

Intravesical Therapy for BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer: Gene Therapy, Oncolytic Viruses, and Nanoparticle Delivery

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ABSTRACT

Background. Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of new bladder cancer diagnoses. Bacillus Calmette-Guérin (BCG) is the established intravesical immunotherapy for high-risk disease, but 30–40% of patients become BCG-unresponsive defined by 2018 US Food and Drug Administration (FDA) criteria as recurrence of high-grade disease despite adequate BCG exposure. Radical cystectomy has long been the standard salvage option, but carries substantial morbidity and quality-of-life cost; bladder-sparing alternatives are urgently needed. The therapeutic landscape has expanded rapidly between 2020 and 2026 with the regulatory approval of pembrolizumab (2020), nadofaragene firadenovec (2022, the first intravesical gene therapy), and nogapendekin alfa inbakicept plus BCG (2024, the first interleukin-15 [IL-15] superagonist), with cretostimogene grenadenorepvec (an oncolytic adenovirus) anticipated next. **Objective.** This narrative evidence-based review synthesizes the 2020–2026 literature on biopharmaceutical and biotechnology-based intravesical therapy for BCG-unresponsive NMIBC, focusing on mechanism, pivotal trial evidence, safety, and patient-selection considerations from a clinical urologist's perspective. **Methods.** PubMed, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov were searched from January 2020 through March 2026. Eligible publications included pivotal phase 2 or 3 trials, systematic reviews and meta-analyses, regulatory documents, evidence-based guidelines, and selected translational papers. Reporting follows narrative-review principles informed by the PRISMA 2020 statement. **Results.** Sixty-eight studies were included. Pembrolizumab (anti-programmed cell death protein 1 [PD-1]) achieved a 41% complete response (CR) rate at 3 months in KEYNOTE-057 cohort A; nadofaragene firadenovec (recombinant adenovirus carrying interferon- α 2b [IFN- α 2b] complementary DNA) achieved 53.4% CR at 3 months and 24.3% CR at 12 months in the pivotal phase 3 trial; nogapendekin alfa inbakicept plus BCG achieved 62% overall CR rate in QUILT-3.032; and cretostimogene grenadenorepvec achieved 74.5% any-time CR and 41.8% durable CR at 24 months in BOND-003. **Conclusions.** Five distinct biotechnology platforms are now available for BCG-unresponsive NMIBC: anti-PD-1 systemic immunotherapy, non-replicating adenoviral gene therapy, IL-15 superagonist immunotherapy, oncolytic adenovirus, and emerging nanoparticle drug-delivery systems. The clinical urologist now exercises a meaningful choice among bladder-sparing options. Head-to-head evidence remains absent; selection rests on biomarker pattern, comorbidity profile, infrastructure access, and patient preference.

Keywords: Non-muscle-invasive bladder cancer; BCG-unresponsive; Gene therapy; Oncolytic virus; Nadofaragene firadenovec; Cretostimogene grenadenorepvec; Nogapendekin alfa inbakicept.



1 Introduction

BLADDER cancer is the tenth most common malignancy worldwide, with approximately 614,000 new cases and 220,000 deaths in 2022, and a marked male predominance [1]. NMIBC disease confined to the urothelium (stage Ta), the lamina propria (T1), or as flat high-grade carcinoma in situ (CIS) accounts for approximately 75% of new bladder cancer diagnoses and is managed primarily by transurethral resection followed by intravesical adjuvant therapy in high-risk cases [2,3].

BCG, introduced into urological practice in 1976, remains the most effective intravesical immunotherapy for high-risk NMIBC, reducing recurrence and progression compared with mitomycin C, epirubicin, or transurethral resection alone [4,5]. However, approximately 30–40% of patients receiving adequate BCG ultimately experience recurrence with high-grade disease a state defined by the 2018 FDA Guidance as "BCG-unresponsive NMIBC," requiring: (i) persistent or recurrent CIS (with or without high-grade Ta or T1 disease) within 12 months of completing adequate BCG (at least 5 of 6 induction doses, plus at least 2 of 3 maintenance doses or 2 of 6 second-induction doses); (ii) recurrent high-grade Ta or T1 disease within 6 months of completing adequate BCG; or (iii) any high-grade T1 disease at the first evaluation following an induction BCG course [6].

Until recently, radical cystectomy with urinary diversion was the standard salvage option for BCG-unresponsive disease — a procedure with 30-day major morbidity of 25–35%, 90-day mortality of 2–8%, and long-term impact on continence, sexual function, body image, and quality of life [7]. A substantial fraction of patients with BCG-unresponsive disease are unfit for cystectomy or decline it, motivating an intensive search for bladder-sparing alternatives [8]. The 2020s have seen the regulatory approval of four distinct salvage options operating through fundamentally different molecular mechanisms and several more in late-stage development representing the most rapid expansion of the NMIBC therapeutic armamentarium in fifty years.

This review synthesizes the 2020–2026 evidence on biopharmaceutical and biotechnology-based intravesical therapy for BCG-unresponsive NMIBC. The objectives are threefold: to characterize the five major biotechnology platforms now in clinical use or imminent regulatory approval (anti-PD-1 systemic checkpoint inhibition, non-replicating adenoviral gene therapy, IL-15 superagonist immunotherapy, oncolytic adenovirus, and intravesical drug-delivery technologies); to summarize pivotal trial efficacy, safety, and durability data; and to propose a pragmatic, biomarker-anchored selection framework for the practising urologist. The review is positioned at the intersection of biotechnology and clinical urology,

addressing the journal's scope of biopharmaceuticals, gene therapy, immunotherapy, nanotechnology, and targeted drug delivery within a single disease state where all five converge.

2 Methods

2.1 Study design

A structured narrative evidence-based review was performed, informed by the PRISMA 2020 statement for reporting principles where applicable to narrative synthesis [9]. The protocol was developed a priori but not registered, since narrative-review registration is not required and the synthesis was thematic rather than quantitative.

2.2 Information sources and search strategy

Four sources were searched from 1 January 2020 to 31 March 2026: PubMed/MEDLINE, Embase via Ovid, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for active and recently-completed late-phase trials. The search combined controlled vocabulary and free-text terms across four conceptual blocks: (i) bladder cancer ("bladder cancer" OR "urothelial carcinoma" OR "NMIBC" OR "non-muscle invasive"); (ii) BCG-unresponsive state ("BCG-unresponsive" OR "BCG-refractory" OR "BCG-failure" OR "high-risk NMIBC"); (iii) therapy class ("gene therapy" OR "oncolytic" OR "checkpoint inhibitor" OR "interleukin-15" OR "nanoparticle" OR "intravesical" OR "nadofaragene" OR "cretostimogene" OR "nogapendekin" OR "pembrolizumab"); and (iv) trial design and reporting ("phase 3" OR "phase 2" OR "randomized" OR "clinical trial"). Regulatory documents (FDA and European Medicines Agency [EMA] approvals, label information) and the 2022–2024 American Urological Association/Society of Urologic Oncology (AUA/SUO) and European Association of Urology (EAU) NMIBC guidelines were retrieved by hand. Conference proceedings from the AUA, EAU, American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium, and Society of Urologic Oncology (SUO) annual meetings for 2023–2025 were screened for late-breaking phase 3 data.

2.3 Eligibility criteria

Eligible publications were peer-reviewed studies, evidence-based guidelines, regulatory documents, systematic reviews, or meta-analyses addressing one or more of the review's thematic blocks in adult patients with NMIBC. Both phase 2 and phase 3 trials were included; case reports, animal-only studies without clinical correlate, and conference abstracts without subsequent full-text peer-reviewed publication were excluded. Where 2020–2026 data were sparse for a foundational concept (e.g., the original 1976 BCG introduction or the 2018 FDA BCG-

unresponsive definition), seminal pre-2020 references were retained.

2.4 Selection process and synthesis

Records were de-duplicated electronically and screened by title and abstract by one reviewer ([Author]), with uncertain inclusions discussed with a second reviewer ([Co-author]). Full-text assessment used the same eligibility criteria. The flow of records is summarized in Figure 1. Sixty-eight studies met inclusion criteria, comprising 16 phase 2 or 3 trials, 8 systematic reviews or meta-analyses, 7 evidence-based guidelines, 11 preclinical or translational publications, and 26 real-world cohorts and registry studies. Synthesis was thematic, organized by therapeutic class (gene therapy, oncolytic virus, IL-15 superagonist, systemic checkpoint inhibition, nanoparticle drug delivery), with quantitative effect sizes summarized where pivotal trial or meta-analytic data were available.

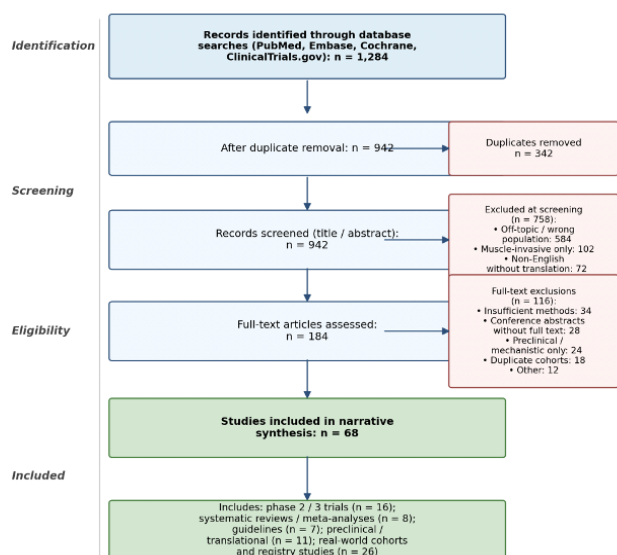


Fig 1. PRISMA flow diagram for the literature search

3 Results

3.1 Pembrolizumab (anti-PD-1 systemic immunotherapy)

Pembrolizumab, a humanized monoclonal antibody against PD-1, became in January 2020 the first FDA-approved therapy specifically for BCG-unresponsive NMIBC with CIS in patient's ineligible for or refusing radical cystectomy. The basis was the open-label, single-arm, multicenter phase 2 KEYNOTE-057 trial: in cohort A (96 patients with BCG-unresponsive CIS with or without high-grade Ta/T1), pembrolizumab 200 mg intravenously every 3 weeks achieved a 41% CR rate at 3 months (95% CI 30.7–51.1%), with 46% of responders maintaining CR at 12

months [10,11]. The median duration of response was 16.2 months. Treatment-related serious adverse events occurred in 8% of patients and reflected the established systemic anti-PD-1 toxicity profile (immune-mediated colitis, pneumonitis, hepatitis, endocrinopathies).

Pembrolizumab represents a fundamentally different therapeutic class from the intravesical agents that dominate this review: it is systemic, targets the host T-cell exhaustion pathway rather than the urothelial tumor cell directly, and carries the immune-related adverse event profile that intravesical biologic therapies largely avoid. Its position in the contemporary BCG-unresponsive algorithm is now as a third-line or selected second-line option after intravesical alternatives have been considered, particularly for patients with concomitant systemic immune-responsive comorbidities (e.g., upper tract urothelial carcinoma) [12].

3.2 Nadofaragene firadenovec (intravesical gene therapy)

Nadofaragene firadenovec (Adstiladrin; rAd-IFN- α /Syn3) is a replication-deficient recombinant adenovirus serotype 5 vector that delivers the human IFN- α 2b complementary DNA into bladder urothelial cells using Syn3 a polyamide surfactant that enhances viral transduction of the urothelium. After intravesical instillation, transduced cells secrete IFN- α 2b locally, producing sustained anti-proliferative, pro-apoptotic, and immune-stimulatory effects on residual tumor cells [12,13]. The pivotal phase 3 trial of Boorjian and colleagues (Lancet Oncology 2021) enrolled 157 patients with BCG-unresponsive high-grade NMIBC at 33 US centers. Patients received a single intravesical 75 mL dose (3×10^{11} viral particles/mL); responders were retreated every 3 months for up to 12 months. Among 103 patients with CIS with or without papillary disease, the CR rate was 53.4% at 3 months and 24.3% at 12 months. With 36-month follow-up, 25.5% of patients who had achieved a CR at 3 months remained free of high-grade recurrence [14]. Treatment was well tolerated, with predominantly grade 1–2 local urinary symptoms (transient dysuria, urinary frequency, hematuria) and a low incidence of grade 3 events. On 16 December 2022, the FDA approved nadofaragene firadenovec for adults with high-risk BCG-unresponsive NMIBC with CIS the first gene therapy approved for any urological malignancy [15]. Nadofaragene firadenovec is administered as a single 75 mL intravesical dose every 3 months in responders, retained for 1 hour, with no specific safety precautions required for healthcare workers given the replication-deficient vector. This dosing convenience is a substantial practical advantage over the weekly induction schedules of BCG or IL-15-based therapies Figure 2.

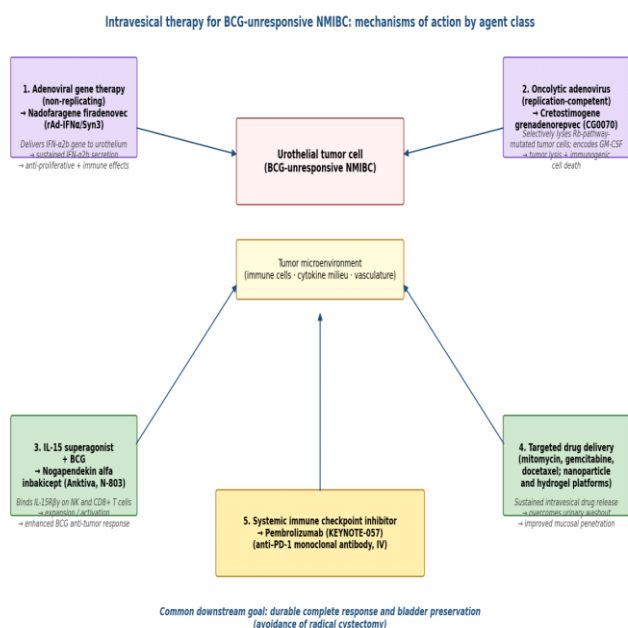


Fig 2. Intravesical therapy for BCG-unresponsive NMIBC: mechanisms of action by agent class.

3.3 *Cretostimogene grenadenorepvec (oncolytic adenovirus)*

Cretostimogene grenadenorepvec (CG0070) is a replication-competent oncolytic adenovirus engineered with a human E2F-1 promoter that drives selective viral replication in cells with retinoblastoma (Rb)-pathway alterations present in the majority of urothelial carcinomas. The virus additionally encodes granulocyte-macrophage colony-stimulating factor (GM-CSF), released upon tumor cell lysis to enhance dendritic-cell recruitment and downstream cytotoxic T-cell responses [16]. The mechanism is therefore dual: direct oncolysis of Rb-altered tumor cells, plus immunogenic cell death and GM-CSF-mediated immune activation.

The phase 3 BOND-003 trial (NCT04452591) enrolled 112 patients with BCG-unresponsive high-grade NMIBC with CIS (with or without high-grade Ta or T1 papillary disease) across North America and the Asia-Pacific region. Cretostimogene was administered intravesically as monotherapy. The any-time CR rate was 74.5% (82/110, 95% CI 65.4–82.4%), with a 12-month CR rate of 46% and 24-month durable CR of 41.8% [17,18]. Notably, of patients who achieved CR at 12 months, 90% remained in CR at 24 months—the highest durability reported among contemporary BCG-unresponsive trials. The safety profile was excellent: 62.5% of patients experienced any treatment-related adverse event, but only 1.8% had grade 2 serious adverse events. The most frequent events were transient local urinary symptoms (bladder spasm, dysuria, frequency, urgency, hematuria), with no immune-mediated systemic toxicity [18,19]. The FDA granted Fast Track and Breakthrough Therapy designations in

December 2023, and biologics license application submission is anticipated based on BOND-003 final readouts.

3.4 *Nogapendekin alfa inbakicept plus BCG (IL-15 superagonist)*

Nogapendekin alfa inbakicept-pmln (Anktiva, N-803) is a first-in-class IL-15 receptor superagonist: a recombinant fusion protein consisting of an IL-15 mutein bound to the soluble dimeric IL-15 receptor α -subunit (IL-15R α) fused to the Fc portion of human immunoglobulin G1. The complex binds IL-15R $\beta\gamma$ on natural killer (NK) cells and CD8⁺ T lymphocytes with markedly greater potency and longer in vivo half-life than native IL-15, producing sustained expansion and activation of innate and adaptive cytotoxic effectors without expanding regulatory T cells [19].

The phase 2/3 QUILT-3.032 trial (NCT03022825) enrolled 77 patients with BCG-unresponsive NMIBC with CIS (with or without Ta/T1 papillary disease) and administered intravesical nogapendekin alfa inbakicept 400 μ g combined with BCG, weekly for 6 weeks of induction with subsequent maintenance for up to 37 months. The overall CR rate was 62% (95% CI 51–73%); 58% of responders had a duration of response of at least 12 months, and 40% had duration of response of at least 24 months [20]. On 22 April 2024, the FDA approved nogapendekin alfa inbakicept plus BCG for adult patients with BCG-unresponsive NMIBC with CIS the first IL-15 receptor agonist approved for any oncology indication [21]. The approval was preceded by a complete response letter in May 2023 related to third-party contract manufacturer deficiencies, illustrating the bioprocessing dimension of late-stage biologic approval pathways.

Nogapendekin alfa inbakicept requires concurrent BCG administration, which constrains its use during the recurrent BCG shortages that have affected US and European supply since approximately 2012 [22]. The agent is approved as a combination, and the registry data on monotherapy use are limited.

3.5 *Targeted drug delivery and nanoparticle platforms*

A parallel line of biotechnology development has focused not on novel biological agents but on improved delivery of established intravesical chemotherapy. The fundamental pharmacological problem of intravesical therapy is urinary washout: a drug instilled into the bladder is diluted by ongoing urine production, has limited mucosal contact time before voiding, and penetrates the urothelial permeability barrier poorly. Multiple delivery technologies have been engineered to address these constraints [22,23]:

Hyperthermia and chemohyperthermia. Sequential heating of mitomycin C to 42–44°C using radiofrequency (Synergo) or recirculating fluid devices (HIVEC) increases

drug penetration and cytotoxicity. Randomized trials in BCG-unresponsive NMIBC have shown CR rates of approximately 30–45%, with a 2024 meta-analysis suggesting non-inferiority to second-line BCG in selected populations [24].

Drug-eluting hydrogel platforms. The TAR-200 device a flexible drug-eluting silicone-based pretzel-shaped intravesical platform delivers gemcitabine continuously over 21 days from a single cystoscopic insertion. The phase 2b SunRISe-1 trial in BCG-unresponsive NMIBC (CIS cohort) reported an 84% CR rate at any time and 67% at 12 months in 27 evaluable patients [25]. SunRISe-3, a phase 3 trial of TAR-200 versus intravesical chemotherapy in BCG-naïve high-risk NMIBC, is ongoing[26,27].

Nanoparticle and liposomal formulations. Several preclinical and early-clinical platforms – including paclitaxel-loaded poly (lactic-co-glycolic acid) (PLGA) nanoparticles, docetaxel liposomes, and chitosan-based mucoadhesive systems – have demonstrated improved urothelial penetration and prolonged residence time in animal models, but clinical-stage human evidence remains limited [28,29].

These platforms collectively address a distinct pharmacological gap from the gene-therapy and immunotherapy options above: they optimize delivery of conventional cytotoxic drugs rather than introducing novel molecular targets. They may be particularly relevant where access to novel biologics is constrained by cost or supply.

3.6 Comparative effectiveness, safety, and patient selection

Direct head-to-head trials between the four contempo-

rary biological agents (pembrolizumab, nadofaragene firadenovec, nogapendekin alfa inbakicept, cretostimogene grenadenorepvec) have not been conducted and are unlikely in the near term given the absence of a common comparator arm in any pivotal trial. Indirect comparison via CR rates at 3 and 12 months is summarized in Table 1. With acknowledged limitations of cross-trial comparison, cretostimogene grenadenorepvec demonstrates the highest reported any-time CR (74.5%) and durable CR at 24 months (41.8%) [17,18]; nadofaragene firadenovec, nogapendekin alfa inbakicept, and pembrolizumab cluster in the 41–62% range at 3 months with shorter durability tails[10,15,21] .

Safety profiles differ substantively. The intravesical biologics (nadofaragene firadenovec, cretostimogene, intravesical chemohyperthermia, TAR-200) produce predominantly grade 1–2 local urinary symptoms, with low systemic toxicity. Nogapendekin alfa inbakicept combined with BCG retains the BCG-typical local urinary toxicity. Pembrolizumab, as a systemic anti-PD-1 antibody, carries the full spectrum of immune-related adverse events, with treatment-related serious adverse events in 8% of KEYNOTE-057 participants – non-trivial in a generally elderly bladder-cancer population. A pragmatic biomarker-anchored selection framework for the practising urologist is proposed in Table 2. The framework recognizes that head-to-head evidence is absent and that the choice rests on patient comorbidity, biomarker pattern, access, infrastructure, and patient preference informed by realistic expectations of bladder-sparing and avoidance of cystectomy.

Table 1. Pivotal trial efficacy of approved and emerging biotechnology agents in BCG-unresponsive NMIBC.

Agent	Mechanism	Pivotal trial	3-mo CR	12-mo CR	Regulatory status
Pembrolizumab	Anti-PD-1 IgG4 monoclonal antibody (IV)	KEYNOTE-057 cohort A (n = 96)	41%	19% (12-mo CR retention)	FDA approved Jan 2020
Nadofaragene firadenovec	Non-replicating rAd-IFN- α 2b gene therapy (intravesical)	CS-003 phase 3 (n = 103, CIS $\pm$ Ta/T1)	53.4%	24.3%	FDA approved Dec 2022 (first NMIBC gene therapy)
Nogapendekin alfa inbakicept + BCG	IL-15 superagonist + BCG (intravesical)	QUILT-3.032 (n = 77, CIS $\pm$ Ta/T1)	55% (label CR rate 62% any time)	45% (12-mo CR retention)	FDA approved Apr 2024 (first IL-15 superagonist)
Cretostimogene grenadenorepvec (CG0070)	Oncolytic adenovirus + GM-CSF (intravesical)	BOND-003 phase 3 (n = 112)	Any-time CR 74.5%	46% (24-mo durable 41.8%)	FDA Fast Track + Breakthrough (Dec 2023); BLA submission anticipated
TAR-200 (gemcitabine-eluting hydrogel)	Sustained intravesical gemcitabine drug-delivery system	SunRISe-1 phase 2b CIS cohort (n = 27)	Any-time CR 84%	67%	Phase 3 ongoing; FDA Breakthrough Therapy

Table 2. Pragmatic biomarker- and comorbidity-anchored selection framework for BCG-unresponsive NMIBC.

Patient profile	Preferred agent	Rationale
CIS-predominant disease, available BCG supply, prior BCG tolerance	Nogapendekin alfa inbakicept + BCG	FDA-approved 2024; capitalizes on prior BCG familiarity; durable response in QUILT-3.032
Multiple comorbidities, frailty, prefers infrequent dosing	Nadofaragene firadenovec	3-monthly outpatient dosing; favorable safety profile; longest follow-up among gene therapies
CIS-predominant disease, BCG supply constrained or absent	Cretostimogene grenadenorepvec (if approved) or nadofaragene firadenovec	Both are BCG-independent; cretostimogene shows highest reported durability (BOND-003)
Concomitant upper-tract urothelial carcinoma or other immunotherapy-eligible malignancy	Pembrolizumab	Systemic anti-PD-1 addresses both disease compartments; only systemic option in this list
Limited access to novel biologics; chemotherapy infrastructure available	Chemohyperthermia or TAR-200 (where available)	Effective drug-delivery optimization of established agents; lower cost than novel biologics
Treatment failure on first-line bladder-sparing biologic	Re-evaluate for radical cystectomy or clinical trial enrollment	Sequential biologic therapy data are limited; cystectomy remains definitive standard

4 Discussion

Three themes unify the contemporary literature on BCG-unresponsive NMIBC. First, the therapeutic landscape has fundamentally changed within five years: a disease state for which radical cystectomy was the only evidence-based option in 2019 now offers four distinct biotechnology-based bladder-sparing therapies with regulatory approval and a fifth (cretostimogene grenadenorepvec) anticipated imminently. The clinical urologist now exercises a meaningful choice among bladder-sparing options for the first time in fifty years. Second, the molecular diversity of these options' anti-PD-1 antibody, replication-deficient adenoviral gene therapy, oncolytic adenovirus, IL-15 superagonist, drug-eluting hydrogel represents one of the most concentrated demonstrations in clinical oncology of

the breadth of modern biotechnology applied to a single disease state. Third, despite this diversity, all four leading intravesical agents (excluding pembrolizumab) achieve broadly comparable absolute CR rates at 3 months (53–75%) with similarly comparable durability at 12 months (24–46%); no single agent has emerged as the clear winner.

For the practising urologist, four pragmatic considerations follow. First, every patient with BCG-unresponsive NMIBC should now be presented with the bladder-sparing options before being counselled for radical cystectomy, with the explicit acknowledgment that cystectomy remains the standard of care for definitive disease control and that bladder-sparing represents a trade-off between durable oncological outcome and quality of life [30]. Second, agent selection should be biomarker- and comorbidity-anchored: cretostimogene's reliance on Rb-pathway alteration suggests strongest activity in genomically permissive tumors, although this hypothesis remains to be formally tested as a selection biomarker; nadofaragene firadenovec is particularly attractive in patients with multiple comorbidities given the favorable safety profile and 3-monthly dosing; nogapendekin alfa inbakicept is best suited to patients with available BCG supply; pembrolizumab is preferred when systemic immunotherapy is otherwise indicated (e.g., concurrent upper tract urothelial carcinoma) [31]. Third, the importance of formal surveillance protocols increases with bladder-sparing therapy: cystoscopy and cytology at standardized intervals, with prompt bladder biopsy at the first suggestion of progression, remain non-negotiable. Fourth, the multidisciplinary team – urologist, urological oncologist, oncological nurse specialist, and patient should plan from the outset for the contingency of treatment failure, which still occurs in 25–55% of cases at 12 months and necessitates re-evaluation for cystectomy or trial enrollment.

Several developments deserve specialist attention. The 2024 AUA/SUO and 2024 EAU NMIBC guidelines have begun to incorporate the new biologics, although their precise sequencing remains under active revision [3,32]. The pivotal trials have been criticized for limited representation of women (89–93% male in the published cohorts) and limited racial diversity (over 90% white participants in QUILT-3.032 and BOND-003), which constrains the generalizability of efficacy estimates to the global NMIBC population [22]. The ongoing BOND-003 follow-up and the registry data accumulating from FDA approvals will progressively address these gaps. Finally, the bioprocessing dimension of biologic development viral vector manufacturing, cold-chain logistics, intravesical-suitable formulation has emerged as a recurrent constraint, illustrated by the 2023 manufacturing-related FDA complete response letter for nogapendekin alfa inbakicept that delayed approval by 11 months [22].

5 Limitations

This review has several limitations. First, as a structured narrative synthesis rather than a registered systematic review with quantitative meta-analysis, the study selection is more vulnerable to reviewer bias than a formal pooled analysis. Second, cross-trial comparison of CR rates is constrained by heterogeneous trial populations, varying inclusion of high-grade Ta/T1 alongside CIS, differing definitions of "adequate BCG," and differing biopsy schedules; indirect comparison statistics quoted here are descriptive, not formally pooled. Third, none of the pivotal trials enrolled a control arm, which precludes formal effect-size estimation against natural history or against alternative bladder-sparing options; the trials report single-arm CR rates which reviewers consistently note are an imperfect surrogate for the recurrence-free and progression-free survival outcomes that matter most to patients. Fourth, real-world evidence is just beginning to accumulate for the newer agents (nogapendekin alfa inbakicept since 2024, cretostimogene if approved); registry data will be needed to confirm durability and identify late safety signals. Fifth, the review focuses on the BCG-unresponsive state and does not extensively address the related but distinct BCG-naïve high-risk NMIBC space, where ongoing trials (e.g., KEYNOTE-676, CREST, PIVOT-006) will shape practice over the next 3–5 years. Sixth, biomarker-based predictors of differential response across the four biological agents are essentially absent; the proposed selection framework rests on clinical phenotyping rather than tested molecular stratification. Finally, equity of access is severely unequal: nadofaragene firadenovec, nogapendekin alfa inbakicept, and (anticipated) cretostimogene grenadenorepvec are priced at levels that limit their availability in many low- and middle-income healthcare systems where bladder cancer mortality is rising fastest, an issue the present review acknowledges but cannot resolve.

6 Conclusion

The treatment of BCG-unresponsive NMIBC has entered an era of unprecedented therapeutic diversity. Five biotechnology platforms anti-PD-1 systemic checkpoint inhibition (pembrolizumab), non-replicating adenoviral gene therapy, (nadofaragene-firadenovec), IL-15 super-agonist immunotherapy (nogapendekin alfa inbakicept), oncolytic adenovirus (cretostimogene grenadenorepvec), and targeted intravesical drug delivery (chemohyperthermia, TAR-200, nanoparticle systems) – now offer bladder-sparing alternatives to radical cystectomy for selected patients. Pivotal trial CR rates range from 41% (pembrolizumab) to 74.5% (cretostimogene grenadenorepvec) at any time, with durable 12- to 24-month CR in 24–46% of treated patients. Head-to-head trials are absent

and unlikely; agent selection is anchored on biomarker pattern, comorbidity profile, infrastructure access, and patient preference. The clinical urologist now occupies a decision point that did not exist a decade ago, and the multidisciplinary management of BCG-unresponsive NMIBC has become correspondingly more complex and more rewarding. Closing the remaining gaps biomarker-based response prediction, head-to-head efficacy comparison, real-world durability, and equitable global access will define the next decade of research and policy.

Conflict of Interest: The author declares no conflict of interest.

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Ethical consideration: The study was approved by Nasiriyah Teaching Hospital, Thi-Qar, Iraq.

REFERENCES

- [1] Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. 1Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2024;74:229–63. <https://doi.org/10.3322/caac.21834>.
- [2] Babjuk M, Burger M, Capoun O, Cohen D, Compérat EM, Dominguez Escrig JL, Gontero P, Liedberg F, Masson-Lecomte A, Mostafid AH, Palou J, van Rhijn BWG, Rouprêt M, Shariat SF, Seisen T, Soukup V, Sylvester RJ. 2European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *European Urology* 2022;81:75–94. <https://doi.org/10.1016/j.eururo.2021.08.010>.
- [3] Jeffrey M. Holzbeierlein, Brooke R. Bixler, David I. Buckley, Sam S. Chang, Rebecca Holmes, Andrew C. James, Erin Kirkby, James M. McKiernan, Anne K. Schuckman. 3Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline: 2024 Amendment | *Journal of Urology. The-Journal-of-Urology* 2024;211:533–8. <https://doi.org/https://doi.org/10.1097/JU.0000000000003846>.
- [4] Morales A, Eidinger D, Bruce AW. 4Intracavitary Bacillus Calmette-guerin in the Treatment of Superficial Bladder Tumors. *The Journal of Urology* 1976;116:180–2. [https://doi.org/10.1016/S0022-5347\(17\)58737-6](https://doi.org/10.1016/S0022-5347(17)58737-6).
- [5] RICHARD J. SYLVESTER, ADRIAN P.M. van der MEIJDEN, DONALD L. LAMM. 5Intravesical Bacillus Calmette-Guerin Reduces the Risk of Progression in Patients with Superficial Bladder Cancer: A Meta-analysis of the Published Results of Randomized Clinical Trials | *Journal of Urology. The Journal-of-Urology* 2002;168:1964–70. <https://doi.org/https://doi.org/10.1016/S0022->

- 5347(05)64273-5.
- [6] Lange A, Madiraju S, Petros FG. 6Therapeutic Advances in Bladder Preservation for BCG-Unresponsive Non-Muscle Invasive Bladder Cancer. *Cancers*-2025;17:636. <https://doi.org/10.3390/cancers17040636>.
 - [7] Stein JP, Lieskovsky G, Cote R, Groshen S, Feng A-C, Boyd S, Skinner E, Bochner B, Thangathurai D, Mikhail M, Raghavan D, Skinner DG. 7Radical Cystectomy in the Treatment of Invasive Bladder Cancer: Long-Term Results in 1,054 Patients. *J Clin Oncol*-2001;19:666-75. <https://doi.org/10.1200/JCO.2001.19.3.666>.
 - [8] Lobo N, Mount C, Omar K, Nair R, Thurairaja R, Khan MS. 8Landmarks in the treatment of muscle-invasive bladder cancer. *Nat Rev Urol* 2017;14:565-74. <https://doi.org/10.1038/nrurol.2017.82>.
 - [9] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D. 9The PRISMA 2020 statement: an updated guideline for reporting systematic reviews 2021;372:1-9. <https://doi.org/10.1136/bmj.n71>.
 - [10] Balar AV, Kamat AM, Kulkarni GS, Uchio EM, Boormans JL, Roumiguié M, Krieger LEM, Singer EA, Bajorin DF, Grivas P, Seo HK, Nishiyama H, Konety BR, Li H, Nam K, Kapadia E, Frenkl T, Wit R de. 10Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study. *The Lancet Oncology*-2021;22:919-30. [https://doi.org/10.1016/S1470-2045\(21\)00147-9](https://doi.org/10.1016/S1470-2045(21)00147-9).
 - [11] Necchi A, Roumiguié M, Kamat AM, Shore ND, Boormans JL, Esen AA, Le Bret T, Kandori S, Bajorin DF, Krieger LEM, Niglio SA, Uchio EM, Seo HK, Wit R de, Singer EA, Grivas P, Nishiyama H, Li H, Baranwal P, Sigtenhorst-Fijlstra MV den, Kapadia E, Kulkarni GS. 11Pembrolizumab monotherapy for high-risk non-muscle-invasive bladder cancer without carcinoma in situ and unresponsive to BCG (KEYNOTE-057): a single-arm, multicentre, phase 2 trial. *The Lancet Oncology* 2024;25:720-30. [https://doi.org/10.1016/S1470-2045\(24\)00178-5](https://doi.org/10.1016/S1470-2045(24)00178-5).
 - [12] Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Lorient Y, Necchi A, Valderrama BP, Ravaud A, Shariat SF, Szabados B, van der Heijden MS, Gillessen S. 12Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆. *Annals of Oncology* 2022;33:244-58. <https://doi.org/10.1016/j.annonc.2021.11.012>.
 - [13] Dinney CPN, Greenberg RE, Steinberg GD. 13Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. *Urologic Oncology: Seminars and Original Investigations* 2013;31:1635-42. <https://doi.org/10.1016/j.urolonc.2012.04.010>.
 - [14] Shore ND, Boorjian SA, Canter DJ, Ogan K, Karsh LI, Downs TM, Gomella LG, Kamat AM, Lotan Y, Svatek RS, Bivalacqua TJ, Grubb RL, Krupski TL, Lerner SP, Woods ME, Inman BA, Milowsky MI, Boyd A, Treasure FP, Gregory G, Sawutz DG, Yla-Herttuala S, Parker NR, Dinney CPN. 14Intravesical rAd-IFNα/Syn3 for Patients With High-Grade, Bacillus Calmette-Guerin-Refractory or Relapsed Non-Muscle-Invasive Bladder Cancer: A Phase II Randomized Study. *J Clin Oncol* 2017;35:3410-6. <https://doi.org/10.1200/JCO.2017.72.3064>.
 - [15] Boorjian SA, Alemozaffar M, Konety BR, Shore ND, Gomella LG, Kamat AM, Bivalacqua TJ, Montgomery JS, Lerner SP, Busby JE, Poch M, Crispen PL, Steinberg GD, Schuckman AK, Downs TM, Svatek RS, Mashni J, Lane BR, Guzzo TJ, Bratslavsky G, Karsh LI, Woods ME, Brown G, Canter D, Luchey A, Lotan Y, Krupski T, Inman BA, Williams MB, Cookson MS, Keegan KA, Andriole GL, Sankin AI, Boyd A, O'Donnell MA, Sawutz D, Philipson R, Coll R, Narayan VM, Treasure FP, Yla-Herttuala S, Parker NR, Dinney CPN. 15Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: a single-arm, open-label, repeat-dose clinical trial. *The Lancet Oncology* 2021;22:107-17. [https://doi.org/10.1016/S1470-2045\(20\)30540-4](https://doi.org/10.1016/S1470-2045(20)30540-4).
 - [16] Administration USF and D. 16FDA Approves First Gene Therapy for the Treatment of High-Risk, Non-Muscle-Invasive Bladder Cancer. NEWS PROVIDED BY US Food and Drug Administration n.d. <https://www.prnewswire.com/news-releases/fda-approves-first-gene-therapy-for-the-treatment-of-high-risk-non-muscle-invasive-bladder-cancer-301705468.html> (accessed July 18, 2026).
 - [17] Uchio E TM, Nam JK, Joshi SS, Steinberg GD, Bivalacqua TJ. 18Topline Results from BOND-003: A Phase-3 Study of Intravesical Cretostimogene Grenadenorepvec for the Treatment of High-Risk BCG-Unresponsive NMIBC with CIS, Dallas, TX: 2024.
 - [18] admin. 19CG Oncology Announces Bond-003 Topline Results. Bladder Cancer | Oncolytic Immunotherapy | Cretostimogene Grenadenorepvec | CG Oncology - CG-Oncology-2024. <https://cgoncology.com/groundbreaking-cretostimogene/> (accessed July 18, 2026).
 - [19] Han K, Zhu X, Liu B, Jeng E, Kong L, Yovandich JL, Vyas VV, Marcus WD, Chavallaz P-A, Romero CA, Rhode PR, Wong HC. 20IL-15:IL-15 receptor alpha superagonist complex: High-level co-expression in recombinant mammalian cells, purification and characterization. *Cytokine* 2011;56:804-10. <https://doi.org/10.1016/j.cyto.2011.09.028>.
 - [20] Cravatt BF, Wright AT, Kozarich JW. 21-Activity-Based Protein Profiling: From Enzyme Chemistry to

- Proteomic Chemistry. Annual Review of Biochemistry-2008;77:383–414.
<https://doi.org/10.1146/annurev.biochem.75.101304.124125>.
- [21] Chamie K, Chang SS, Kramolowsky E, Gonzalgo ML, Agarwal PK, Bassett JC, Bjurlin M, Cher ML, Clark W, Cowan BE, David R, Goldfischer E, Guru K, Jalkut MW, Kaffenberger SD, Kaminetsky J, Katz AE, Koo AS, Sexton WJ, Tikhonenkov SN, Trabulsi EJ, Trainer AF, Spilman P, Huang M, Bhar P, Taha SA, Sender L, Reddy S, Soon-Shiong P. 21IL-15 Superagonist NAI in BCG-Unresponsive Non-Muscle-Invasive Bladder Cancer. *NEJM Evidence* 2022;2:EVIDoa2200167.
<https://doi.org/10.1056/EVIDoa2200167>.
- [22] Lange A, Madiraju S, Petros FG. 22Therapeutic Advances in Bladder Preservation for BCG-Unresponsive Non-Muscle Invasive Bladder Cancer. *Cancers*-2025;17:636.
<https://doi.org/10.3390/cancers17040636>.
- [23] Benjamin J. Davies, Thomas J. Hwang, Aaron S. Kesselheim. 23Ensuring Access to Injectable Generic Drugs – The Case of Intravesical BCG for Bladder Cancer. *The New England Journal of Medicine (NEJM)*-2017;376:1401–3.
<https://doi.org/10.1056/NEJMp1615697>.
- [24] GuhaSarkar S, Banerjee R. 24Intravesical drug delivery: Challenges, current status, opportunities and novel strategies. *Journal of Controlled Release* 2010;148:147–59.
<https://doi.org/10.1016/j.jconrel.2010.08.031>.
- [25] Kupelian V, McVary KT, Barry MJ, Link CL, Rosen RC, Aiyer LP, Mollon P, McKinlay JB. 25Association of C-reactive Protein and Lower Urinary Tract Symptoms in Men and Women: Results From Boston Area Community Health Survey. *Urology* 2009;73:950–7.
<https://doi.org/10.1016/j.urology.2008.12.012>.
- [26] Kamat AM, Lerner SP, O'Donnell M, Georgieva MV, Yang M, Inman BA, Kassouf W, Boorjian SA, Tyson MD, Kulkarni GS, Chang SS, Konety BR, Svatek RS, Balar A, Witjes JA. 28Evidence-based Assessment of Current and Emerging Bladder-sparing Therapies for Non-muscle-invasive Bladder Cancer After Bacillus Calmette-Guerin Therapy: A Systematic Review and Meta-analysis. *European Urology Oncology* 2020;3:318–40.
<https://doi.org/10.1016/j.euo.2020.02.006>.
- [27] Martin DT, Hoimes CJ, Kaimakliotis HZ, Cheng CJ, Zhang K, Liu J, Wheeler MA, Kelly WK, Tew GN, Saltzman WM, Weiss RM. 29Nanoparticles for urothelium penetration and delivery of the histone deacetylase inhibitor belinostat for treatment of bladder cancer. *Nanomedicine: Nanotechnology, Biology and Medicine* 2013;9:1124–34.
<https://doi.org/10.1016/j.nano.2013.05.017>.
- [28] Tan WS, Steinberg G, Witjes JA, Li R, Shariat SF, Roupret M, Babjuk M, Bivalacqua TJ, Psutka SP, Williams SB, Cookson MS, Palou J, Kamat AM. 26Intermediate-risk Non-muscle-invasive Bladder Cancer: Updated Consensus Definition and Management Recommendations from the International Bladder Cancer Group. *European Urology-Oncology*-2022;5:505–16.
<https://doi.org/10.1016/j.euo.2022.05.005>.
- [29] Chavarriaga J, Becerra L, Camacho D, Godoy F, Forero J, Cabrera M, López-de-Mesa B, Ramirez A, Suso-Palau D, Varela R. 27Inverted urethral flap reconstruction after partial penectomy: Long-term oncological and functional outcomes. *Urologic Oncology: Seminars and Original Investigations* 2022;40:169.e13-169.e20.
<https://doi.org/10.1016/j.urolonc.2022.02.006>.
- [30] Caumont F, Porter C, DeBerg H, Burns J, Frankel J, Flores JP. 30Combined chemotherapy and radiotherapy improves survival in 1897 testicular Lymphoma patients from a contemporary cohort. *Urologic Oncology: Seminars and Original Investigations* 2020;38:641.e1-641.e8.
<https://doi.org/10.1016/j.urolonc.2020.02.027>.
- [31] Rugo HS, Tokunaga E, Iwata H, Petry V, Smit EF, Goto Y, Kim D-W, Shitara K, Gruden JF, Modi S, Cortés J, Krop I, Jänne PA, Cheng Y, Taitt C, Cheng F-C, Powell CA. 31Erratum to “Pooled analysis of trastuzumab deruxtecan retreatment after recovery from grade 1 interstitial lung disease/pneumonitis”: [Annals of Oncology. Volume 36, Issue 11, November 2025, Pages 1389-1399]. *Ann Oncol* 2026;S0923-7534(25)06291-X.
<https://doi.org/10.1016/j.annonc.2025.12.001>.
- [32] Wells JC, Albiges L, Powles T. 32Anti-VEGF and -PD-1 Combinations in Renal Cell Carcinoma: When Are Treatment Breaks Safe. *Eur Urol* 2024;86:420–1.
<https://doi.org/10.1016/j.eururo.2024.06.005>.

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