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Review – Bladder Cancer

A Systematic Review of Novel Intravesical Approaches for the Treatment of Patients with Non–muscle-invasive Bladder Cancer

Saum Ghodoussipour[a,*], *Trinity Bivalacqua*[b], *Richard T. Bryan*[c], *Roger Li*[d], *M. Carmen Mir*[e], *Joan Palou*[f], *Sarah P. Psutka*[g], *Debasish Sundi*[h], *Mark D. Tyson*[i], *Brant A. Inman*[j]

[a] *Section of Urologic Oncology, Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA;* [b] *Department of Urology, University of Pennsylvania, Philadelphia, PA, USA;* [c] *Bladder Cancer Research Centre, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham, UK;* [d] *Department of Genitourinary Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, USA;* [e] *Department of Urology, Hospital Universitario La Ribera, Valencia, Spain;* [f] *Department of Urology, Fundació Puigvert, Autonoma University of Barcelona, Barcelona, Spain;* [g] *Department of Urology, University of Washington, Seattle, WA, USA;* [h] *Department of Urology, The Ohio State University Wexner Medical Center, Columbus, OH, USA;* [i] *Department of Urology, Mayo Clinic, Phoenix, AZ, USA;* [j] *Division of Urology, Department of Surgery, Western University, London, Ontario, Canada*

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Abstract

Background and objective: Intravesical therapy is central to managing non–muscle-invasive bladder cancer (NMIBC); yet, recurrence and progression remain common, underscoring the need for new treatments. This systematic review evaluates clinical trials of novel intravesical therapies for all risk categories of NMIBC.

Methods: A comprehensive literature search was conducted to identify the clinical trials assessing the effectiveness, safety, and tolerability of intravesical therapies for NMIBC. The search focused on studies published from 2020 to 2024, including trials on bacillus Calmette-Guérin (BCG)-unresponsive/refractory disease as well as on BCG-naïve and intermediate-risk patients. Mechanisms of action and drug delivery methods were summarized. No statistical syntheses were performed due to limited comparative data.

Key findings and limitations: Out of 2998 studies identified, 36 reported on efficacy and safety, and six provided patient-reported outcomes (PROs). Intravesical therapies included BCG-based therapies, chemotherapy combinations, chemical-drug conjugates, thermogels, hyperthermic chemotherapy, osmotic pumps, and gene therapy. Initial response rates ranged from 42% to 85% for BCG-unresponsive/refractory patients and from 65% to 100% for treatment-naïve patients. The 12-mo recurrence-free survival rates ranged from 22% to 83% and 39% to 92%, respectively. Progression and severe toxicity (grade $\geq$3) were rare (0–17% and 0–20%, respectively). PROs were stable. The limitations included early-phase studies, heterogeneous outcome assessments, and a need for research on long-term durability, comparative effectiveness, quality of life, and cost.

Conclusions and clinical implications: This systematic review highlights the promising efficacy and tolerability of novel intravesical therapies for NMIBC. However, further research is needed to refine treatment strategies and assess long-term outcomes, quality

* Corresponding author. Section of Urologic Oncology, Rutgers Cancer Institute and Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA. Tel. +1-732-569-4081.
E-mail address: saum.ghodoussipour@rutgers.edu (S. Ghodoussipour).

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of life, and economic factors. Future studies should include multiarm, multistage designs with a focus on patient-centered outcomes.

ADVANCING PRACTICE

What does this study add?
Recent investigations have led to the development of numerous novel intravesical therapies for non–muscle-invasive bladder cancer, including novel combinations to enhance efficacy, novel drugs and drug targets, and novel mechanisms for enhanced drug delivery. Many of these agents have shown acceptable efficacy and tolerability; yet, treatment selection remains a challenge, with several considerations being underappreciated in the literature. These include comparative data, data on treatment intensity, side effects, cost, and patients' quality of life.

Clinical Relevance
Intravesical therapy remains a cornerstone in the management of non-muscle-invasive bladder cancer. However, up to 30–50% of patients may not respond adequately to the current standard of care. This systematic review highlights several promising novel intravesical agents, demonstrating encouraging results in terms of safety, efficacy, and patient-reported outcomes for this patient population. Nevertheless, the evidence is limited by the lack of long-term follow-up data, cost-effectiveness assessment, and direct comparative analyses between agents, which are essential to inform optimal treatment sequencing. To advance the field, multi-arm, multi-stage clinical trials encompassing various risk groups represent the ideal next step. Associate Editor: Gianluca Giannarini, MD.

Patient Summary
This review highlights the studies on new intravesical therapies for non–muscle-invasive bladder cancer, published between 2020 and 2024. Several promising agents have been approved recently, with more likely to follow. Future research should compare these new treatments with one another and with existing therapies, while also considering factors that influence treatment decisions for both patients and physicians.

1. Introduction

Non–muscle-invasive bladder cancer (NMIBC) is characterized by local recurrence, which occurs in up to two-thirds of patients in the highest-risk groups. It is also characterized by progression to muscle-invasive bladder cancer (MIBC) in up to 20% of high-risk patients [1]. Treatment to reduce the risk of recurrence and progression is therefore a critical part of NMIBC management.

Intravesical therapy has been a mainstay of NMIBC management for over 50 yr. Chemotherapy agents (eg, mitomycin C [MMC] and gemcitabine) and immunotherapy agents (eg, bacillus Calmette-Guérin [BCG]) are used widely to reduce recurrence, progression, or both. Unfortunately, 30–50% of patients will experience cancer recurrence despite intravesical therapies; consequently, new agents and approaches are required [2]. To stimulate the development of novel therapeutics, particularly in patients with BCG-unresponsive disease, the United States Food and Drug Administration (FDA) recommended single-arm trials with attainable benchmarks for success [3]. International groups have since provided consensus statements to guide clinical trial design across all risk groups of NMIBC (Table 1) [4,5]. These factors have provided an impetus for the recent development of novel intravesical therapies and delivery approaches to treat NMIBC. Some of these have been approved recently by the FDA and European Medicines Agency (EMA), but most are still under investigation. Given the extensive volume of ongoing research and the anticipation of further approvals, clinicians are faced with uncertainty regarding how to interpret study results and which novel intravesical therapies to implement in practice. To address this uncertainty, we conducted a systematic review of contemporary clinical trials on novel intravesical approaches for all risk groups of NMIBC, published between 2020 and 2024.

2. Methods

2.1. Search strategy

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols [6]. A systematic literature search of the PubMed-Medline, EMBASE, and Scopus databases was performed in September 2024, including literature from 2000 through 2024. The ClinicalTrials.gov and international conference proceedings were also searched for trials pertaining to NMIBC and intravesical therapy.

The search strategy was developed based on the exploration of relevant databases. The key search terms were

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Table 1 – Risk stratification in non–muscle-invasive bladder cancer and recommended study design

	American Urological Association	European Association of Urology	Recommended clinical trial design
Low-risk tumors	LG solitary Ta ≤3 cm	Primary, solitary, TaT1 LG/G1 <3 cm, no CIS, ≤70 yr old	Ablative trials: single arm, nonrandomized Adjuvant trials: randomized, controlled
	Papillary urothelial neoplasm of low malignant potential	Papillary urothelial neoplasm of low malignant potential	Primary endpoints: ○ Ablative trials: complete response assessed with cystoscopy, photographic documentation, and urine cytology at 3 mo ○ Adjuvant trials: time to first recurrence
		Ta LG/G1 without CIS with at most one additional risk factor (age >70 yr, multifocal, >3 cm)	Threshold for success: ○ Complete response rate >60% ○ 10% increase in recurrence-free survival
Intermediate-risk tumors	LG Ta with recurrence within 1 yr	Patients without CIS not defined by low- and high-risk categories	Ablative trials: single arm, nonrandomized Adjuvant trials: randomized, controlled
	Solitary LG Ta >3 cm		Primary endpoints: ○ Ablative trials: Complete response assessed with cystoscopy, photographic documentation, and urine cytology at 3 mo ○ Adjuvant trials: time to first recurrence
	Multifocal LG Ta		Threshold for success: ○ Complete response rate >60% ○ 10% increase in recurrence-free survival
	HG Ta, ≤3 cm		
	LG T1		
High-risk tumors	HG T1	All T1 HG/G3	BCG naïve and BCG exposed: randomized, controlled BCG unresponsive: single arm
	Any recurrent HG Ta	All CIS	Primary endpoints: BCG naïve/exposed/unresponsive: ○ CIS ± Ta/T1: complete response rate at 3 and/or 6 mo ○ Ta/T1 only: recurrence-free survival ○ All assessed by cystoscopy and urine cytology at 3-month intervals, and CT or MRI urography at 6–12-mo intervals
	HG Ta >3 cm or multifocal	Ta LG/G2 or T1G1, no CIS, with all 3 additional risk factors (age >70, multifocal, >3 cm)	Threshold for success: ○ BCG-naïve CIS: complete response rate of 70% ○ BCG-exposed CIS: complete response rate of 60% ○ BCG-unresponsive CIS: complete response rate of 50% ○ BCG-naïve and BCG-exposed Ta/T1: 10% increase in 2-yr recurrence-free survival ○ BCG-unresponsive Ta/T1: 1-yr recurrence-free survival rate of 30%
	Any CIS	Ta HG/G3 or T1LG, no CIS with at least 2 additional risk factors	
	Any BCG failure in HG patient	T1G2, no CIS, with at least 1 additional risk factor	
	Any variant histology	Very high risk *:	
	Any lymphovascular invasion	Ta HG/G3 + CIS with 3 risk factors	
		T1 G2 + CIS with 2 risk factors	
	Any HG prostatic urethral involvement	T1 HG/G3 + CIS with 1 risk factor	
		T1 HG/G3, no CIS with 3 risk factors	

BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CT = computed tomography; G = grade; HG = high grade; LG = low grade; MRI = magnetic resonance imaging.

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Table 2 – BCG-based therapies

Therapy	Design	Status	Population	Primary endpoint	Key results/objectives
BCG + pembrolizumab (systemic)					
	Phase 1	Published (2021) [15,73]	BCG-unresponsive HG NMIBC or after two induction courses (BCG + chemo, *n* = 13)	Safety and tolerability	1. 3-mo CR = 69% 2. 12-mo DFS = 69%, 24-mo DFS = 38.5% 3. 88% G1–2 AEs, 1 G4 treatment-related AE (adrenal insufficiency) 4. 2/13 progressed 5. 1/13 had cystectomy 6. No change in urinary bother (IPSS) or QoL
	Phase 3 KEYNOTE-676	Ongoing (NCT03711032)	Cohort A: HR NMIBC that is either persistent or recurrent following adequate BCG induction Cohort B. BCG-naïve HR NMIBC	Cohort A: CR in patients with CIS Cohort B: EFS	1. Cohort A: To evaluate whether the combination of pembrolizumab plus BCG induction and maintenance has a superior complete response rate to BCG induction and maintenance in participants with carcinoma in situ (CIS) 2. Cohort B: To evaluate whether the combination of pembrolizumab plus BCG (either reduced maintenance or full maintenance) has superior EFS to BCG induction and full maintenance
BCG + pembrolizumab (intravesical)					
	Phase 1	Published (2022) [18]	BCG-unresponsive HG NMIBC	Safety and tolerability	1. 12-mo RFS = 22% 2. 12-mo PFS = 56% 3. 100% G1–2 AEs, 1 G5 treatment-related AE (myasthenia gravis)
BCG + atezolizumab					
	Phase 1b/2	Published (2023) [16]	BCG-unresponsive CIS ± Ta/T1; *n* = 12 combination, 12 atezolizumab alone	Safety and 6-mo CR	1. 6-mo CR = 42% with BCG + atezolizumab (33% with atezolizumab alone) 2. 100% any AE, 25% serious AEs, zero G4/5 AEs 3. 17% progressed to MIBC
	Phase 3 ALBAN	Ongoing (NCT03799835)	BCG-naïve HR NMIBC	RFS	To evaluate the efficacy of BCG alone vs BCG in combination with atezolizumab, as measured by recurrence-free survival stratified by center and presence of CIS
BCG + durvalumab					
	Phase 1 ADAPT-BLADDER	Published (2023) [17]	BCG-unresponsive HR NMIBC; *n* = 13 BCG + durvalumab, 12 durvalumab + EBRT, 3 durvalumab alone	Recommended phase 2 dose	1. 3-mo CR = 85%, durvalumab + BCG (a) 33% with durvalumab alone and 50% with durvalumab + EBRT 2. 6-mo CR = 83%, durvalumab + BCG (a) 0% durvalumab alone, 33% durvalumab + EBRT 3. 12-mo CR = 73%, durvalumab + BCG (a) 33% with durvalumab + EBRT 4. 15% G3–4 AEs (durvalumab + BCG) 5. 0% progressed on TURBT 6. 6 (21%) had cystectomy and 1 had MIBC
	Phase 3 POTOMAC	Ongoing (NCT03528694)	BCG-naïve HR NMIBC	DFS	To evaluate the efficacy of durvalumab + BCG (induction plus maintenance) compared with durvalumab + BCG induction only or standard of care BCG alone
	Phase 3b PATAPSCO	Ongoing (NCT05943106)	BCG-naïve HR NMIBC	G3 or G4 possibly related AEs	To assess the safety, tolerability, and efficacy profile of durvalumab + BCG (induction and maintenance). Patients will be followed until 2 yr from the date of treatment initiation of the last participant enrolled in this study
BCG + sasanlimab	Phase 3 CREST	Ongoing (NCT04165317)	Cohort A: BCG-naïve HR NMIBC Cohort B (discontinued): BCG-unresponsive HR NMIBC	Cohort A: EFS Cohort B: CR (CIS) and EFS (papillary only)	1. Cohort A: To evaluate the efficacy of subcutaneous sasanlimab + BCG (induction + maintenance) compared with BCG alone (induction and maintenance) in prolonging EFS and to demonstrate that sasanlimab + BCG induction only is superior to BCG alone (induction and maintenance) 2. Cohort B: To evaluate the CR of sasanlimab alone in patients with BCG-unresponsive CIS and EFS in patients with BCG-unresponsive papillary NMIBC

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Table 2 – Continued

Therapy	Design	Status	Population	Primary endpoint	Key results/objectives
BCG + N803					
	Phase 1b	Published (2021) [74]	BCG-naïve IR or HR NMIBC (n = 9)	Maximum tolerated dose of N803	1. 3-mo CR = 78%, 6-mo CR = 89% 2. No dose-limiting toxicity 3. 100% G1–2 AEs, 0 G3–5 AEs 4. 0/9 progressed or required cystectomy
	Phase 2/3	Published (2023, 2024) [20,21]	Cohorts A + C: BCG-unresponsive CIS ± Ta/T1 (A = 82, C = 10) Cohort B: BCG-unresponsive HG Ta/T1 (n = 72)	Cohorts A and C: CR at 3 or 6 mo Cohort B: DFS rate at 12 mo	Cohort A: 1. CR = 71% any time (3 mo = 55%, 6 mo = 56%) 2. 24-mo PFS = 84.7% 3. 24-mo cystectomy-free survival = 89.2% in responders, 63.2% in nonresponders 4. 24-mo DSS = 100%Cohort B: 1. 12-mo DFS = 55.4% 2. 24-mo PFS = 88.8% 3. Cystectomy performed in 5 patients (7%) 4. 24-mo DSS = 97.7%Cohort C: 1. 3-mo CR = 20%Cohorts A and B: 1. AEs (G1–2: 86%, G3: 20%, G4: 2%, G5: 1%) 2. EORTC QLQ-C30 and QLQ-NMIBC24 scores stable at 6, 12, 18, and 24 mo 3. 6-mo physical function scores higher with CR
	Phase 1/2 QUILT 2.005	Ongoing (NCT02138734)	Cohort A: BCG-naïve CIS ± Ta/T1 Cohort B: BCG-naïve Ta/T1	Cohort A: 12-mo CR Cohort B: 24-mo DFS	1. Phase 1b: to evaluate the safety, identify the maximum tolerated dose of N803 and determine the recommended dose level of N803 in combination with BCG for the phase 2b expansion 2. Phase 2b: patients will be randomized to receive either BCG + N803 or BCG alone
Recombinant BCG (VMP1002BC)					
	Phase 1 SAKK 06/14	Published (2020) [22]	IR or HR NMIBC after prior BCG (n = 6)	Dose-limiting toxicity (DLT)	1. G2 AEs in 4/6 patients, 0 G3 AE 2. No DLT-defining AEs
	Phase 2 SAKK 06/14	Published (2022) [23]	IR or HR NMIBC after prior BCG (n = 42)	Recurrence-free rate (RFR) at 60 wk	1. 60-wk RFR = 49.3%, 2-yr RFR = 47.4%, 3-yr RFR = 43.7% 2. 12-wk CR (CIS only) = 55.6% 3. G3 AEs: 4.8%, G4 AEs: 0% 4. EORTC QLQ-C30 and QLQ-NIMBC24: (a) 49% with improvement in emotional functioning (b) 30% with deterioration in physical well-being, 33% in global health status, and 30% in fatigue during induction 5. 60-wk PFS = 77.3% 6. 30% had cystectomy

AE = adverse event; BCG = bacillus Calmette-Guérin; chemo = chemotherapy; CIS = carcinoma in situ; CR = complete response; DFS = disease-free survival; DSS = disease-specific survival; EBRT = external beam radiation therapy; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; G = grade; HG = high grade; HR = high risk; IPSS = International Prostate Symptom Score; IR = intermediate risk; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; N803 = nogapendekin alfa-inbakicept; PFS = progression-free survival; QoL = quality of life; RFS = recurrence-free survival; TURBT = transurethral resection of a bladder tumor.

Table 3 – Intravesical chemotherapy-based combination therapies

Therapy	Design	Status	Population	Primary endpoint	Key results/objectives
Gemcitabine + docetaxel					
	Phase 2	Published (2024) [29]	BCG-naïve HR NMIBC (n = 25)	3-mo CR	1. 3-mo CR = 100% 2. 12-mo RFS = 92% 3. 92% G1/2 AEs, 20% G3 AEs 4. 0 progressed or had cystectomy
	Phase 3 BRIDGE	Ongoing (NCT05538663)	BCG-naïve HG NMIBC	2-yr EFS	To determine EFS of BCG-naïve NMIBC treated with intravesical BCG vs gemcitabine + docetaxel
Cabazitaxel, gemcitabine + cisplatin					
	Phase 1	Published (2020) [30]	BCG-unresponsive or recurrent/relapsing NMIBC (n = 18)	Safety and tolerability	1. 12-mo RFS = 83%, 24-mo RFS = 64% 2. 67% G1/2 AEs, 0 G3–4 AEs 3. 5 had cystectomy, 3 with MIBC 4. 12-mo cystectomy-free survival = 94%, 24-mo cystectomy-free survival = 85%
	Phase 2	Ongoing (NCT02202772)	BCG-unresponsive or recurrent/relapsing NMIBC	3-mo CR	To investigate the efficacy of intravesical chemotherapy consisting of sequential cabazitaxel (100 mg), gemcitabine (2 g), and cisplatin (5 mg) in the salvage setting. Each drug is instilled weekly for 6 wk except for cisplatin, which is given every other week. CR is assessed on postinduction biopsy and urine cytology

AE = adverse event; BCG = bacillus Calmette-Guérin; CR = complete response; DFS = disease-free survival; EFS = event-free survival; G = grade; HG = high grade; HR = high risk; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; RFS = recurrence-free survival.

the following: (1) "bladder cancer," (2) "intravesical therapy," and (3) "outcomes." Different synonyms and terminologies including "recurrence, progression, response, tolerability, adverse event, quality of life, and patient-reported" were taken into account within this search string. The key search terms were combined by using the Boolean operator "AND."

2.2. Eligibility and selection criteria

The eligibility criteria for the selection of relevant studies were defined according to the population, intervention, comparator, and outcome (PICO) framework. The aim was to include clinical trials that reported on the effectiveness, safety, and tolerability of intravesical approaches in NMIBC. Studies were excluded if those were retrospective, not published in English, or reported prior to 2020. Manuscript references were also screened for inclusion. After duplicate removal and based on the eligibility criteria, titles and abstracts were screened by the lead author and verified by the senior author, using the web application Rayyan [7]. Study results that appeared in multiple publications were considered only once or in aggregate. Full texts were reviewed based on the same eligibility criteria.

2.3. Data collection

After study selection, the lead author collected data on outcomes of interest. These included general study characteristics (author, year, publication status, study design, intravesical approach, mechanism of action, treatment schedule, and primary endpoint), oncologic outcomes (recurrence, progression, complete response [CR], durability of response, and cystectomy-free survival), safety/tolerability/adverse events (AEs), and patient-reported outcomes (PROs). Effect measures included response and event rates, survival rates, and PRO measures.

2.4. Synthesis

The identified approaches to intravesical therapy included BCG-based combination therapy, chemotherapy combinations, and novel approaches to drug delivery, including drug conjugates, ablative chemotherapy, device-assisted therapies, and gene therapies.

Relevant information on abstracted studies is presented in Tables 2–9, and select mechanisms of action highlighted in Figs. 1 and 2. Pertinent study characteristics are described in the full text.

No statistical syntheses were performed given that the comparative data were sparse.

3. Results

A total of 2998 articles and six conference proceedings were identified, of which 36 were selected and critically analyzed for evidence synthesis based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses protocols (Supplementary Fig. 1).

3.1. BCG-based therapy

BCG is a toll-like receptor agonist that works mainly via immune system activation [8,9]. Numerous agents have been assessed in combination with BCG to either enhance its efficacy or rescue patients in whom BCG has stopped working (Fig. 1 and Table 2).

3.1.1. BCG + PD-1/PD-L1 immune checkpoint inhibitors

The rationale for testing systemic immune checkpoint inhibitors (ICIs) in NMIBC came from studies showing increased PD-L1 expression in bladder cancers that recurred despite BCG treatment [10,11]. KEYNOTE-057 demonstrated that systemic pembrolizumab monotherapy could rescue some

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Table 4 – Chemical-drug conjugates

Therapy	Mechanism of action	Design	Status	Population	Primary endpoint	Key results/objectives
Oncofid-P-B	Cytotoxic: Chemical conjugation of paclitaxel with hyaluronic acid (HA), leading to improved water solubility and bladder mucoadhesive properties by binding of HA moiety to CD44 receptors					
		Phase 1	Published (2022) [31]	NMIBC unresponsive or intolerant to BCG (n = 21)	Safety and tolerability	1. 6-mo CR = 65%, 15-mo CR = 40% 2. 90% any AE, 30% G3–4 (0 drug related) 3. Cystectomy in 7/12, progression in 2/12
		Phase 3	Ongoing (NCT05024773)	BCG-unresponsive CIS ± Ta/T1	3-mo CR	To assess the efficacy and safety of Oncofid-P-B after induction therapy consisting of 12 weekly intravesical instillations. Patients who achieve a CR will enter the maintenance phase and receive monthly treatment for an additional 12 mo or until recurrence of CIS/Ta-T1 or progression to MIBC or extravesical disease
Large surface area microparticle docetaxel	Immune mediated + cytotoxic: Microparticles formulated for tissue entrapment and sustained local drug release. Direct injection with resultant tumor necrosis, inflammation, and immune cell infiltration	Phase 1/2	Published (2022) [32]	HR NMIBC (n = 19)	Safety	1. 3-mo RFS = 100%, 6-mo RFS = 78%, 12-mo RFS = 50% 2. 100% G1 AEs, 57.8% G2 AEs, 0 G3/4 AEs 3. 1 patient had cystectomy
Onco-Therad	Nanometric components induces immune stimulation through toll-like receptor 4, increased IFN-α and IFN-γ production, and downregulation of RANK and RANK-L	Phase 1/2	Published (2023) [34]	BCG refractory, intolerant, replapsed NMIBC (n = 44)	CR	1. 24-mo CR = 73% 2. 0 progression 3. 67% G1/2 AEs, 13.6% G3/4 AEs

AE = adverse event; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; G = grade; HR = high risk; IFN = interferon; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer.

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Table 5 – Reversed-phase thermogels

Therapy	Mechanism of action	Design	Status	Population	Primary endpoint	Key results/objectives
UGN-102	Cytotoxic: Reverse thermal gel containing mitomycin					
		Phase 2 Optima II	Published (2022) [75]	LG IR NMIBC (n = 63)	3-mo CR	1. 3-mo CR = 65%, 12-mo CR = 39% 2. 90.5% any AE, 8% G ≥3 (0 drug related)
		Phase 3 ATLAS	Published (2023) [35]	LG IR NMIBC (n = 282)	DFS	1. 3-mo CR = 65% with UGN-102 vs 64% with TURBT 2. 15-mo DFS = 72% with UGN-102 vs 50% for TURBT 3. 75% any AE with UGN-102 vs 48% with TURBT (a) Zero treatment-related serious AEs with UGN-102 vs 1 with TURBT 4. EORTC QLQ-NMIBC24 either improved or not worsened in those treated with UGN-102 or TURBT alone 5. 8.5% progressed to HG NMIBC with UGN-102 vs 6.4% with TURBT
		Phase 3 ENVISION	Ongoing (NCT05243550)	LG IR NMIBC	3-mo CR	1. Single-arm, multinational study to evaluate the efficacy and safety of UGN-102 as primary chemoablative therapy 2. Preliminary data (n = 240) [39] (a) 3-mo CR = 79.6% (b) 12-mo duration of response = 82.3%
		Phase 3b	Ongoing (NCT05136898)	LG IR NMIBC	Treatment-related AEs and feasibility	To demonstrate that home instillation of UGN-102 is a feasible alternative to instillation in a clinical setting, which might mitigate some of the challenges in the patient experience (logistical, expense, and comfort)
UGN-201 and UGN-301	Reverse thermal gel containing imiquimod (UGN-201) and zalifrelimab (UGN-301)	Phase 1	Ongoing (NCT05375903)	Recurrent NMIBC	Dose-limiting toxicities	To investigate intravesical delivery of UGN-301 either as monotherapy or in combination with UGN-201, or gemcitabine given once weekly for 6 wk and then once every 3 mo until 12 mo

AE = adverse event; CR = complete response; DFS = disease-free survival; EORTC = European Organisation for Research and Treatment of Cancer; G = grade; HG = high grade; IR = intermediate risk; LG = low grade; NMIBC = non–muscle-invasive bladder cancer; TURBT = transurethral resection of a bladder tumor.

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Table 6 – Ablative aqueous chemotherapies

Therapy	Design	Status	Population	Primary endpoint	Key results/objectives
Mitomycin	Phase 2 CALIBER	Published (2020) [36]	Recurrent LG NMIBC (n = 82)	3-mo CR	1. 3-mo CR = 37% (20/54) with chemoablation vs 80.8% (21/26) with surgical resection 2. 0 G3/4 AEs 3. No difference in PROs (EORTC QLQ-C30 and QLQ-NMIBC24)
Mitomycin	Randomized controlled trial DaBlaCa-13	Published (2020, 2023) [37,38]	Recurrent LG and HG Ta NMIBC (n = 120)	CR at 4 wk	1. CR in 33/59 (57%) after chemoablation 2. 12-mo RFS = 36% with chemoablation vs 43% with surgical resection and adjuvant MMC induction 3. 1 G3 AE (cystitis) with chemoablation, 2 G3 (cystitis, fever) with surgical resection, 0 G4/5 AEs

AE = adverse event; CR = complete response; EORTC = European Organisation for Research and Treatment of Cancer; G = grade; HG = high grade; LG = low grade; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; PRO = patient-reported outcome; RFS = recurrence-free survival.

patients with BCG-unresponsive NMIBC, which led to its FDA approval [12,13]. A similar result was found in SWOG-1605 using systemic atezolizumab, although it failed to pass the predefined futility analysis [14]. The next step was to combine these systemic agents with BCG, and several early phase trials were completed in the BCG-unresponsive setting to investigate whether reintroducing BCG in combination with a checkpoint inhibitor can enhance therapeutic activity. Three phase 1 trials using pembrolizumab, atezolizumab, and durvalumab in combination with BCG after prior failure of BCG have reported outcomes with CR rates ranging from 42% to 85% [15–17]. While all three trials included a cohort receiving BCG + ICI, the trial of BCG + atezolizumab included an atezolizumab monotherapy comparator arm, and the ADAPT-BLADDER trial of BCG + durvalumab included durvalumab monotherapy and combination of durvalumab + external beam radiation therapy (EBRT; 6 Gy for three cycles). The latter two studies demonstrated superior efficacy with BCG + ICI (42–83% 6-mo CR) to ICI alone (0–33% 6-mo CR) or with durvalumab + EBRT (33% 6-mo CR). The latter studies also mandated bladder biopsy at 6 mo in contrast to the trial of BCG + pembrolizumab, where efficacy was assessed using cystoscopy and cytology, and for-cause biopsy only. AEs were common (88–100%) but were largely limited to grade (G) 1 and 2 events typical for patients receiving intravesical therapy, with only one reported case of G4 treatment-related adrenal insufficiency in a patient receiving BCG + pembrolizumab. PROs were reported in a 2-yr follow-up of the phase 1 trial of BCG + pembrolizumab using the American Urological Association (AUA) International Prostate Symptom Score and quality of life validated surveys, which showed no change throughout treatment. While the published literature is limited to early-phase trials, there are several ongoing phase 3 trials investigating checkpoint inhibitors alone or in combination with BCG in patients who are BCG naïve or exposed to BCG. These include ALBAN (atezolizumab, NCT03799835), POTOMAC (durvalumab, NCT03528694), phase3b expansion PATOPSCO trial (NCT05943106), and KEYNOTE-676 (pembrolizumab, NCT03711032).

Alternative dosing strategies have also been attempted to decrease the risk of toxicity with systemic administration of ICIs. A small phase 1 trial of nine patients with BCG-unresponsive high-risk NMIBC investigated BCG + intravesical administration of pembrolizumab. Intravesical pembrolizumab was administered once 2 wk prior to induction therapy, which consisted of BCG once a week for 6 wk and intravesical pembrolizumab every other week. Maintenance was carried out with intravesical pembrolizumab only every 2 wk until week 17 and then every 4 wk for the remainder of 1 yr. The 12-mo recurrence-free survival (RFS) was 22% and G1–2 AEs occurred in all patients, with one G5 event in a patient who died of myasthenia gravis [18]. The safety of an intravesical suburothelial injection of durvalumab was assessed in a phase 1 trial of 11 patients with urothelial carcinoma 2 wk prior to radical cystectomy. Durvalumab was diluted with normal saline and injected via cystoscope in 1-ml aliquots across 25 locations throughout the bladder. There were no significant changes in PROs assessed by the AUA Symptom Score and O'Leary Interstitial Cystitis Scale, and 14 AEs were recorded (ten G1, three G2, and one G3 events), but there were no G4 or G5 events and none that were considered immune related [19]. An ongoing phase 3 trial (CREST, NCT04165317) is investigating a subcutaneous injection of the ICI sasanlimab alone and in combination with BCG for patients with BCG-naïve high-risk NMIBC.

3.1.2. *BCG + nogapendekin alfa-inbakicept*

Nogapendekin alfa-inbakicept (N803) is an interleukin-15 superagonist that activates natural killer cells as well as effector and memory T cells. The combination of N803 and BCG was assessed in QUILT 3.032 in patients with BCG-unresponsive high-risk NMIBC. Cohort A included patients with carcinoma in situ (CIS) with or without papillary disease. A CR was achieved at any time in 58/82 (71%) patients (3- and 6-mo CR = 55% and 56%, respectively), with a median duration of response of 27 mo. N803 was instilled with BCG weekly for 6 wk, with an option for repeat induction when response was not achieved and so long as there was no evidence of ≥T1 disease. At 24 mo, cystectomy-free survival rates were 89% and 63.2% in patients with a CR and in nonresponders, respectively. The disease-specific survival rate was 100%. In patients with papillary disease, the 12-mo disease-free survival (DFS) rate was 55%, with median DFS of 19 mo. Notably, N803 was tested

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Table 7 – Hyperthermic intravesical chemotherapy

Therapy	Mechanism of action	Design	Status	Population	Primary endpoint	Key results/objectives
Gemcitabine via BR-PRG	Immune mediated + cytotoxic: Conductive hyperthermia with gemcitabine	Phase 1	Published (2023) [44]	IR and HR NMIBC (n = 18)	Adverse events	1. 12-mo recurrence: IR = 23.8%, HR = 37.5% 2. 55.6% any AE, 16.7% G3 (acute cystitis) AEs, 0 systemic toxicity
MMC via COMBAT BRS	Immune mediated + cytotoxic: Conductive hyperthermia with MMC					
		Prospective trial	Published (2021) [76]	IR and HR NMIBC (n = 502)	Treatment effectiveness (RFS, PFS, OS)	1. 5-yr RFS = 50.37% (a) 53.3% IR, 47.14% HR 2. 5-yr PFS = 89.83% (a) 94.02% IR, 84.23% HR 3. AEs in 31.4% (a) G1/2: 28.72%, G3/4 2.7%
		Prospective trial	Published (2021) [51]	IR and HR NMIBC (n = 14)	Safety	1. Disease free = 85% (median follow-up 11 mo) 2. Zero progressions 3. 50% any AEs, 0 G3–5 AEs, 6 discontinued treatment
		Phase 2 HIVEC-HR	Published (2022) [46]	HR NMIBC without CIS (n = 50)	24-mo RFS	1. 24-mo RFS (a) ITT: 86.5% for HIVEC vs 71.8% for BCG (p = 0.214) (b) Per protocol: 95.0% for HIVEC vs 75.1% for BCG (p = 0.322) 2. G3 AEs: 16.7% with HIVEC vs 16.7% with BCG 3. No G4–5 events with HIVEC 4. 24-mo PFS (a) ITT: 95.7% with HIVEC vs 71.8% with BCG (p = 0.071) (b) Per protocol: 100% with HIVEC vs 75.1% with BCG (p = 0.102) 5. Cystectomy rate: 4% with HIVEC vs 20% with BCG
		Phase 3 HIVEC I	Published (2023) [50]	IR NMIBC (n = 319)	24-mo RFS	1. 24-mo RFS (a) ITT: 77% vs 82% vs 80% (b) Per protocol: 77% vs 83% vs 80% 2. Adverse events: 33% vs 36% vs 48% (a) Dysuria/bladder spasm: 28% vs 39% vs 40% (b) Serious adverse events: 9% vs 9% vs 9% (0 treatment related) 3. No difference in IPSS or FACT-BI 4. Progression to MIBC: 3.7% vs 0.9% vs 0.9%
		Phase 2 HIVEC II	Published (2023) [49]	IR NMIBC (n = 259)	24-mo DFS	1. 24-mo DFS = 61% HIVEC vs 60% control (a) hazard ratio 0.92, 95% CI 0.62-1.37 2. Any AE: 66% HIVEC vs 60% control (a) G3: 9.9% HIVEC vs 5.5% control 3. PFS: HR 2.87, 95% CI 0.83-9.98 (per protocol)

AE = adverse event; BCG = bacillus Calmette-Guérin; chemo = chemotherapy; CI = confidence interval; CIS = carcinoma in situ; DFS = disease-free survival; FACT-BI = Functional Assessment of Cancer Therapy—Bladder; G = grade; HIVEC = hyperthermic intravesical chemotherapy; HR = high risk; IPSS = International Prostate Symptom Score; IR = intermediate risk; ITT = intention to treat; MIBC = muscle-invasive bladder cancer; MMC = mitomycin C; NMIBC = non–muscle-invasive bladder cancer; OS = overall survival; PFS = progression-free survival; RFS = recurrence-free survival.

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Table 8 – Intravesical osmotic pumps

Therapy	Mechanism	Design	Status	Population	Primary endpoint	Key results/objectives
TAR-200	Cytotoxic: Slow-release osmotic pump containing gemcitabine exchanged every 3 wk					
		Phase 1	Published (2024) [55]	IR NMIBC (n = 12)	Safety and tolerability	1. CR = 42% 2. AEs: (a) 92% G1/2 (b) Zero G ≥3 (c) 2/12 refused reinsertion
		Phase 1	Published (2023) [52]	MIBC refusing or unfit for curative-intent therapy (n = 35)	Safety and tolerability	1. 3-mo CR = 31.4% 2. 3-mo partial response = 8.6% 3. Overall response = 40.0% 4. 2 had pretzel removed for poor tolerability 5. 12-mo PFS = 70.5%
		Phase 1	Published (2022) [53]	Cisplatin refusing or ineligible T2a-T3b N0-N1 M0 undergoing radical cystectomy (n = 23)	Safety	1. Arm 1 (residual tumor >3 cm) (a) Path downstaging in 4/10 (b) 1/10 with CR 2. Arm 2 (residual tumor <3 cm) (a) Path downstaging in 6/10 (b) 3/10 with CR 3. Zero G ≥3 AEs
		Phase 3 SunRISe-5	Ongoing (NCT06211764)	Recurrent papillary only HR NMIBC	DFS	To compare DFS in participants with recurrence of papillary-only HR NMIBC within 1 yr of last dose of BCG therapy versus investigator's choice of single-agent intravesical chemotherapy
		Phase 3 SunRISe-4	Ongoing (NCT04919512)	Cisplatin ineligible or refusing MIBC scheduled for radical cystectomy	Pathologic CR	To evaluate the antitumor effects of TAR-200 in combination with intravenous cetrelimab and IV cetrelimab alone
		Phase 3 SunRISe-3	Ongoing (NCT05714202)	BCG-naïve HR NMIBC	EFS	To compare EFS in participants with BCG-naïve HR NMIBC between treatment with TAR-200 plus cetrelimab (group A) and TAR-200 alone (group C) versus intravesical BCG (group B)
		Phase 3 SunRISe-2	Ongoing (NCT04658862)	MIBC refusing or unfit for radical cystectomy	Bladder intact EFS	To compare bladder intact EFS in participants receiving TAR-200 in combination with intravenous cetrelimab versus concurrent chemoradiotherapy
		Phase 2b SunRISe-1	Ongoing (NCT04640623)	BCG-unresponsive HR NMIBC	Cohorts 1, 2, 3: CR Cohort 4: DFS	1. To evaluate overall CR in participants treated with TAR-200 in combination with cetrelimab (cohort 1), or TAR-200 alone (cohort 2), or cetrelimab alone (cohort 3) with CIS ± Ta/T; and DFS in participants treated with TAR-200 alone with papillary disease only (cohort 4) 2. Preliminary data (n = 85, 55 evaluable for efficacy) [54] (a) CR = 83% with TAR-200 monotherapy (b) 1-yr duration of response = 75% (c) Treatment-related AEs: 72% (i) Grade ≥3: 8% (ii) Serious: 5% (iii) No treatment-related deaths

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Table 8 – Intravesical osmotic pumps

Therapy	Mechanism	Design	Status	Population	Primary endpoint	Key results/objectives
TAR-210	Cytotoxic: Slow-release osmotic pump containing erdafitinib exchanged every 12 wk					
		Phase 1	Ongoing (NCT05316155)	MIBC or NMIBC with FGFR alterations	Safety	1. To determine safety and preliminary clinical activity (a) Cohort 1: BCG experienced NMIBC refusing or unfit for cystectomy (b) Cohort 2: BCG experienced NMIBC willing and eligible for radical cystectomy (c) Cohort 3: recurrent, intermediate-risk NMIBC (d) Cohort 4: MIBC willing and eligible for radical cystectomy 2. Preliminary data (57) (a) Cohort 1 (n = 11): 82% recurrence free (b) Cohort 3 (n = 15): 86.7% recurrence free (c) Zero dose-limiting toxicities, 2 pts discontinued due to low-grade urinary symptoms, 1 had serious AEs of pyelonephritis and sepsis
		Phase 3 MoonRISe-1	Ongoing (NCT06319820)	Low-grade IR NMIBC	DFS	To compare DFS between participants receiving treatment with TAR-210 and those receiving investigator's choice of intravesical chemotherapy for treatment of IR NMIBC with susceptible FGFR alterations

AE = adverse event; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; DFS = disease-free survival; EFS = event-free survival; EORTC = European Organisation for Research and Treatment of Cancer; FGFR = fibroblast growth factor receptor; G = grade; HR = high risk; IR = intermediate risk; IV = intravenous; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; PFS = progression-free survival; pts = patients.

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Table 9 – Viruses and vectors

Therapy	Mechanism	Design	Status	Population	Primary endpoint	Key results/objectives
Cretostimogene + DDM	Immune mediated + cytotoxic: Replication-competent oncolytic adenovirus that selectively replicates in retinoblastoma defective bladder tumor cells. The adenovirus also causes transgene expression of granulocyte-macrophage colony-stimulating factor for immune activation. DDM is a nonionic detergent that enhances the viral transduction of the urothelium					
		Phase 2 BOND-002	Published (2018) [60]	HG NMIBC and previously failed BCG (n = 45)	6-mo response	1. 6-mo CR = 47% a. CIS = 58% b. CIS ± Ta/T1 = 50% c. CIS + Ta/T1 = 33% d. Pure Ta/T1 = 33% 2. 87% at least 1 AE, 3% G3 AEs, 0 G4/5 AEs 3. 2 progressed to MIBC
		Phase 3BOND-003	Ongoing (NCT04452591)	BCG-unresponsive HR NMIBC	CIS containing: CR at any time Papillary only: HG EFS	1. Open-label, single-arm trial to evaluate cretostimogene in patients with NMIBC who have failed prior BCG therapy 2. Preliminary data (all CIS containing, n = 112) [61] (a) CR at any time = 75.2% (i) 83% of responders with ongoing response at 12 mo (b) 12-mo cystectomy-free survival = 92.4% (c) 12-mo progression-free survival = 96.7% (d) Treatment-related AEs: 62.5% (i) Zero G ≥3 AEs
		Phase 2CORE-001	Published (2024) [62]	BCG-unresponsive CIS ± Ta/T1 (n = 35)	12-mo CR	1. CR at any time = 83%, 12-mo CR = 57%, 24-mo CR = 51% 2. 14% G3 AEs (ICI related), 0 G4–5 AEs 3. 12-mo cystectomy-free survival = 80% (a) Zero progressions
		Phase 3PIVOT-006	Ongoing (NCT06111235)	LG IR NMIBC	RFS	To evaluate the RFS of TURBT followed by cretostimogene induction and quarterly maintenance vs TURBT followed by observation for IR NMIBC

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Table 9 – Viruses and vectors

Therapy	Mechanism	Design	Status	Population	Primary endpoint	Key results/objectives
		Phase 1	Ongoing (NCT04610671)	Cisplatin-ineligible MIBC	AEs	To evaluate the safety and efficacy of combination neoadjuvant therapy using intravesical CG0070 and IV nivolumab in cisplatin-ineligible patients with MIBC
Nadofaragene firadenovec + Syn3	Immune mediated: Nonreplicating recombinant adenovirus vector–based gene therapy that delivers a copy of the human interferon alfa-2b gene to urothelial cells and Syn3, a polyamide surfactant that enhances the viral transduction of the urothelium					
		Phase 3	Published (2021) [64]	BCG-unresponsive NMIBC (n = 151)	12-mo CR	1. 3-mo CR in CIS ± HG Ta/T1 = 53.4% 2. Durable 12-mo CR = 45.5% 3. 93% any AE (a) Drug-related AE: 70% (b) G3/4: 18%, 4%, drug related; G5: 0 4. 8 progressed to MIBC (a) 5 with CIS and 2 with papillary 5. 40 (26%) underwent cystectomy (a) 5/40 (12.5%) upstaged to MIBC or extravesical disease at cystectomy
		Phase 4 ABLE-41	Ongoing NCT06026332	Any patient prescribed and scheduled treatment with nadofaragene	3- and 12-mo CR in CIS ± HG Ta/T1	Multicenter, prospective, noninterventional study to collect data on the early use of nadofaragene in the USA
EG-70	Nonviral gene therapy; nanoparticle containing a DNA plasmid that encodes interleukin-12 and stimulates the retinoic acid-inducible gene I pathway	Phase 1/2 LEGEND	Ongoing (NCT04752722)	Phase 1: BCG-unresponsive NMIBC Phase 2: BCG-naïve, BCG-unresponsive, and BCG-exposed NMIBC	Phase 1: AEs Phase 2: 48-wk CR	To evaluate the safety and efficacy of intravesical EG-70: 1. Phase 1 dose escalation to establish safety and recommended the phase 2 dose 2. Phase 2 study to establish efficacy

AE = adverse event; BCG = bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; DDM = n-dodecyl-β-D-maltoside; EFS = event-free survival; G = grade; HG = high grade; HR = high risk; ICI = immune checkpoint inhibitor; IR = intermediate risk; IV = intravenous; LG = low grade; MIBC = muscle-invasive bladder cancer; NMIBC = non–muscle-invasive bladder cancer; RFS = recurrence-free survival; TURBT = transurethral resection of a bladder tumor.

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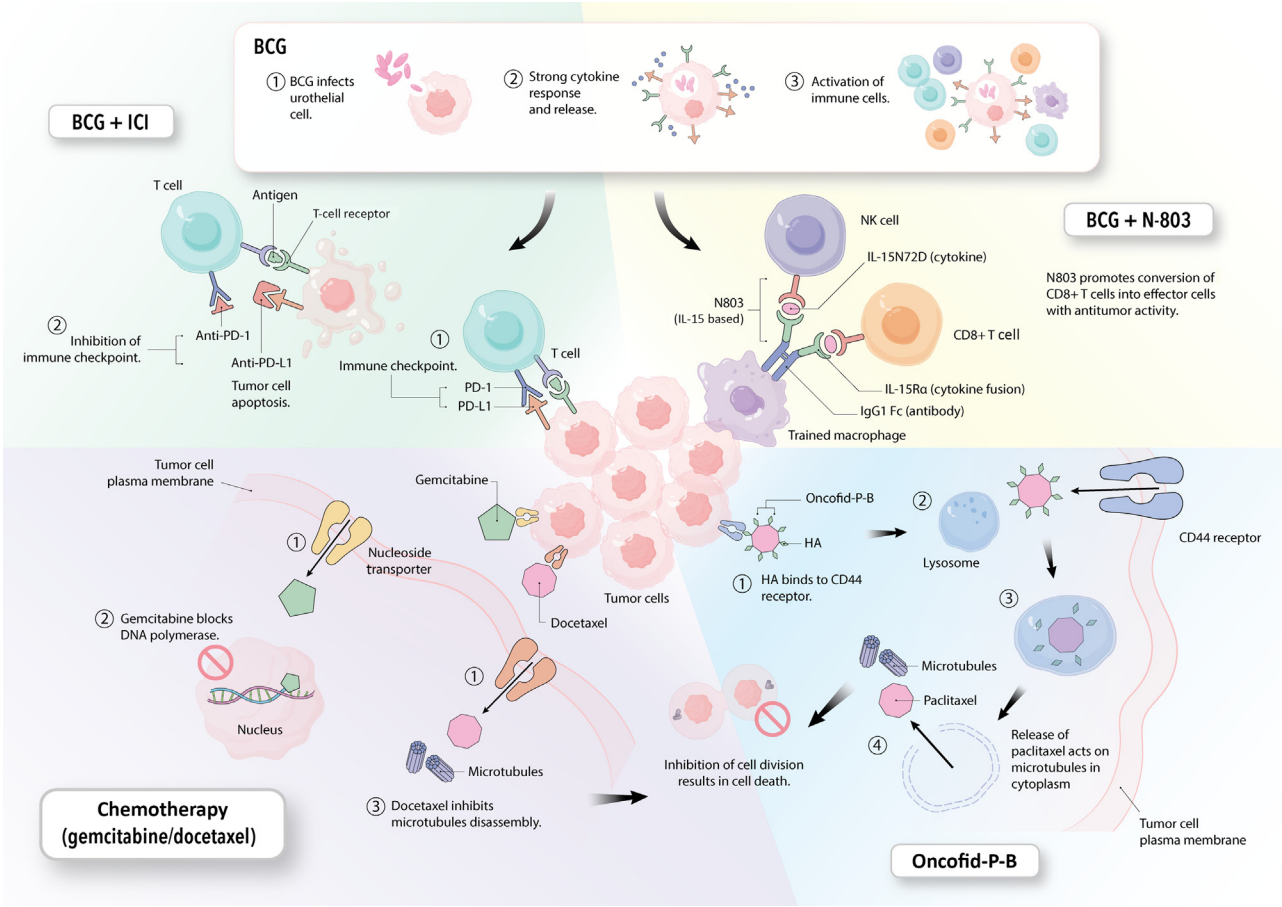

Fig. 1 – Intravesical therapies and mechanisms of action: BCG: attaches to urothelial cells for internalization and stimulation of cytokine response, activating immune cells with resultant tumor-cell death. BCG + immune checkpoint inhibitor (ICI): monoclonal antibody blocks immune inhibiting interaction of programmed cell death-ligand 1 (PD-L1) on tumor cells and programmed cell death receptor protein 1 (PD-1) on immune cells, leading to tumor cell apoptosis. BCG + nogapendekin alfa-inbakicept (N-803): IL-15 based fusion protein complex composed of a mutated form of IL-15 (IL-15N72D) complexed with the dimeric high-affinity receptor alpha (IL-15Rα) and IgG1 FC antibody that promotes enhanced activation of CD8 T cells and natural killer (NK) cells. Combination chemotherapy (gemcitabine/docetaxel): Gemcitabine is a nucleoside analog that is internalized into urothelial cells and inhibits DNA synthesis by blocking DNA polymerase. Docetaxel is sequentially instilled and inhibits microtubule disassembly, resulting in impairment of mitotic progression, leading to cell cycle arrest. Oncofid-P-B: paclitaxel conjugated with hyaluronic acid (HA) improves water solubility and urothelial penetration via binding of HA to CD44 receptors for receptor-mediated endocytosis, lysosomal degradation, and cytoplasmic release of paclitaxel that interferes with microtubule disassembly. BCG = bacillus Calmette-Guérin; IL = interleukin; N803 = nogapendekin alfa-inbakicept.

alone in cohort C, but the 3-mo CR rate was 20%, and this arm was closed for futility [20]. AEs were again largely limited to G1 and G2 events (86%) such as dysuria, hematuria, and pollakiuria (daytime frequency); 15% of patients were hospitalized for G3 events, including four with hematuria, and one patient had a cardiac arrest resulting in death. PROs were recorded using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-NMIBC24 questionnaires and remained stable after 24 mo, supporting the tolerability of this treatment approach [21]. The combination of N803 and BCG was FDA approved for BCG-unresponsive NMIBC in April 2024. A phase 1b dose escalation trial with 2b expansion to a randomized trial of N803 plus BCG versus BCG alone, in BCG-naïve patients with high-grade NMIBC, is ongoing (QUILT 2.005, NCT02138734).

3.1.3. *Recombinant BCG*

VPM1002BC is a recombinant live strain of BCG that has been engineered, in which the *urease C* gene is deleted by insertion of the gene encoding the hemolysin listeriolysin, which may enhance immune response and reduce the lifespan of the agent to reduce treatment-associated side effects. Safety was shown in a phase 1 trial of six patients [22], and the phase 2 expansion included 42 patients [23]. This study found a recurrence-free rate of 47.4% at 2 yr, with only two G3 urinary tract infections. PROs were assessed using the validated EORTC QLQ-C30 and QLQ-NIMBC24 questionnaires. While there was some impairment in urinary symptoms, future worries, and sexual issues during induction treatment, most of the scales were stable from baseline through maintenance therapy, and 49% reported an improvement in emotional functioning during induction.

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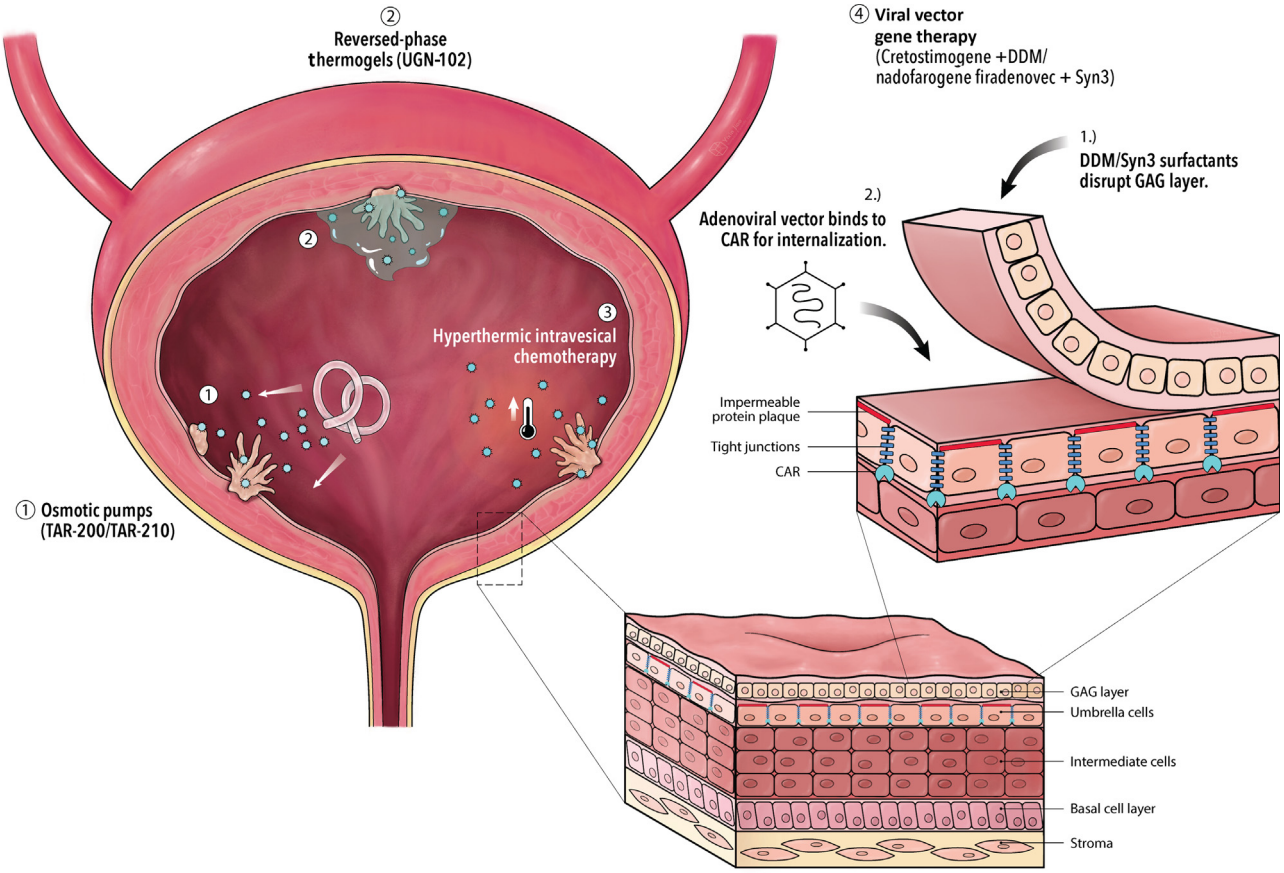

Fig. 2 – Novel mechanisms of drug delivery: Osmotic pumps: semipermeable silicone tubes that self-coil in the bladder and slowly dissolve their contents osmotically. This includes the nucleoside analog, gemcitabine (TAR-200), and the FGFR tyrosine kinase inhibitor erdafitinib (TAR-210). Reversed-phase thermogels: cross-linked polymers create a hydrophilic compound that is liquid at room temperature but converts to a gel form at body temperature. Hydrogels containing drugs such as mitomycin (UGN-102) prolong dwell time compared with aqueous instillations. Hyperthermic intravesical chemotherapy: addition of heat to intravesical chemotherapy improves drug delivery through the bladder wall, sensitizes tumor cells to chemotherapy, and enhances immune activity. Viral vector gene therapy: intravesical delivery of genes to urothelial cells for sustained drug exposure by cancerous and potentially precancerous urothelial cells. Syn3 and n-dodecyl-β-D-maltoside (DDM) are nonionic surfactants that disrupt the polyanionic glycosaminoglycan (GAG) layer, impermeable plaques, and tight junctions to facilitate viral interaction with the coxsackie/adenovirus receptor (CAR). This facilitates viral entry for expression of immune-stimulating transgenes, such as interferon alfa2b (IFNα-2b) in the nonreplicating vector, nadofaragene firadenovec, and granulocyte-macrophage colony-stimulating factor (GM-CSF) in cretostimogene, which selectively replicates in cells defective in the retinoblastoma (Rb) pathway. FGFR = fibroblast growth factor receptor.

3.2. *Chemotherapy-based combinations*

The combination of gemcitabine and docetaxel (GEM/DOCE; Fig. 1) has shown intriguing results in several retrospective series, albeit no prospective study has been conducted to date in the BCG-unresponsive setting (Table 3). Gemcitabine is a nucleoside analog that inhibits DNA synthesis by blocking DNA polymerases [24], while docetaxel binds to microtubulin and impairs mitosis, leading to cell cycle arrest and cell death [25]. Steinberg et al [26] reported a multi-institutional series of 276 patients treated with GEM/DOCE after BCG failure. They found a 2-yr RFS rate of 46% with excellent tolerability and a low rate of progression (4% on transurethral resection of a bladder tumor [TURBT] and 4% at the time of cystectomy). This regimen has since shown promising efficacy in intermediate-risk NMIBC (85% 12-mo RFS) [27] and in BCG-naïve NMIBC (82% 24-mo RFS) [28]. A recently completed single-arm phase 2 trial of 25 patients with BCG-naïve high-risk NMIBC confirmed the efficacy seen in the retrospective study (92% 12-mo RFS), with 23/25 patients experiencing G1 AEs [29]. BCG and GEM/DOCE are being compared in BCG-naïve NMIBC patients in BRIDGE (NCT05538663), a randomized phase 3 trial that is prospectively collecting PROs. Further prospective studies such as BRIDGE are needed to validate this combination therapy.

A phase 1 trial showed excellent responses and tolerability for a combination of gemcitabine, cisplatin, and cabazitaxel, and further investigation continues in a phase 2 expansion (NCT02202772) [30].

3.3. *Novel mechanisms of action and drug delivery*

3.3.1. *Chemical-drug conjugates*

3.3.1.1. Oncofid-P-B. Paclitaxel is a taxane that interferes with microtubule disassembly similar to docetaxel [25] but is much less water soluble (Table 4). Oncofid-P-B is a novel agent that consists of paclitaxel conjugated with hyaluronic acid, which improves its water solubility and

urothelial penetration (Fig. 1). A phase 1 trial demonstrated the safety and efficacy of Oncofid-P-B in 20 patients with BCG-unresponsive NMIBC [31]. The agent is given intravesically with weekly 12× induction followed by monthly maintenance for 1 yr. A CR was observed in 15/20 (75%) patients after induction, and 8/15 (40%) remained disease free after 12 mo of maintenance. Any AE was reported in 18/20 (90%) patients, but only three were drug related and included nausea, hematuria, proteinuria, and urticaria. PROs were not recorded. Oncofid-P-B is currently being studied in a larger trial in patients with BCG-unresponsive CIS (NCT05024773).

3.3.1.2. Micro- and nanoparticles. These are organic or inorganic materials of varying sizes that can be conjugated to drugs to facilitate penetration and delivery to the urothelium. Large surface area microparticle docetaxel (LSAM-DTX) was assessed in a phase 1 trial [32]. The authors performed a direct endoscopic injection of LSAM-DTX into the tumor bed at the time of TURBT. This was followed immediately by a 30-min intravesical instillation of a 25 ml aqueous solution containing additional LSAM-DTX. After 4 wk, patients then began an induction course of once weekly intravesical instillation for 6 wk followed by 6 wk of rest and then a 3-wk maintenance course. The rationale for a direct injection was based on preclinical studies showing significant tumor reduction and immune cell infiltration due to a proinflammatory and immunogenic response to chemotherapy-induced tumor cell necrosis [33]. Thus, the mechanism of action includes both direct cytotoxic effects of chemotherapy and indirect stimulation of immune effector cells. In the 19 patients enrolled in the trial, including 14 with prior BCG treatment, the drug was found to be well tolerated and without any serious drug-related AEs. The estimated RFS rates in the high-dose cohort at 3, 6, and 12 mo were 100%, 78%, and 50%, respectively. A phase 1/2 trial of 14 patients with previously BCG-treated or BCG-intolerant NMIBC assessed Onco-Therad, a nanoparticle-based immunotherapeutic that stimulates toll-like receptor 4, leading to increased production of interferon and down-regulation of the receptor activator of nuclear factor-κB (RANK) system. Treatment consisted of a 1-h intravesical instillation and an intramuscular injection once weekly for 6 wk, followed by biweekly maintenance for 3 mo and monthly treatment for 9 mo. Quarterly treatments were continued in the 2nd year. The CR rate at 24 mo was 73%; AEs were mostly limited to G1/2 events in 63.7% of patients, but 13.6% experienced G3/4 events, including skin rash, diarrhea, and shortness of breath [34].

3.3.2. Reversed-phase thermogels

Reversed-phase thermogels (Fig. 2 and Table 5) are formed by crosslinking polymers to create a hydrophilic compound that is liquid at −3°C to 5°C but becomes a gel at 19°C. Hydrogels dissolve within the body slowly and, when mixed with chemotherapy agents, release the agent slowly, increasing urothelial dwell and contact times.

3.3.2.1. UGN-102 and ablative chemotherapy. UGN-102 is a reversed-phase thermogel containing MMC that is administered at a volume of 60 ml and a concentration of 1.33 mg/ml. The ATLAS trial enrolled patients with low-grade intermediate-risk NMIBC diagnosed on biopsy and with visible tumor left in situ. Patients received either chemoablative UGN-102 once weekly for 6 wk followed by TURBT for residual disease or TURBT alone. The study was powered to assess DFS, but only 282 of a planned sample of 632 patients were enrolled. Residual low-grade disease was considered a DFS event only after TURBT. The 3-mo CR occurred in 65% of the 142 patients who had upfront UGN-102 and in 64% treated with TURBT. The estimated DFS rates at 15 mo were 72% for UGN-102 and 50% for TURBT. However, recurrence rates in the TURBT arm were higher than expected since this group did not receive adjuvant intravesical therapy [35]. PROs were either improved or not worsened in both groups, and there were no serious drug-related AEs but one serious treatment-related AE in a patient with hematuria after TURBT. Chemoablation using aqueous MMC has been assessed in several trials (Table 6), including the phase 2 CALIBER trial, where 54 patients with recurrent low-grade NMIBC were treated with four once-weekly instillations of 40 mg MMC and compared with 26 patients treated with standard surgical resection [36]. Recruitment was ended early as chemoablation did not meet its prespecified threshold (37% 3-mo CR vs 81% with surgical resection). However, greater efficacy was seen with a more intensive regimen of 40 mg MMC three times a week for 2 wk in the DaBlaCa-13 randomized trial of standard MMC for chemoablation. This trial included patients with both low- and high-grade noninvasive papillary disease and randomized them to either chemoablative MMC and TURBT for an incomplete response, or TURBT and 6-weekly adjuvant intravesical instillations. Investigators found a 57% CR rate with chemoablation and an overall decrease in the number of TURBTs performed in the intervention group (71% vs 100%, $p < 0.001$), with similar 12-month RFS (36% vs 43%, $p = 0.5$) [37,38]. An ongoing single-arm phase 3 trial (ENVISION) is investigating UGN-102 as primary chemoablative therapy in low-grade intermediate-risk NMIBC, with preliminary results showing a 3-mo CR rate of 79.6% and a 12-mo duration of response in 82.3% [39]. A phase 3b trial is investigating home instillation of UGN-102 to mitigate patient challenges and burden of clinic treatments (NCT05136898). Other reversed-phase thermogel agents are being developed and tested in phase 1 trials including UGN-301, which contains the CTLA4 inhibitor zalifrelimab, and UGN-201, which contains the toll-like receptor agonist imiquimod (NCT05375903).

3.3.3. Hyperthermic intravesical chemotherapy

In this review, we use hyperthermic intravesical chemotherapy (HIVEC) to indicate any form of heated intravesical chemotherapy (Fig. 2 and Table 7). In HIVEC, intravesical therapy solutions are heated to 41–45°C and sometimes recirculated. The addition of heat has three potential benefits: improvement of drug delivery through the bladder wall, sensitization of cancer cells to chemotherapy, and stimulation of the immune system [40–42]. Several devices have been used to heat the intravesical fluid, including recirculating convective fluid heaters (eg, Combat

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BRS and Unithermia), intravesical radiofrequency antennae (eg, Synergo), and extracorporeal deep regional radiofrequency devices (eg, Pyrexar BSD-2000). The most commonly utilized chemotherapy agent in HIVEC is MMC, although other agents have also been tested [43–45].

3.3.3.1. Combat BRS. The Combat BRS device is a conductive and recirculating bladder fluid heater that has been evaluated in several recent clinical trials. The HIVEC-HR trial assessed the Combat BRS in 50 patients with high-risk NMIBC without CIS and randomized them to receive BCG induction with 1 yr of maintenance versus HIVEC with MMC (40 mg, 40 ml) for 60 min, performed weekly for 6 wk followed by once monthly for 6 mo. The 2-yr RFS rate was similar between the treatment groups (87% with HIVEC vs 72% with BCG, $p = 0.214$). The secondary endpoint of 2-yr progression-free survival showed a trend for better outcomes with HIVEC than with BCG (96% vs 72%, $p = 0.071$) [46]. The exclusion of patients with CIS was based on prior data with the Synergo system where hyperthermia is achieved with an intravesical antenna for a radiofrequency-induced thermochemotherapeutic effect (RITE). Earlier studies of RITE suggested similar efficacy among patients with or without CIS [47], but the HYMN trial randomized patients with BCG-exposed intermediate- or high-risk NMIBC to RITE (20 mg in 50 ml), demonstrating that while 2-yr RFS was better with RITE in patients with papillary tumors (hazard ratio [HR] = 0.50, 95% confidence interval [CI] 0.22–1.17), the 3-mo CR in CIS patients was worse (HR = 2.06, $p = 0.01$) [48].

The HIVEC-I and HIVEC-II trials assessed the Combat BRS in intermediate-risk bladder cancer patients in Spain and the UK, respectively. These trials compared normothermic MMC (40 mg) with HIVEC MMC (40 mg, 85 ml). There were some small differences between the trials. In HIVEC-I, the control arm MMC was diluted in 50 ml, while in HIVEC-II, it was diluted in 40 ml. Additionally, HIVEC-I compared a 30-min versus a 60-min dwell time. Neither trial found a difference between the arms with respect to the 2-yr DFS (HIVEC-I HR = 0.78, $p = 0.6$; HIVEC-II HR = 0.92, $p = 0.8$), indicating no benefit for HIVEC over normothermic MMC [49,50]. AEs across these trials were typically of low grade and not systemic, including one trial of 14 patients treated with high-dose MMC (120 mg) using the COMBAT BRS system, where there were zero G $\geq$3 AEs [51]. PROs were recorded in HIVEC-I and were no different between patients receiving normothermic or HIVEC MMC [50].

3.3.4. Intravesical osmotic pumps

The TAR-200 and TAR-210 devices are 5-cm semipermeable silicone tubes that self-coil in the bladder, and are loaded with drug tablets that slowly dissolve and release their content osmotically (Fig. 2 and Table 8). Approximately 60–70% of the drug is released over a 2-wk period.

3.3.4.1. TAR-200 (GemRIS). TAR-200 is loaded with gemcitabine and was first assessed in a phase 1 trial of 35 patients with MIBC who either refused or were unfit for curative intent therapy. TAR-200 was inserted for four consecutive 21-d cycles, and the investigators found a 3-mo CR in 11/35 (31%) and a partial response in 3/35 (9%) patients. The median overall survival and duration of response were 27 and 14 mo, respectively, and two patients required removal of the device [52].

In the TAR-200-101 trial, TAR-200 was tested as neoadjuvant therapy in MIBC patients who were cisplatin ineligible. Regarding patients with residual tumors of >3 cm after TURBT, four of ten patients exhibited pathologic downstaging. Among those with tumors of <3 cm, six of ten patients exhibited downstaging. There were no G $\geq$3 AEs [53]. In the randomized phase 2 SunRISe-4 trial (NCT04919512), cetrelimab (anti–PD-1) with and without TAR-200 is being assessed in MIBC patients who are ineligible for or refuse neoadjuvant platinum-based chemotherapy. In the randomized phase 3 SunRISe-2 trial, the combination of cetrelimab plus TAR-200 is being compared with chemoradiation in MIBC patients ineligible for cystectomy (NCT04658862).

In the randomized phase 2b SunRISe-1 trial (NCT04640623), patients with BCG-unresponsive CIS are assigned to receive TAR-200 + cetrelimab, TAR-200, or cetrelimab. TAR-200 is inserted every 3 wk for 24 wk, followed by every 12 wk through week 96. From the most recent analysis, 85 patients had received TAR-200 alone and 58 were evaluable for efficacy. A CR was achieved in 83% of patients, with an estimated 1-yr duration of response rate of 75%. Treatment-related AEs occurred in 61 patients (72%) and were mostly of low grade, including pollakiuria (35%), dysuria (29%), urgency (15%), and urinary tract infection (15%). AEs required treatment discontinuation in four patients (5%) [54]. TAR-200 has also shown efficacy in a phase 1 marker lesion ablation trial of recurrent low-grade papillary NMIBC, with a CR of 42% [55]. In December 2023, the FDA granted the breakthrough therapy designation to TAR-200 based on these results. TAR-200 is being studied against single-agent intravesical chemotherapy in SunRISE-5 (NCT06211764), a phase 3 randomized trial. Another phase 3 trial, SunRISe-3 (NCT05714202), is randomizing patients with BCG-naïve high-risk NMIBC to TAR-200 + cetrelimab, TAR-200 alone, or intravesical BCG.

3.3.4.2. TAR-210. TAR-210 has a similar structure to TAR-200, but it is loaded with erdafitinib, a pan-FGFR tyrosine kinase inhibitor. The rationale for this is that 60–70% of NMIBC cases harbor fibroblast growth factor receptor (FGFR) alterations [56]. Preliminary results of a phase 1 study assessing the safety of TAR-210 in patients with NMIBC and FGFR alterations included 27 patients with intermediate-risk NMIBC and identified a 3-mo CR rate of 82% with no dose-limiting or systemic toxicities [57]. In the randomized phase 3 MoonRISe-1 trial (NCT06319820), patients with intermediate-risk NMIBC and FGFR alterations received either TAR-210 (inserted every 12 wk) or the investigator's choice of single-agent intravesical chemotherapy (MMC or gemcitabine).

3.3.5. Viruses and vectors

Viral vectors have been in development for patients with NMIBC for decades (Fig. 2 and Table 9). These agents are usually administered intravesically, typically in combination with an excipient/detergent to disrupt the bladder gly-

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cosaminoglycan layer with the goal of improving urothelial penetration [58]. The virus then infects urothelial cells and, depending on the nature of the vector, leads to additional intracellular events. Nonviral gene therapies such as EG-70, a nanoparticle containing DNA plasmid that encodes interleukin-12 and stimulates the retinoic acid-inducible gene I (RIG-I) pathway, are also in development in early-phase trials (NCT04752722).

3.3.5.1. Cretostimogene grenadenorepvec. Cretostimogene grenadenorepvec (cretostimogene) is a type 5 oncolytic adenovirus that conditionally replicates in Rb-pathway–deficient cells via the E2F promoter [59]. Cretostimogene is administered intravesically after 15-min permeabilization of the bladder with 100 ml of 0.1% n-dodecyl-β-D-maltoside, a nonionic detergent. Cretostimogene infects urothelial cells and can kill the cells directly, but it also is engineered to express granulocyte-macrophage colony-stimulating factor, which triggers a boosted immune reaction. In the phase 2 BOND-002 trial, cretostimogene was administered to 45 participants with BCG-refractory NMIBC. The overall CR rate was 47% at 6 mo, with a stronger response of 58% in patients with pure CIS. Side effects were limited (three G3 and zero G4/5 AEs), and temporary irritative urinary symptoms were most frequent [60].

BOND-003 is a phase 3, single-arm trial of cretostimogene monotherapy in patients with BCG-unresponsive CIS (NCT04452591). A preliminary analysis of 112 patients demonstrated an anytime CR of 75.2%, with 83% of responders remaining disease free at 12 mo. Cystectomy-free and progression-free survival rates at 12 mo were 92.4% and 96.7%, respectively, with no G $\geq$3 treatment-related AEs [61]. Cretostimogene received the FDA fast-track and breakthrough therapy designation in December 2023. CORE-001 was a phase 2 single-arm trial combining cretostimogene with intravenous pembrolizumab in patients with BCG-unresponsive CIS. A final analysis showed overall CR rates of 83% at any time, 57% at 12 mo, and 51% at 24 mo. There were no progression events, and the safety profile was favorable with 5/35 patients experiencing G3 AEs not related to cretostimogene, consistent with pembrolizumab monotherapy studies [62]. Two additional trials are underway. PIVOT-006 CG is a randomized phase 3 trial of cretostimogene versus observation in intermediate-risk NMIBC following TURBT (NCT06111235), and there is a small phase 1 trial of cretostimogene + intravenous nivolumab prior to cystectomy in cisplatin-ineligible patients with MIBC (NCT04610671). A multiarm, multicohort trial in patients with both BCG-naïve and BCG-exposed high-risk NMIBC is also planned (CORE-008).

3.3.5.2. Nadofaragene firadenovec. Nadofaragene firadenovec (NF) is an E1-deleted, replication-deficient type 5 adenovirus that is engineered to carry human interferon alfa2b ($IFN\alpha_{2b}$) gene. It is administered after bladder permeabilization with Syn3, a detergent, once every 3 mo [63,64]. In a single-arm phase 3 trial of 157 patients with BCG-unresponsive NMIBC, the 3-mo CR was 53.4% in patients with CIS, with a median duration of response of 10 mo. The rate of 12-mo freedom from high-grade recurrence was 24%. G1/2 AEs were noted in 66% of patients, and 4% had drug-related G3 AEs, including bladder spasm, urgency, urinary incontinence, and syncope and hypertension (one patient each) [64]. NF was approved by the FDA in December 2022. A follow-up of the phase 3 trial after a median follow up of 50.8 mo showed estimated 57-mo high-grade RFS rates of 13% and 57% for patients with CIS and papillary disease, respectively. At 5 yr, cystectomy-free survival rate was 49%, overall survival rate was 80%, and only five patients experienced progression to MIBC [65]. ABLE-42 is a phase 4 trial that is evaluating retreatment with NF for high-grade BCG-unresponsive NMIBC patients with or without papillary tumors, who had not responded to NF at the first 3-mo assessment (NCT06026332). Upcoming trials include ABLE-32, a phase 3b study of NF versus observation in patients with intermediate-risk NMIBC, and ABLE-22, a phase 2, randomized, multicenter, open-label study to evaluate the safety and efficacy of NF alone or in combination with GEM/DOCE or pembrolizumab in patients with high-grade BCG-unresponsive NMIBC.

4. Discussion

The current landscape of bladder cancer treatment is promising, with numerous novel intravesical therapies emerging. These therapies have demonstrated efficacy across various risk categories of NMIBC, including low-grade intermediate-risk NMIBC, treatment-naïve high-risk NMIBC, and BCG-unresponsive high-risk NMIBC. However, the increasing number of options poses challenges for treatment selection.

4.1. Strengths and limitations

A significant strength of the studies in this systematic review is the robust efficacy demonstrated in rigorously designed clinical trials. Many of the trial designs were informed by the initial FDA guidelines for BCG-unresponsive disease, alongside subsequent recommendations regarding trial design, endpoints, and success thresholds for other risk groups [3–5]. Some agents, such as combination chemotherapy with GEM/DOCE, have been adopted in clinical practice due to promising efficacy in retrospective studies of patients with BCG-unresponsive disease (2-yr RFS = 46%) [26]. However, this regimen is currently undergoing prospective evaluation to ensure that it undergoes the same rigorous assessment as other novel agents.

Intravesical therapies offer the advantage of safety, minimizing systemic toxicity for a localized disease managed typically by urologists. This is evident in the low rates of G $\geq$3 AEs reported across the studies in this review. The introduction of ICIs as a salvage therapy after BCG failure has sparked interest in novel immune-based approaches. Although reported studies of the combination of BCG and ICIs are in an early phase, larger studies are underway to better understand the benefits of integrating systemic and intravesical therapies. Efforts are also being made to refine dosing strategies to minimize toxicity and facilitate ICI administration for urologists. Cross-trial comparisons

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remain challenging; however, for BCG-unresponsive high-risk NMIBC, the combination of an ICI and the novel intravesical agent cretostimogene has demonstrated the highest 2-yr CR among the ongoing trials in this space [62]. The increasing use of systemic agents in urology, coupled with studies evaluating the benefits of modified dosing strategies such as subcutaneous delivery over infusion, indicates a shift in treatment paradigms for urologists. Nonetheless, the continued interest in exclusive intravesical therapy suggests that systemic options may be reserved for patients at the highest risk of progression or treatment failure.

Another strength of these studies is the exploration of diverse mechanisms of action, including nonspecific and targeted immune stimulation, checkpoint inhibition, permeability-enhancing methods for chemotherapeutics, drug conjugates, device-assisted therapies to optimize dwell times, and gene therapy. Additionally, ablative therapies for intermediate-risk NMIBC could reduce the need for surgical interventions in high-risk patient populations.

However, the review highlights critical limitations in the existing evidence base. Although several phase 3 trials are currently underway, the majority of the published literature consists of phase 1 and 2 studies, with many novel therapies still being explored in early-phase trials. Comparative effectiveness trials are also scarce due to the FDA's initial policy supporting the approval of single-arm trials in this area. While this has resulted in the approval of three novel agents by the FDA, EMA approval remains uncertain. Consequently, clinicians often lack comprehensive data to inform treatment decisions. Although success thresholds are generally clear, subtle differences in trial design and response assessment methods (eg, the necessity of mandatory biopsy) complicate cross-trial comparisons. While safety profiles are established through monitoring of treatment-related AEs and disease progression, each novel therapy exhibits unique treatment protocols, schedules, and intensities that affect the patient experience. Alarmingly, PROs were evaluated only in 6/36 studies, highlighting a significant gap in the literature.

Additionally, financial considerations are poised to become major determinants in treatment selection across various jurisdictions. As therapeutic strategies multiply, there is an urgent need for randomized trials to guide decision-making and treatment sequencing. The limited long-term follow-up data further complicate our understanding of the lasting implications of these therapies.

4.2. *Implications for future research*

Several important questions remain for future investigation. Even within well-defined and narrow risk group categories, there are considerable differences in response rates between patients, highlighting the need for predictive biomarkers. Molecular risk groups show great promise for more accurate prognostication for cases with NMIBC of the same grade and stage [66,67], inferring more nuanced treatment approaches based upon gene expression profiles. However, their validation for treatment stratification remains a work in progress. Furthermore, it is likely that urine- or plasma-based biomarkers can identify molecular/minimal residual disease overlooked by cystoscopy, cytology, and imaging [68,69], providing opportunities for earlier intervention. However, to fully capitalize upon such approaches, clinicians will need to become comfortable in treating nonvisible biomarker-positive disease. It would be rational to combine treatments with different modes of action to achieve better efficacy, and treatment sequencing may also optimize outcomes, especially given the potential for upfront chemoresection.

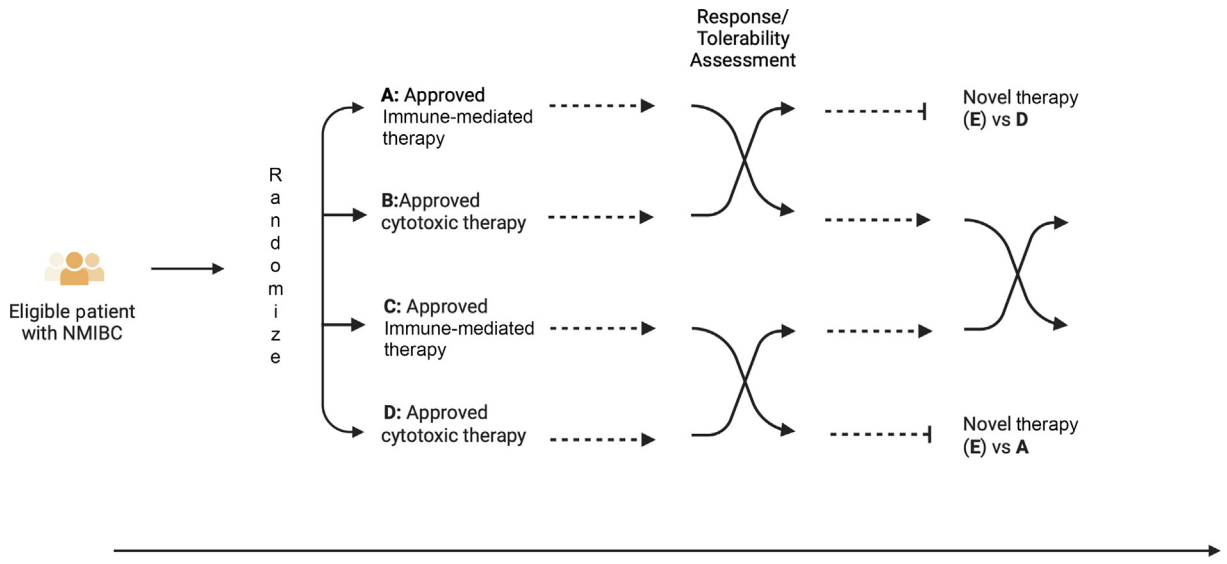

Fig. 3 – Hypothetical multiarm, multistage trial design. Patients with NMIBC, classified according to their appropriate risk group, are randomized to receive treatments based on the predominant mechanism of action. Those who respond to treatment will continue for durability assessment, while patients who do not meet the predefined outcome criteria will be eligible to crossover to approved agents or combinations with complementary mechanisms of action, or to novel therapeutics under investigation. NMIBC = non–muscle-invasive bladder cancer.

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Given the increasing number of new treatments for NMIBC, the variability in response assessment, and the lack of comparative or long-term data to guide clinical decision-making, we propose the need for multiarm, multistage studies that encompass all risk categories of NMIBC [70,71]. These studies could include potential treatment stratification based on the predominant mechanisms of action. Additionally, sequencing should be explored through crossover to complementary therapies or combinations when desired outcomes are not achieved, considering factors such as therapeutic response and tolerability (Fig. 3). However, such investigations will require significant national and international collaboration between investigators, cooperative groups, and industry partners. Furthermore, treatment intensity, side effects, and patients' quality of life remain underappreciated factors in the NMIBC treatment landscape and should be prioritized in future research [72].

5. Conclusions

Bladder cancer is a prevalent and challenging malignancy marked by diverse biology and treatment response. This systematic review underscores the exciting array of novel intravesical therapies demonstrating efficacy. However, the limitations in long-term follow-up and comparative effectiveness data necessitate further investigation. Future studies should prioritize comparative analyses focusing on cost effectiveness, PROs, and appropriate treatment sequencing to enhance clinical decision-making.

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Study concept and design: Ghodoussipour, Inman.
Acquisition of data: Ghodoussipour.
Analysis and interpretation of data: Ghodoussipour, Inman.
Drafting of the manuscript: Ghodoussipour, Inman.
Critical revision of the manuscript for important intellectual content: Ghodoussipour, Bivalacqua, Bryan, Li, Mir, Palou, Psutka, Sundi, Tyson, Inman.
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