomarker for BCa and show a correlation between urine levels, tumor expression, and serum levels in the analysis of nectin-4 (54). The use of urinary nectin biomarkers in combination with EV may yield clinical benefits.

Role in NMIBC

EV is now approved for clinical trials aimed at investigating the efficacy and potential side effects of EV treatment in the context of high-risk NMIBC. Preclinical experimentation in an orthotopic xenograft mouse model of NMIBC revealed the efficacy of intravesical EV (55). In a luciferase-expressing orthotopic xenograft mouse model of NMIBC, the anti-tumor effects mediated by intravesical EV were validated by assessing tumor burden through bioluminescence imaging and the evaluation of nectin-4 expressing cancer cells with immunohistochemistry before and after intravesical EV treatment. Notably, intravesical EV therapy exhibited excellent tolerability, with no evidence of systemic absorption and consequent toxicities.

Currently, an ongoing phase I study (NCT05014139) is investigating the dose safety, tolerability, and efficacy of intravesical dosing in humans (56). This study intends to recruit approximately 58 high-risk BCG-unresponsive NMIBC participants with CIS to receive intravesical doses of EV using a catheter to determine the highest tolerable dose. Researchers will utilize the dose identified in the initial phase for the second phase of this study to assess efficacy. As of December 2022, six participants tolerated intravesical EV well across two dose levels (125 and 250 mg) without systemic exposure at 125 mg (26). The mature results from this study are eagerly anticipated.

Overall, there has been much progress in second-line treatment alternatives to salvage chemotherapy for locally advanced and metastatic urothelial carcinoma. EV has exhibited encouraging levels of effectiveness and safety during phase I and II trials, even among individuals with poor prognostic indicators such as liver metastases. Thus, ongoing research endeavors investigating the utilization of this agent in combination with other treatments and in earlier disease states such as NMIBC, especially via intravesical dosing, are both necessary and exciting to evolve the treatment landscape of BCa (57).

Strengths and limitations

We conducted a literature review on current status of immunotherapy, molecularly targeted therapy, and ADCs for NMIBC, utilizing PubMed, Google Scholar,

ClinicalTrials.gov, and ASCO. Our search included peer-reviewed studies, systematic reviews, clinical trial overviews, and ASCO abstracts. Our search strategy encompassed publications as far back as January 2009 for a more historically thorough review regarding the considered treatments. Despite efforts, limitations exist, as our search may have missed relevant literature in databases like Scopus or MEDLINE. Unpublished studies and non-English findings may also be overlooked. Additionally, our approach did not address variations in cohort sizes or variables across previous and ongoing trials for NMIBC treatment studies.

Conclusions

This literature review discusses contemporary promising treatments for NMIBC: pembrolizumab, atezolizumab, erdafitinib, and EV. Pembrolizumab and atezolizumab are ICIs targeting PD-1 and have demonstrated promising results in BCG-unresponsive NMIBC patients, offering promise for bladder preservation in NMIBC treatment. Erdafitinib, an FGFR inhibitor, has achieved accelerated approval for locally advanced and metastatic urothelial cancers with *FGFR2/3* gene variants. Understanding FGFR alterations in BCa at various disease stages should help identify suitable candidates for this targeted therapy. Finally, EV targeting nectin-4 has shown significant survival benefits in advanced urothelial carcinoma. Future research should focus on optimizing patient selection, identifying prognostic biomarkers, developing rational combination therapy regimens, and optimizing intravesical dosing and delivery (i.e., TAR-210) to minimize systemic toxicity. Such milestones would represent a ground-breaking paradigm shift and offer hope for patients with NMIBC. Urologists, medical oncologists, and medical researchers should continue to stay abreast of the rapidly expanding indications for the use of these drugs.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://amj.amegroups.com/article/view/10.21037/amj-23-222/rc

Peer Review File: Available at https://amj.amegroups.com/article/view/10.21037/amj-23-222/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://amj.amegroups.com/article/view/10.21037/amj-23-222/coif). M.J.W. serves as an unpaid editorial board member of *AME Medical Journal* from September 2023 to August 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/amj-23-222
Cite this article as: Drouaud AP, Boyarsky B, Wang Y, Antar R, Sivanesan N, Xu VE, Whalen MJ. Novel immunotherapies and targeted molecular therapies for non-muscle invasive bladder cancer: a literature review. AME Med J 2025;10:4.

Supplementary

Table S1 Example of detailed search strategy for PubMed (pembrolizumab)

Items	Specification
Date of search	28 October 2023
Database	PubMed
Search terms	"non-muscle invasive bladder cancer" AND "pembrolizumab" OR "cancer"
Filters applied	Publication date: January 2009–October 2023
	Language: English
	Study type: clinical trial, reviews, research articles

https://dx.doi.org/10.21037/amj-23-222