Traditional and next-generation bacillus Calmette-Guérin based treatment strategies for bacillus Calmette-Guérin unresponsive non-muscle-invasive bladder cancer in the era of emerging therapies

Alberto Artiles Medina[a,*], *José Daniel Subiela*[a,*], *Renate Pichler*[b], *Felix Guerrero-Ramos*[c,d,e] *and Francisco Javier Burgos Revilla*[a]

Purpose of review
Bacillus Calmette–Guérin (BCG) remains the standard of care for high-risk non-muscle-invasive bladder cancer (NMIBC), yet up to 40–50% of patients experience treatment failure, leaving limited alternatives to avoid radical cystectomy. This narrative review critically examines both traditional and emerging BCG-based strategies – including repeat induction and modern combination regimens – for patients with BCG-unresponsive NMIBC.

Recent findings
BCG monotherapy after BCG failure has shown limited effectiveness, with recent studies reporting 12-month disease-free survival (DFS) rates of 60–70%. Nonetheless, BCG continues to serve as an immunotherapeutic backbone in combination strategies. Chemo-immunotherapy regimens, particularly those using gemcitabine or mitomycin C, have achieved 1-year DFS rates of up to 80%. Combinations with cytokines and immunocytokines – such as interferon-α or nogapendekin alfa inbakicept-pmln (NAI) – have demonstrated DFS rates of 45–61%, and NAI has recently received FDA approval. Immune checkpoint inhibitors (e.g., pembrolizumab, durvalumab, atezolizumab) in combination with BCG have shown DFS rates ranging from 42 to 73% at 12 months. However, many studies are limited by small sample sizes and heterogeneous designs.

Summary
Despite its limited efficacy as monotherapy in unresponsive cases, BCG retains therapeutic relevance as part of combination strategies that enhance its immunologic activity. Emerging data suggest that these BCG-based regimens offer a promising, bladder-sparing alternative for patients who are ineligible for or decline radical cystectomy. Ongoing and future trials will be essential to define optimal combinations and identify which patients are most likely to benefit, thereby enabling appropriate patient selection.

Keywords
BCG vaccine, immune checkpoint inhibitors, nonmuscle invasive bladder neoplasms, urinary bladder neoplasms

INTRODUCTION

A significant subset of patients with high-risk non-muscle-invasive bladder cancer (NMIBC) either fail to respond to bacillus Calmette-Guérin (BCG), the current standard of care, or experience disease recurrence despite adequate BCG therapy. Approximately 20% of these patients ultimately progress to muscle-invasive bladder cancer (MIBC). In fact, BCG failure occurs in up to 50% of cases [1], leaving limited treatment options for high-risk NMIBC following BCG failure.

In 2018, the U.S. Food and Drug Administration (FDA) defined "BCG-unresponsive" disease as

[a]Department of Urology, Hospital Universitario Ramón y Cajal, IRYCIS, Universidad de Alcala, Madrid, [b]Medical University of Innsbruck, Department of Urology, Comprehensive Cancer Center Innsbruck (CCCI), Innsbruck, Austria, [c]Department of Urology, Hospital Universitario 12 de Octubre, [d]ROC Clinic and [e]Department of Urology, Hospital Universitario HM Sanchinarro, Madrid, Spain

Correspondence to José Daniel Subiela, Department of Urology, Hospital Universitario Ramón y Cajal, Universidad de Alcalá, Madrid 28034, Spain. Tel: +34 913 368 760; e-mail: jdsubiela@gmail.com

*Alberto Artiles Medina and José Daniel Subiela contributed equally to this work and share first authorship.

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KEY POINTS

- Although not formally recommended, BCG reinduction and rechallenge remain commonly used in real-world clinical practice.
- Nogapendekin alfa inbakicept-pmln (N-803), an IL-15 superagonist, has demonstrated a 71% complete response rate and 100% disease-specific survival at 24 months when combined with BCG. Based on these findings, it received FDA approval in 2024 for patients with BCG-unresponsive NMIBC.
- Combination strategies involving BCG and agents such as chemotherapy (e.g., gemcitabine, MMC), cytokines (e.g., IFN-α, IL-2), and immune checkpoint inhibitors (e.g., pembrolizumab, durvalumab, atezolizumab) have shown promising efficacy in early-phase trials.
- Alternative immunotherapeutic combinations with BCG – including the vaccines PANVAC and Vesigenurtacel-L, as well as eciskafusp alfa, a PD-1-targeted immunocytokine – are under investigation, with results pending, and may offer novel bladder-sparing strategies.

persistent or recurrent carcinoma in situ alone or with Ta/T1 recurrence within 12 months of adequate BCG, recurrent high-grade Ta/T1 disease within 6 months, or T1 high-grade disease at first evaluation after BCG induction. "Adequate" BCG is defined as at least five of six doses of an initial induction course plus at least two of three doses of maintenance therapy or at least two of six doses of a second induction course. The FDA also issued guidance to support drug and biologic development for this population and to standardize clinical trial design [2].

In the context of BCG unresponsiveness, four agents have received FDA approval for patients with NMIBC who are ineligible for or decline radical cystectomy: valrubicin (1998), pembrolizumab (2020), nadofaragene firadenovec-vncg (2022), and, most recently, nogapendekin alfa inbakicept-pmln (NAI) in 2024. Several other therapeutic candidates are currently under investigation [1,3], and some older therapies remain in use in clinical practice, albeit with limited success. Figure 1 summarizes traditional and next-generation BCG-based treatment strategies for BCG-unresponsive NMIBC.

For the aforementioned FDA-approved therapies, reported outcomes in terms of 12-month disease-free survival (DFS) remain suboptimal: 13% for valrubicin [4], 43.5% for pembrolizumab [5], 30.5% for nadofaragene firadenovec-vncg [6], and 55.4% for NAI in combination with BCG [7].

This context raises a critical question: Is there a role for BCG immunotherapy in the era of novel treatments for BCG-unresponsive NMIBC? Despite the emergence of new FDA-approved therapies and ongoing research into alternative agents, BCG continues to be used in clinical practice. The persistence of BCG use in real-world settings, combined with evolving definitions and treatment paradigms, underscores the need to reassess its value. The present study aims to provide a comprehensive and up-to-date review of the most recent and relevant findings regarding the use of BCG – both as monotherapy and in combination with other agents – and to explore its potential role beyond the current criteria for BCG failure.

EFFICACY OF ADDITIONAL BACILLUS CALMETTE-GUÉRIN THERAPY IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER: RE-INDUCTION AND RECHALLENGING STRATEGIES

In the management of NMIBC following BCG failure, two commonly referenced approaches are repeat BCG induction (also referred to as reinduction) and BCG rechallenge (or retreatment). Repeat BCG induction involves administering an additional BCG course shortly after initial therapy in patients with persistent disease in order to reinforce the antitumor immune response. In contrast, BCG rechallenge refers to re-exposure to BCG after a treatment-free interval or in patients previously classified as having BCG failure, despite not meeting formal BCG-unresponsive criteria [8▪].

The reinduction approach has traditionally not been recommended due to limited clinical benefit. While approximately one-third of patients who do not respond to a single BCG course may still achieve a durable response, this benefit declines with successive treatments. In cases of persistent disease, a second induction cycle may achieve response rates of up to 50% [9]. However, beyond this point, the effectiveness drops markedly, with success rates falling below 10–20% [10,11].

Despite reports indicating that additional BCG therapy following treatment failure is largely ineffective and that radical cystectomy remains the standard of care, repeat use of BCG continues in clinical practice. Radical cystectomy is associated with significant early perioperative morbidity (approximately 60%) and a nonnegligible mortality (1–3%), in addition to permanent alterations in body image and functional complications. Consequently, radical cystectomy is not feasible for many patients, and a considerable number electively decline the procedure. Thus, nonsurgical alternatives for BCG-unresponsive NMIBC are urgently needed to improve patient outcomes and quality of life [1].

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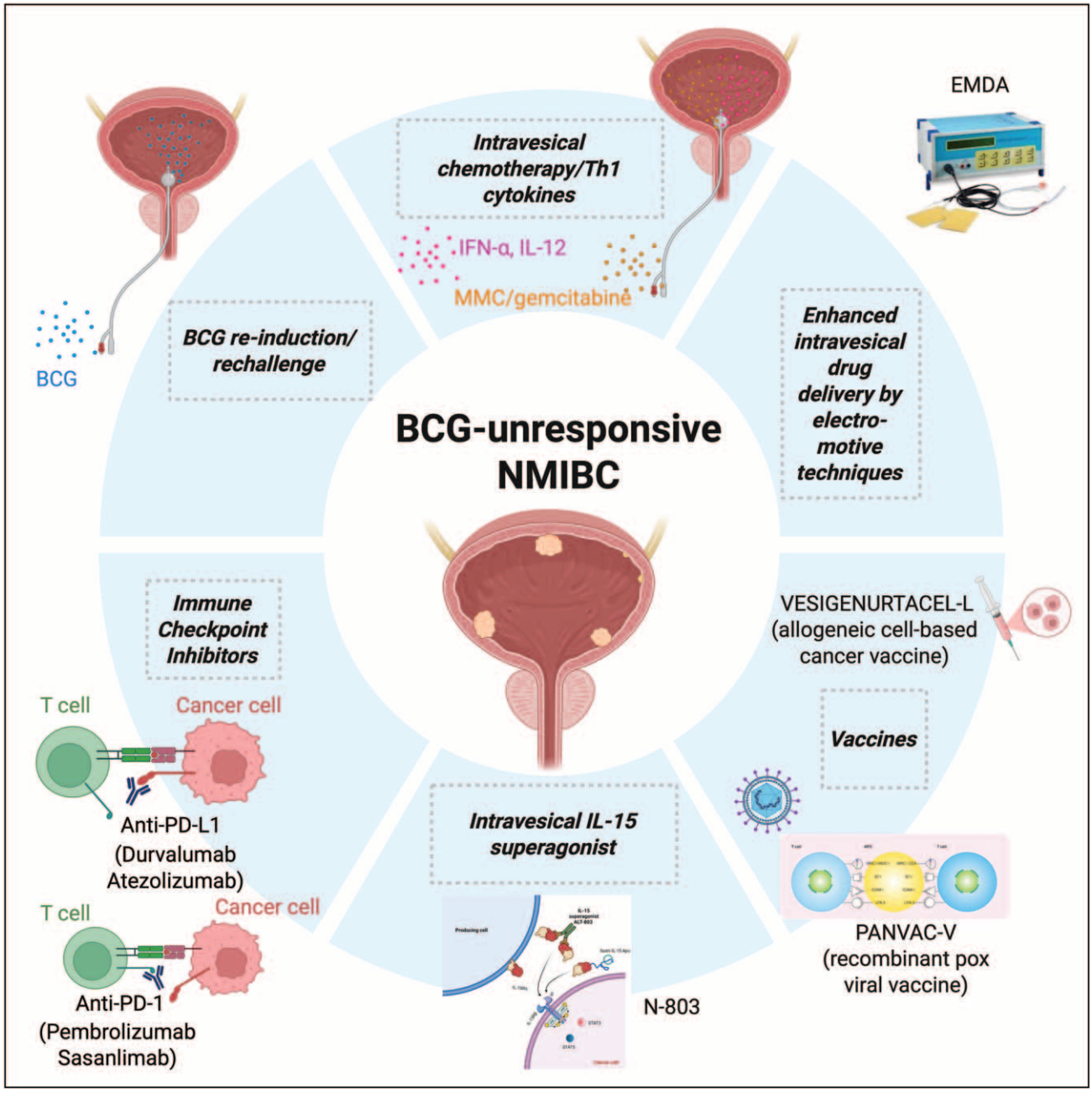

FIGURE 1. Pictorial representation of traditional and next-generation Bacillus Calmette-Guérin based treatment strategies for Bacillus Calmette-Guérin unresponsive nonmuscle-invasive bladder cancer.

Although some urologists consider BCG rechallenge no longer viable – given that it falls outside the FDA's established criteria for BCG responsiveness – it remains widely used in real-world settings, particularly in patients ineligible for radical cystectomy. A recent multicenter study by Kulkarni *et al.* [12] evaluated treatment patterns in 129 patients from 15 centers and found BCG rechallenge with or without interferon-α to be the most frequently employed initial nonsurgical approach (63.6%), followed by intravesical mitomycin C with or without electromotive drug administration (EMDA) or thermochemotherapy (15.5%) and valrubicin (10.9%). Notably, 54.8% of patients who received BCG rechallenge alone required at least two additional non-BCG therapies, and over 25% experienced disease progression within the first 3 years [12].

Table 1 summarizes studies reporting outcomes of additional BCG courses in patients with BCG-unresponsive or BCG-refractory NMIBC ([13,14▪, 15–19]). The most recent studies ([13,14▪,15–17]) report 12-month DFS rates ranging from 50.9 to

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Table 1. Studies reporting outcome data for additional Bacillus Calmette-Guérin monotherapy after Bacillus Calmette-Guérin unresponsiveness or Bacillus Calmette-refractory tumors

Author	Year	Country	Type of study	Retreatment scheme	n	Age (years) (median and range or mean ± SD)	Stage	3-month complete response rate	DFS at last follow-up	Median duration of response	Cystectomy-free rate	DFS at 12 months	PFS at 12 months	DFS at 24 months	PFS at 24 months	CSS	Median follow-up
Guske *et al.* [13]	2025	USA	Single-center retrospective	Rescue BCG, defined as reinduction or continued maintenance	55	71.8 (65.0–76.5)	*NR*	*NR*	*NR*	13.6 months (95% CI 6.4–not reached)	*NR*	50.9% (95% CI 38.9–66.4%)	*NR*	*NR*	*NR*	*NR*	33.0 months (IQR 15.5–55.1)
Myers *et al.* [14]	2024	USA	Single-center retrospective	Rescue BCG: reinduction with BCG (≥5 doses) or continued maintenance (3 doses)	36	69 (62–76)	BCG-unresponsive disease: high-grade disease (20 T1, 7 Ta, 9 CIS only, 8 concomitant CIS	CIS: 82% (14/17)	75%	83 months (95% CI 35–not reached)	89% (79–100%) at 12 months 79% (67–94%) at 24 months	69% (55–86)	89% (79–100%)	63% (95% CI 48–81)	86% (95% CI 75–98)	97% (91–100%) at 24 months	4.7 years (2.1–7.9)
Taylor *et al.* [15]	2024	USA	Multicenter retrospective	*NR* (additional BCG as BST)	204	<50: 5 (2.5%) 50–59: 27 (13%) 60–69: 58 (28%) 70–79: 72 (35%) ≥80: 42 (21%)	T1 disease after induction: 80 (39%) HG Ta 6 months after last maintenance: 55 (27%) CIS 12 months after last maintenance: 69 (34%)	*NR*	38% at 60 months	*NR*	87% at 12 months 71% at 24 months	63%	91%	47%	83%	95% at 24 months	47 months (IQR 14–86)
Elsawy *et al.* [16]	2023	Egypt	Single-center retrospective	Additional intravesical BCG	231	59.2 (±10.4)	Persistent/recurrent tumors at 3 months after BCG induction T1 209 (90.5%) Tis 22 (9.5%)	*NR*	119 (51.5%)	26 months (range 9–152)	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	148 months (range 24–224)
Daniels *et al.* [17]	2019	USA	Multicenter retrospective	Subsequent second 6-week induction therapy for patients with recurrent or persistent disease	116	67.31 (±10.39)	TaHG: 48 (41.4%) T1: 29 (25.0%) CIS 39 (33.6%)	89.7%	62%	*NR*	*NR*	76.7%	*NR*	67.2%	*NR*	*NR*	45.4 months
Di Lorenzo *et al.* [18]	2010	Italy	Multicenter, prospective, randomized, phase 2 trial	Intravesical BCG (Connaught strain, 81 mg/50 mL) over a 6-week induction course and each week for 3 weeks at 3, 6, and 12 months	40	*NR*	Ta: 8 T1: 32	*NR*	*NR*	*NR*	62.8%, although 40% of patients received RT	25%	*NR*	3%; 95% CI 0%–21%	*NR*	*NR*	15.2 months (range 6–22)
Gacci *et al.* [19]	2006	Italy	Single-center retrospective	Further conservative endovesical BCG administration (induction and maintenance)	10	73.6 (±11.9)	BCG-refractory T1G3 patients previously treated with at least two courses of transurethral resection followed by BCG	*NR*	*NR*	*NR*	*NR*	10%	*NR*	10%	*NR*	*NR*	19.9 months (range 7–27)

BST, bladder-sparing treatment; CSS, cancer-specific survival; DFS, disease-specific survival; IQR, interquartile range; NR, not reported; PFS, progression-free survival; RT, radiation therapy.

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76.7% for bladder-preserving strategies, though heterogeneity in study design and inclusion criteria limits direct comparisons.

Only two studies reported 12-month progression-free survival (PFS), with rates ranging from 89 to 91% [14▪,15]. These same studies also provided data on 24-month cystectomy-free survival and cancer-specific survival (CSS), with reported rates of 71–79% and 95–97%, respectively. Regarding treatment-related side effects, Di Lorenzo *et al.* [18] reported that BCG was generally well tolerated. In their study, 12 out of 40 patients (30%) experienced grade 2 adverse events, while three out of 40 patients (7.5%) experienced grade 3 events. According to Daniels *et al.* [17], adverse effects were more frequent and varied with repeated BCG instillations compared to the initial course. These side effects were typically mild and included hematuria, dysuria, fever, chills, flu-like symptoms, fatigue or weakness, pelvic pain or spasms, and urinary incontinence. Adverse effects during a second course of BCG occurred in 41.4% of patients.

CHEMOTHERAPY-BASED COMBINATION APPROACHES WITH BACILLUS CALMETTE-GUÉRIN IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

Combinations of mitomycin C (MMC) or gemcitabine with BCG instillations have been investigated in the context of BCG-unresponsive NMIBC. Combining intravesical agents with different antitumor mechanisms may enhance treatment effectiveness and help prevent the emergence of drug-resistant tumors. MMC works by damaging cancer cell DNA through cross-linking, alkylation, and free radical-induced strand breakage. Apart from its direct antitumor action, intravesical chemotherapy also stimulates the immune response by activating $CD8^+$ T cells and reducing T cell exhaustion. BCG facilitates recruitment of activated T cells. In preclinical models, combining BCG plus MMC inhibits growth of bladder cancer more effectively than either individual agent [20,21].

Wald *et al.* [22] conducted a trial involving patients with recurrent high-grade Ta, high-grade T1, and/or carcinoma in-situ NMIBC who had been exposed to BCG within the previous 24 months, but did not meet the criteria for BCG-unresponsive NMIBC. Preliminary results from this phase II trial demonstrated that intravesical chemo-immunotherapy with gemcitabine and BCG shows promising efficacy in this setting. Complete response (CR) rates were 98% at 3 months, 94% at 6 months, and 81% at 12 months. Among patients with carcinoma in situ with or without concomitant papillary disease, CR rates were 100%, 97%, and 80% at the same respective time points. High-grade recurrence-free survival was 97% at 6 months, 85% at 12 months, and 76% at 18 months, with a 12-month cystectomy-free survival rate of 100%. The regimen was well tolerated, with only two patients (5%) experiencing grade 3 treatment-related adverse events and no grade 4 or 5 toxicities reported. Based on these encouraging findings, a phase III clinical trial is currently underway.

Table 2 summarizes studies of other BCG-based therapies for BCG-unresponsive NMIBC [7,22–26].

DEVICE-ASSISTED CHEMOTHERAPY-BASED COMBINATIONS WITH BACILLUS CALMETTE-GUÉRIN IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

The integration of EMDA into intravesical BCG immunotherapy has emerged as a promising approach to enhance efficacy in patients with BCG-unresponsive NMIBC. In a retrospective study by Juvet *et al.* [25], 26 patients with high-grade NMIBC who experienced BCG failure were treated with sequential instillations of BCG and MMC administered via EMDA. CR rates were 61.5% at 6 months, 44.0% at 12 months, and 30.4% at 18 months. At a median follow-up of 2.4 years, PFS and recurrence-free survival at 24 months were 48.9 and 27.2%, respectively. The regimen was well tolerated, with 19.2% of patients experiencing mild adverse events such as dysuria or hematuria, and no grade 4 or 5 toxicities reported.

More recently, Sanz Gómez *et al.* [26] assessed a similar sequential regimen in a cohort of 22 patients with high-risk NMIBC who had failed BCG therapy. Alternating BCG and MMC delivered via EMDA led to notably higher CR rates: 100% at 3 and 6 months, 82.4% at 12 months, and 68.8% at 24 months among the BCG-unresponsive subgroup. Only one patient (4.5%) progressed to muscle-invasive disease and required radical cystectomy. These findings underscore the potential of BCG/EMDA-MMC as an effective and well tolerated bladder-sparing strategy in selected patients with BCG-unresponsive NMIBC.

CYTOKINE-BASED COMBINATION THERAPY WITH BACILLUS CALMETTE-GUÉRIN IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

The addition of cytokines, such as interferon-alpha (IFN-α), to BCG therapy has also been investigated as a means to enhance BCG's immunotherapeutic efficacy. This strategy aims to amplify cytokine-mediated stimulation and promote T helper type 1 (Th1)

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Table 2. Summary of other studies of Bacillus Calmette-Guérin based therapies for Bacillus Calmette-Guérin unresponsive or Bacillus Calmette-Guérin exposed nonmuscle-invasive bladder cancer

Author	Year	Country	Type of study	Treatment scheme	n	Median age (years)	Stage	3-month complete response rate	DFS at last follow-up	Median duration of response	Cystectomy-free rate	DFS at 12 months	PFS at 12 months	DFS at 24 months	PFS at 24 months	CSS	Adverse events	Median follow-up
NAI plus BCG																		
Chamie *et al.* [7]	2022	USA	Clinical trial	Intravesical NAI (400 µg/instillation) plus intravesical BCG (50 mg/instillation)	82	NR	BCG-unresponsive bladder CIS with or without Ta/T1	55%	71%	NR	NR	45% (95% CI 34.1– 56.5)	NR	NR	84.7%	100% at 24 months	NR	23.9 months (range 3.2–37.5)
BCG/IFN-α therapy																		
Steinberg *et al.* [23]	2022	USA	Clinical trial	1/3 dose BCG, plus 50 million units IFN-α (Intron A, Schering-Plough, Kenilworth, NJ)	197	71	Recurrent NMIBC after at least 1 prior induction course of BCG CIS: 40 (20.3%) T1: 38 (19.3%) T1 + CIS: 5 (2.5%) Ta: 106 (53.8%) *Ta+CIS: 8 (4.1%)*	NR	NR	NR	NR	61%	NR	53%	NR	NR	NR	NR
BCG, interferon, interleukin-2, and granulocyte-macrophage colony-stimulating factor																		
Steinberg *et al.* [24]	2017	USA	Retrospective	One-third dose BCG in 50 ml of saline, 50 million units IFN-α, which comes as a powder with 1 ml diluent to reconstitute, and 22 million units IL-2	52	69.5 (50–88)	Patients with prior BCG failure CIS alone: 30 (58%) TaLG: 3 (6%) TaLG + CIS: 2 (4%) TaHG: 3 (6%) TaHG + CIS: 1 (2%) T1HG: 7 (13%) T1HG + CIS: 6 (11%)	NR	NR	NR	75%	55%	NR	53%	NR	95% at 2 years and 82% at 5 years	52 patients (90%) noted a side effect during therapy	41.8 months
Gemcitabine–BCG combination therapy																		
Wald *et al.* [22]	2024	USA	Clinical trial	Gemcitabine 200 mg twice weekly in weeks 1, 4, 7, and 10 and BCG 50 mg TICE strain weekly in weeks 2, 3, 5, 6, 8, and 9	43	70 (66–76)	Pathologic HG Ta, HG T1, and/or Tis. BCG exposure within the prior 24 months	98% (39/40)	NR	NR	100% at 12 months	81%	NR	NR	NR	NR	Only two patients (5%) experienced a grade 3 treatment-related adverse event	NR
Combination of device-assisted chemotherapy and BCG																		
Sanz Gómez *et al.* [26]	2023	Spain	Retrospective	Sequential treatment with BCG/MMC + EMDA, with an induction and a 1-year maintenance according to the treating physician's decision	22	73	Ta: 9 (40.9%) T1: 9 (40.9%) TIS: 3 (13.6%) Tx: 1 (4.5%)	95.5%	NR	37.8 months (3.14 years)	21/22 (95.5%)	81%	NR	70%	NR	NR	22%	28.8 months (95% CI 17.39–41.12)

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Table 2 (Continued)

Author	Year	Country	Type of study	Treatment scheme	n	Median age (years)	Stage	3-month complete response rate	DFS at last follow-up	Median duration of response	Cystectomy-free rate	DFS at 12 months	PFS at 12 months	DFS at 24 months	PFS at 24 months	CSS	Adverse events	Median follow-up
Juvet *et al.* [25]	2020	Canada	Retrospective	Initial induction course included 9 weekly visits with administration of EMDA-MMC (40 mg in 100 ml normal saline) at 3, 6, and 9 weeks, with standard OncoTice BCG (81 mg in 50 ml; Merck) instilled during the remaining weeks.	26	NR	53.8% of patients had CIS, 34.6% pT1, and 11.6% pTa HG	NR	NR	NR	NR	41.9%	58.3%	27.2%	48.9%	23/26 (88.5%)	Three patients (11.5%) were admitted to the hospital (grade 3)	871 days (IQR 435–1203)

CSS, cancer-specific survival; DFS, disease-free survival; EMDA, electromotive drug administration; IFN-α, interferon-alpha; IQR, interquartile range; MMC, mitomycin C; NAI, nogapendekin alfa inbakicept-pmln; NR, not reported; PFS, progression-free survival.

immune responses, along with enhanced T cell recruitment to the bladder microenvironment [10]. However, outcomes have varied across studies. Early research demonstrated that intravesical IFN-α monotherapy yielded a 2-year DFS rate of only 12% in patients with BCG-refractory carcinoma in situ [27]. In contrast, phase I and II trials combining BCG with IFN-α2b in patients with prior BCG failure reported improved response rates of approximately 50% [28,29]. Paradoxically, the only randomized trial evaluating BCG combined with IFN-α2b in BCG-naive patients failed to demonstrate superiority over BCG monotherapy, although the reduced-dose BCG–IFN-α2b combination was associated with a lower toxicity profile [10,30]. As summarized in Table 2, Steinberg *et al.* [23] reported a 1-year DFS rate of 61% with this combination, indicating a potential role in selected clinical scenarios.

QUADRUPLE IMMUNOTHERAPY WITH BACILLUS CALMETTE-GUÉRIN, IFN-α, INTERLEUKIN-2, AND GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

The use of interleukin-12 (IL-12), a cytokine that promotes Th1 immune responses and enhances interferon production, along with other immune system modulators, has been explored in patients with BCG-refractory NMIBC [10]. Steinberg *et al.* [24] reported the outcomes of a quadruple immunotherapy regimen combining BCG, IFN-α, IL-2, and granulocyte-macrophage colony-stimulating factor in a cohort of 52 patients with prior BCG failure. The study showed a 12-month DFS rate of 55%, although it was associated with increased toxicity, observed in 90% of patients. The authors concluded that while this multimodal immunotherapy demonstrated promising efficacy in a subset of patients, further investigation is warranted to better define its therapeutic role.

INTERLEUKIN-15 SUPERAGONIST NOGAPENDEKIN ALFA INBAKICEPT-PMLN IN COMBINATION WITH BACILLUS CALMETTE-GUÉRIN FOR BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

Nogapendekin alfa inbakicept-pmln (N-803), an IL-15 superagonist, is a novel immunocytokine that enhances BCG-induced trained immunity by activating natural killer and memory $CD8^+$ T cells in patients with BCG-unresponsive NMIBC. In the QUILT-3.032 phase I/II trial [7], intravesical N-803

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combined with BCG achieved a 71% CR rate in patients with carcinoma in situ, with a median CR duration of 26.6 months. At 24 months, disease-specific survival was 100%, and 89% of responders avoided cystectomy. In patients with high-grade Ta/T1 disease, 12-month DFS reached 55.4%. The regimen showed a favorable safety profile, with most adverse events being grade 1–2 and limited to local bladder symptoms; only 3% experienced grade $\geq$3 immune-related toxicity. Based on these results, N-803 was granted FDA approval in April 2024 for use in combination with BCG in patients with BCG-unresponsive NMIBC who are ineligible for or decline radical cystectomy.

COMBINATION THERAPY WITH PD-L1 INHIBITORS PLUS BACILLUS CALMETTE-GUÉRIN

Adaptive immune resistance via the PD-L1 pathway has been implicated in a subset of patients who experience recurrence following BCG therapy, suggesting a potential benefit from combining BCG with immune checkpoint inhibitors targeting the PD-1/PD-L1 axis [31]. In response, several clinical trials are evaluating the efficacy and safety of these combinations in BCG-unresponsive NMIBC [32]. Table 3 summarizes the available data from ongoing studies exploring BCG in combination with immune checkpoint inhibitors [33–37].

Among these, the phase III KEYNOTE-676 trial is assessing pembrolizumab in combination with BCG in patients with persistent or recurrent high-risk NMIBC after BCG induction therapy [38]. Preliminary findings by Montgomery *et al.* [33,34] have reported a 12-month DFS rate of 69.2% with systemically administered pembrolizumab plus BCG. In contrast, intravesical administration of pembrolizumab with BCG has shown limited efficacy, with a 12-month DFS of only 22% [35].

For durvalumab, a phase I trial reported a CR rate of 73% at 12 months in patients treated with the durvalumab–BCG combination [36]. Similarly, atezolizumab has been evaluated in the phase Ib/II GU-123 study in BCG-unresponsive NMIBC, yielding a 12-month CR rate of 42% [37].

Other immune checkpoint inhibitors are also under active investigation. The CREST study is evaluating subcutaneous sasanlimab (a PD-1 inhibitor) in patients with BCG-unresponsive NMIBC [39]. Additionally, trials such as CheckMate 7G8 and CheckMate 9UT are assessing the efficacy of nivolumab combined with BCG in similar patient populations [40].

One of the main barriers to using PD-L1 inhibitors (e.g., pembrolizumab) in BCG-unresponsive NMIBC is the relatively high incidence of immune-related adverse effects, occurring in up to 23.7% of patients [41]. These toxicities can lead to early treatment discontinuation. As these drugs are typically administered intravenously every two to three weeks, they require close monitoring, frequent clinic visits, and proactive management of side effects, factors that pose a significant clinical challenge [42].

THERAPEUTIC VACCINE-BASED COMBINATION STRATEGIES WITH BACILLUS CALMETTE-GUÉRIN IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

Alternative immunotherapeutic approaches, including vaccine and gene therapy strategies, are currently under investigation for the treatment of BCG-unresponsive NMIBC. Cancer vaccines represent an attractive option, aiming to enhance antitumor immunity by presenting tumor-associated antigens and stimulating specific immune responses. Nevertheless, most ongoing clinical trials involving vaccines – such as Ty21a and RUTIVAC-1 – are currently focused on BCG-naive patients, leaving limited data available for the BCG-exposed population [11].

In the context of BCG-unresponsive disease, two vaccine-based strategies have been evaluated in combination with BCG: PANVAC, a recombinant viral vector vaccine encoding human carcinoembryonic antigen (CEA), mucin-1 (MUC1), and three costimulatory molecules, and Vesigenurtacel-L (HS-410), an intradermal allogeneic tumor cell vaccine expressing a broad array of bladder cancer-associated antigens.

The combination of PANVAC with BCG was assessed in a prospective phase II trial in patients who had failed prior BCG therapy. Unfortunately, the results were disappointing. At 12 months, the recurrence-free survival was 42.9% in the BCG monotherapy arm and 44.4% in the BCG+PANVAC arm (P=0.971), showing no significant benefit from the addition of the vaccine [43].

In the case of Vesigenurtacel-L combined with BCG, early safety data indicate that the vaccine is well tolerated, with immunologic responses consistent with its proposed mechanism of action; however, efficacy outcomes are still pending [44].

OTHER EMERGING THERAPEUTIC COMBINATIONS WITH BACILLUS CALMETTE-GUÉRIN IN BACILLUS CALMETTE-GUÉRIN UNRESPONSIVE NONMUSCLE-INVASIVE BLADDER CANCER

Other emerging BCG-based therapies for BCG-unresponsive NMIBC include eciskafusp alfa, a PD-1-targeted immunocytokine engineered to enhance

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Table 3. Data from studies investigating a combination of PD-1/PD-L1 and Bacillus Calmette-Guérin

Author	Year	Country	Type of study	Treatment scheme	n	Median age (years)	Stage	3-month complete response rate	DFS at last follow-up	Median duration of response	Cystectomy-free rate	DFS at 12 months	PFS at 12 months	DFS at 24 months	PFS at 24 months	CSS	Adverse events	Median follow-up
Intravesical BCG in combination with systemic pembrolizumab																		
Montgomery *et al.* [33,34]	2024	USA	Clinical trial	Six doses of pembrolizumab administered every 3 weeks over 16 weeks concurrently with six weekly doses of BCG beginning at week 7	13	73	High-grade NMIBC with or recurrent disease after prior intravesical therapy with BCG *pTa in 6 (46.2%), CIS in 6 (46.2%), and pT1 in 1 (7.7%)*	9 (69%)	NR	NR	NR	69.2%	NR	38.5%	NR	NR	NR	NR
Pembrolizumab (intravesical) plus BCG																		
Meghani *et al.* [35]	2022	USA	Clinical trial	BCG (TICE, 50 mg) (weeks 0–5), intravesical pembrolizumab (weeks 0, 2, 4)	9	76	Tis: 1 TaHG: 2 TaHG + CIS: 2 T1: 3	100%	NR	6.2 months (95% CI 5–NA)	7/10	22% (95% CI 6.5%–75%)	56% (95%CI 31%–100%)	NR	NR	NR	One patient died due to treatment-related myasthenia gravis	35 months
Durvalumab plus BCG																		
Hahn *et al.* [36]	2023	USA	Clinical trial	1120 mg of D intravenously every 3 weeks for eight cycles. D + BCG patients also received full-dose intravesical BCG weekly for 6 weeks with BCG maintenance recommended	13	74	CIS-only (50%), CIS with concurrent papillary (14%), and high-grade papillary-only (36%)	85%	NR	NR	NR	73%	NR	NR	NR	NR	Two patients (15%) experienced a grade 3–4 AE	NR
Atezolizumab plus BCG																		
Inman *et al.* [37]	2023	USA	Clinical trial	Atezolizumab 1200 mg IV every 3 weeks for ≤96 weeks + standard BCG induction and maintenance courses	12	73.0 (52–84)	T1: 6 (50) Ta: 3 (25) Tis only: 3 (25)	42%	NR	NR	NR	42%	NR	NR	NR	NR	Grade 3 AEs: 3 (25)	NR

AE, adverse event; CSS, cancer-specific survival; DFS, disease-free survival; NA, not available; NR, not reported; PFS, progression-free survival.

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intravesical immunotherapy. A multiphase clinical trial is currently underway to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, biomarker activity, and preliminary antitumor efficacy of intravesical eciskafusp alfa in combination with BCG in patients with high-risk, BCG-unresponsive NMIBC [45]. The outcomes of this study are expected to provide valuable insights into the potential role of cytokine-augmented immunotherapy as a bladder-sparing alternative in this challenging clinical setting.

CONCLUSION

Although BCG monotherapy demonstrates limited efficacy in patients with BCG-unresponsive NMIBC, growing evidence supports an evolving role for BCG within combination treatment strategies. Multiple approaches – such as regimens combining BCG with chemotherapeutic agents, cytokines, immunocytokines, immune checkpoint inhibitors, and therapeutic vaccines – have shown encouraging clinical outcomes with acceptable safety profiles. Notably, agents like nogapendekin alfa inbakicept-pmln illustrate how enhancing BCG-induced immunity can lead to durable responses while enabling bladder preservation in selected patients. Thus, although BCG alone may no longer suffice in the setting of unresponsive disease, its integration with novel immunomodulatory agents represents a promising and rational strategy for bladder-sparing therapy. Ongoing and future clinical trials will be crucial in order to define optimal combination regimens and identify patient subgroups most likely to benefit from these innovative approaches.

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Conflicts of interest

There are no conflicts of interest.

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- ■ of special interest
- ■■ of outstanding interest

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