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# Combination Strategies to Enhance Bacillus Calmette-Guérin Efficacy for Nonmuscle-Invasive Bladder Cancer

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*Data analysis and interpretation:* Pietzak, Alkazemi, Lang, Wahba.

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**Purpose:** Bacillus Calmette-Guérin (BCG) is the standard of care therapy for high-risk nonmuscle-invasive bladder cancer (NMIBC). However, up to half of patients will experience treatment failure, and many face considerable adverse effects, which can lead to dose reduction and intolerance. Novel bladder-sparing approaches with favorable risk-to-benefit ratio are thus critical in NMIBC.

**Materials and Methods:** A narrative review of the literature was performed of English-language MEDLINE indexed articles and abstracts of resistance mechanisms to BCG and combination-based strategies to enhance the efficacy of BCG intravesical therapy in high-risk NMIBC.

**Results:** Treatment options for high-risk NMIBC have expanded considerably over the last few years. Combination strategies represent an opportunity to enhance the effectiveness of BCG and promote durable response. Combination therapies that aim to reduce immunosuppressive cellular populations (regulatory T cells, myeloid-derived suppressor cells) and immune checkpoint blockade offer mechanisms to overcome resistance to BCG therapy. Chemoimmunotherapy and immunotherapy-based combinations represent a bladder preservation strategy that needs to be weighed against oncological efficacy, toxicity, and cost-effectiveness.

**Conclusions:** BCG-based combination therapies have emerged as a strategy to overcome BCG resistance and promote durable responses. Despite their promise, combination design is endless, and adoption remains challenging due to overlapping mechanisms of resistance, adverse events associated with systemic therapy and/or additional intravesical therapy, and financial burden. Long-term multiarm trials are needed for direct comparative analyses between combinations of agents to inform oncological efficacy, safety profile, and cost-effectiveness.

**Key Words:** chemoimmunotherapy, combination therapy, BCG, immune checkpoint blockade, NMIBC

Bladder cancer is the seventh most commonly diagnosed cancer in the United States, with an estimated 84,870 new diagnoses and 17,420 deaths in 2025.[1] Approximately 75% of newly diagnosed cases do not invade into the muscularis propria and are classified as nonmuscle-invasive bladder cancer (NMIBC). Bacillus Calmette-Guérin (BCG) intravesical immunotherapy is the current standard of care in the management of high-risk NMIBC as it significantly reduces rates of recurrence and is historically the sole agent to have demonstrated reduction in risk of progression to muscle-invasive bladder cancer in



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randomized controlled trials.[2] Despite the therapeutic benefits of BCG, up to 50% of patients with high-risk disease will experience treatment failure.[3] Furthermore, toxicity from BCG, including local side effects (cystitis, urgency/frequency, gross hematuria) and systemic side effects (malaise, fever), results in incomplete therapy or BCG intolerance; an estimated 30% to 60% of patients receive a full 3-year maintenance course of BCG.[4,5] These deficiencies have magnified the need for alternative therapies for high-risk NMIBC in patients who experience inadequate response to BCG.

Moreover, the global shortage of BCG has negatively affected the care of high-risk NMIBC. During the shortage, several alternative non-BCG treatments have been evaluated, including gemcitabine-based approaches such as gemcitabine with docetaxel in the BRIDGE trial (NCT05538663). In parallel, many efforts have been initiated to overcome the BCG shortage, including the construction of a new Merck manufacturing facility in Durham, North Carolina; the PRIME SWOG 1602 trial (NCT03091660) investigating the noninferiority of Tokyo-172 BCG strain compared with TICE BCG; and the recently announced US Food & Drug Administration Expanded Access Program for recombinant BCG as an alternative source of BCG. As there finally seems to be an end to the decade-long shortage and utilization of BCG increases, a unique opportunity arises to evaluate BCG combination therapy as a bladder-sparing approach.

In this review, we examine potential mechanisms of resistance to BCG to underscore the biological rationale for using BCG combination therapies. We then contextualize the historical landscape of agents aimed at enhancing the efficacy of BCG and minimizing toxicity as well as recent trials investigating chemotherapeutic and immunotherapeutic agents and their challenges (Table 1). Finally, we discuss ongoing trials and future directions for salvage treatment in NMIBC (Table 2).

## MATERIALS AND METHODS

A narrative review with systematic search components was performed of English-language MEDLINE indexed articles and abstracts of resistance mechanisms to BCG, as well as strategies to enhance the efficacy of BCG therapy in NMIBC. Studies were included if they were preclinical, observational studies, or human clinical trials (randomized or nonrandomized). A comprehensive search was performed from review inception on July 31, 2025. The search strategy combined Medical Subject Headings and free-text terms with Boolean operators, including "BCG," "NMIBC," "resistance," "tumor microenvironment," "immunotherapy," "immune checkpoint blockade," "chemotherapy," "mitomycin C," and "gemcitabine." Given the heterogenous nature of available data and ongoing clinical trials, a qualitative synthesis was performed, enabling a detailed review of the existing literature while highlighting key gaps that require further investigation.

## MECHANISMS OF RESISTANCE TO BCG

Mechanisms of resistance to BCG in NMIBC involve an interplay between the host, tumor-intrinsic factors, and the tumor microenvironment (TME). Of these, the TME has been most thoroughly studied and most likely to be modifiable (Figure). The pretreatment immunosuppressive TME affects response to BCG: an immunologically "cold" pretreatment TME is associated with poor response to BCG.[14] This finding is consistent with previous studies demonstrating that tumor-extrinsic factors within the pretreatment TME strongly influence response to BCG immunotherapy.[15-17] Specifically, an "inflamed," $CD4^+$ and $CD8^+$ effector T-cell-infiltrated TME is associated with improved response rates to BCG, whereas a "noninflamed" immunosuppressive TME, enriched with myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages, and T regulatory cells (Tregs), is associated with resistance to BCG.[16-20] In a prospective, longitudinal study of 28 patients assessing the immune cell composition of patients' urine during BCG treatment, a ratio $< 1$ of T cells to monocytic MDSCs in post-BCG urine samples was associated with significantly worse median recurrence-free survival.[16] Although promising, identifying biomarkers for BCG response that can be used clinically remains a challenge but are urgently needed to guide personalized decision making as more therapeutic options and combinations emerge.

Although serial instillations of BCG result in recruitment of antitumor innate immune cells and effector T-cell populations into the tumor, there is a parallel increase in the number of immunosuppressive cells (MDSCs and Tregs), which can offset antitumor effects.[16,18,19,21] Thus, the ratio of antitumor cytotoxic T cells vs protumor immunosuppressive cells in the TME, a major determinant of BCG response, is pre-established and cannot be overcome by BCG alone.[16,21] This supports the rationale for combining BCG with other therapies that can reduce immunosuppressive cell populations without reducing the number and/or activity of antitumor immune cells.

Downregulation of human leukocyte antigen class I (HLA-I) in urothelial tumor cells after BCG has also been implicated in BCG resistance and associated with poor prognosis. A 2022 study analyzing TME characteristics before and after BCG, using ex vivo freshly resected bladder tumors and in vitro bladder cancer cell lines, found that patients with HLA-I deficient urothelial cancer cells

**Table 1.** *Contemporary Results of Bacillus Calmette-Guérin Combination Trials*

| Study, year of publication | Phase | ClinicalTrials.gov ID | Study population | Treatment arms | Patients (n) | Key findings | Status |
|---|---|---|---|---|---|---|---|
| Alanee et al (2021)[6] | 1 | NCT02324582 | High-grade recurrent/persistent NMIBC after BCG or 2 induction courses of intravesical therapy | IV pembrolizumab + BCG | 13 | 69% no evidence of disease at 3 mo | Completed |
| Meghani et al (2022)[7] | 1 | NCT02808143 | BCG-unresponsive NMIBC | Intravesical pembrolizumab + BCG | 9 | 3-mo, 6-mo, and 1-y RFS were 100%, 67%, and 22%, respectively | Completed |
| Chamie et al (2023)[8] | 2/3 | NCT03022825 (QUILT) | Cohorts A and C: BCG-unresponsive CIS ± papillary disease<br>Cohort B: BCG-unresponsive high-grade papillary NMIBC | IL-15 superagonist NAI + BCG (cohorts A and B); intravesical NAI alone (cohort C) | 82 | Cohort A: 71% CRR; 3-, 6-, and 12-mo CRRs were 55%, 56%, and 45%, respectively (median duration of CR, 26.6 mo)<br>Cohort B: 55.4% DFS at 12 mo (median DFS, 19.3 mo)<br>Cohort C: 20% CRR at 3 mo, 10% at 6 mo. Cohort discontinued for futility | Ongoing |
| Hahn et al (2023)[9] | 1 | NCT02844816 (ADAPT-BLADDER) | BCG-unresponsive NMIBC | D + BCG vs D + EBRT vs D monotherapy | 28 | D + BCG: 3-mo and 12-mo CRR 85%, 73%<br>D + EBRT: 3-mo and 12-mo CRR 50%, 33%<br>D: 3-mo CRR 33% | Completed |
| Inman et al (2023)[10] | 1b/2 | NCT02792192 | BCG-unresponsive CIS ± papillary NMIBC | Atezolizumab + BCG (cohort 1B) vs atezolizumab monotherapy (cohort 1A) | 24 | Cohort 1A: 33% 6-mo CRR (median duration of CR, 6.8 mo)<br>Cohort 1B: 42% 6-mo CRR (median duration of CR not reached [≥12 mo]) | Completed |
| Wald et al (2024)[11] | 2 | NCT04179162 | BCG-exposed high-grade NMIBC | Gemcitabine + BCG | 43 | CRR 98% at 3 mo, 94% at 6 mo, and 81% at 12 mo<br>HG RFS 97% at 6 mo, 85% at 12 mo, 76% at 18 mo | Ongoing |
| Shore et al (2025)[5] | 3 | NCT04165317 (CREST) | High-risk BCG-naïve NMIBC | Sasanlimab + BCG induction/maintenance vs BCG induction/maintenance | 703 | Sasanlimab + BCG results in 32% increase in event-free survival probability (HR = 0.68, 95% CI: 0.49-0.94, $P = .019$)<br>Probability of being event-free at 36 mo: 82.1% (95% CI: 77.4-85.9) compared with 74.8% (95% CI: 69.7-79.2) | Completed |
| De Santis et al (2025)[12] | 3 | NCT03528694 (POTOMAC) | High-risk BCG-naïve NMIBC | D + BCG vs BCG | 678 | Recurrence of high-risk disease or death by any cause was 32% lower in D + BCG vs BCG (95% CI: 0.50-0.93)<br>24-mo DSS: 86.5% (95% CI: 82.2-89.8) vs 81.6% (95% CI: 76.9-85.3) | Completed |
| Roupret et al (2025)[13] | 3 | NCT03799835 (ALBAN) | High-risk BCG-naïve NMIBC | Atezolizumab + BCG vs BCG | 517 | No significant difference in EFS between both arms, HR 0.98 (95% CI: 0.71-1.36) | Completed |

Abbreviations: BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; CR, complete response; CRR, complete response rate; D, durvalumab; DFS, disease-free survival; DSS, disease-specific survival; EBRT, external beam radiation therapy; EFS, event-free survival; HG, high-grade; NAI, nogapendekin alfa inbakicept; NMIBC, nonmuscle-invasive bladder cancer; RFS, recurrence-free survival.

**Table 2.** *Anticipated Combination Chemoimmunotherapy Trials*

| Trial name or site (ClinicalTrials.gov ID) | Phase | Study population | Treatment arms | Primary end point | Expected enrollment |
|---|---|---|---|---|---|
| ANZUP 1301 (NCT02948543) | 3 | High-risk BCG-naïve NMIBC (high-grade Ta, T1, ± CIS; CIS alone excluded) | BCG + MMC vs BCG | RFS | 500 |
| SunRISe-3 (NCT05714202) | 3 | BCG-naïve high-risk NMIBC | Group A, TAR-200 + cetrelimab; group B, BCG alone; group C, TAR-200 alone | EFS | 1050 |
| MSK 17-602 (NCT03504163) | 1/2 | BCG-naïve "high-risk T1" NMIBC[a] | Pembrolizumab + BCG | CRR at 6 mo | 37 |
| GAIN (Alliance A032303) | 3 | BCG-exposed NMIBC | Gemcitabine + BCG vs BCG alone | High-grade RFS | 330 |
| KEYNOTE-676 (NCT03711032) | 3 | High-risk NMIBC following BCG induction or BCG naïve | Pembrolizumab + BCG vs BCG alone | CRR in patients with CIS | 1400 |
| NCI (NCT04164082) | 2 | BCG-unresponsive NMIBC | Intravesical gemcitabine + IV pembrolizumab | CRR at 6 mo; EFS at 18 mo | 161 |
| ADAPT-BLADDER (NCT03317158) | 1/2 | BCG-unresponsive NMIBC | Intravesical gemcitabine/docetaxel + IV durvalumab | CRR | 40 |
| PRIME S1602 (NCT03091660) | 3 | BCG-naïve high-risk NMIBC | Intravesical BCG TICE vs intravesical BCG Tokyo vs priming intradermal Tokyo BCG + intravesical Tokyo BCG | Time to high-grade recurrence | 1000 |

Abbreviations: ANZUP, Australia and New Zealand Urogenital Prostate Cancer Trials Group; BCG, bacillus Calmette-Guérin; CIS, carcinoma in situ; CRR, complete response rate; EFS, event-free survival; MMC, mitomycin C; MSK, Memorial Sloan Kettering Cancer Center; NCI, National Cancer Institute; NMIBC, nonmuscle-invasive bladder cancer; RFS, recurrence-free survival.

[a] High-risk T1 defined as having one of the following disease states: T1 on restaging biopsy, plus CIS; multiple T1 recurrences, plus CIS; T1b (extensive/deep invasion into lamina propria) plus CIS; lymphovascular invasion plus CIS; T1 with variant histology, plus CIS; T1 with urothelial carcinoma of prostatic urethra (Ta, Tis, or T1 within prostatic urethra), plus CIS; large (≥3 cm) T1 tumor, plus CIS.

after BCG had a myeloid suppressive TME with epithelial-mesenchymal transition characteristics and poor outcomes.[22] Conversely, HLA-I proficient urothelial cancer cells post-BCG had increased $CD8^+$ T-cell infiltrates, immune checkpoint-inhibitory molecules including the PD-L1 ligand, PD-1, and CTLA-4 receptors, and upregulation of inflammatory cytokines. Furthermore, HLA-I deficiency likely implies a lack of response to immune checkpoint inhibitors. Thus, HLA-I status may serve as a marker for prognostic and therapeutic response and merits further investigation.[22]

Finally, BCG resistance has been associated with a pretreatment adaptive immune response characterized by increased baseline PD-L1 expression and colocalization with $CD8^+$ T cells. A 2020 study of 63 pretreatment NMIBC specimens found pretreatment PD-L1 expression in 25% to 28% of non-responders to BCG and 0% to 4% of responders, suggesting that baseline PD-L1 expression may influence the adaptive immune response to BCG and predict for poor response.[18] However, the association between baseline PD-L1 expression and BCG outcomes is not straightforward. In another study evaluating the predictive ability of PD-L1 at transurethral resection for BCG-unresponsiveness, the absence of PD-L1 expression in treatment-naive patients was associated with higher rates of BCG-unresponsive disease (OR 7.14, 95% CI: 1.32-33.3).[23] Moreover, the accuracy of PD-L1 as a biomarker was poor, with an area under the receiver operative curve of 0.574, thereby limiting its prognostic value. While a prevailing theory is that PD-1/PD-L1 expression is a mechanism of resistance to BCG, conflicting data about the prognostic status of immune checkpoint genes may reflect tissue processing, variability of detection methods, or assessment of expression intensity. In addition, studies supporting PD-1/PD-L1 as a mechanism of resistance typically have not adjusted for clinicopathologic factors such as carcinoma in situ (CIS) that can also affect BCG response.

## IMMUNOTHERAPY COMBINATION STRATEGIES

### BCG + ICB

Over the past decade, immune checkpoint blockade (ICB) has revolutionized the treatment paradigm for metastatic urothelial carcinoma. Given its clinical efficacy in the second-line metastatic setting and now in combination with enfortumab vedotin as first-line therapy, there is increased interest in the use of ICB in NMIBC. Preclinical evidence suggests that patients who relapse after BCG treatment may be more susceptible to ICB.[24] Pembrolizumab, a PD-1 inhibitor, was therefore investigated as monotherapy in 2 cohorts in KEYNOTE-057, an open-label, single-arm, multicenter phase 2 study. In cohort A, patients with BCG-unresponsive CIS, with or without papillary disease, received IV pembrolizumab every 3 weeks for up to 24 months. After a median follow-up time of 36.4 months, 41% of patients (95% CI: 30.7-51.1) had a complete response (CR) at 3 months as assessed by cystoscopy and urinary cytology. The median duration of response (DOR) from initiation of pembrolizumab was 16.2 months (95% CI: 6.7-36.2) and 46% of

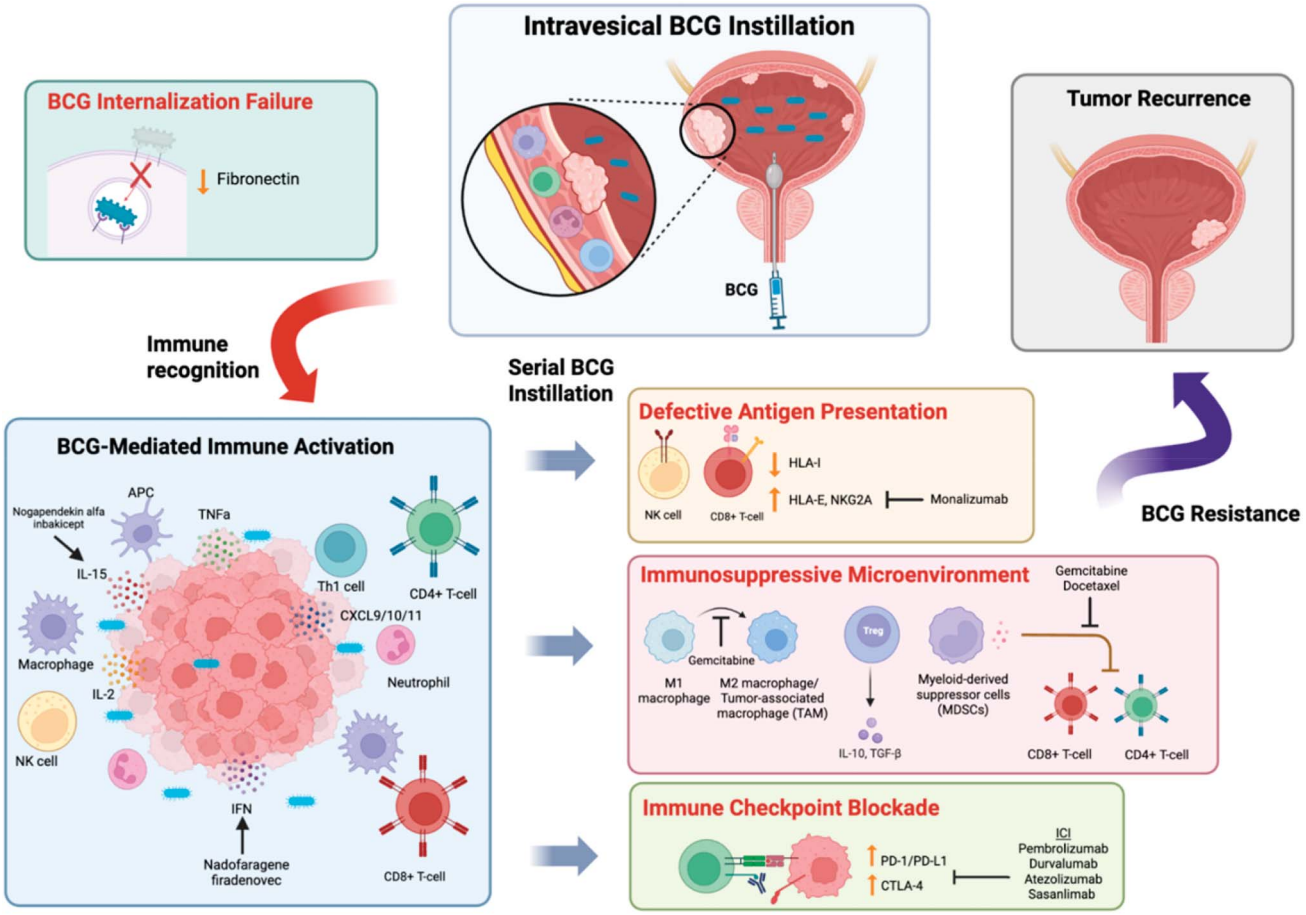


**Figure.** Mechanisms of resistance to bacillus Calmette-Guérin (BCG) therapy in nonmuscle-invasive bladder cancer. Intravesical BCG instillation elicits locally sustained immune-mediated antitumor response. However, BCG internalization failure and defective antigen presentation serve as potential resistance mechanisms, which can prevent durable responses. Moreover, while serial instillations of BCG result in recruitment of innate immune cells and effector T-cell populations, there is a parallel increase in the number of immunosuppressive cells (myeloid-derived suppressor cells and Tregs), which can offset any antitumor effects. Chemoimmunotherapy and immunotherapy-based combinations aim to reduce immunosuppressive cellular populations and immune checkpoint blockade. These combinations offer a biological rationale to overcome resistance to BCG therapy and represent novel bladder preservation strategies in high-risk nonmuscle-invasive bladder cancer.

responders remained in CR for at least 12 months. Grades 1 to 2 treatment-related adverse events (TRAE) occurred in 54% of patients, although 13% of patients experienced grade 3 to 4 complications.[25] Although the results of this trial are modest, the Food and Drug Administration–approved pembrolizumab in January 2020 for the treatment of BCG-unresponsive CIS in patients who are ineligible for, or decline, radical cystectomy. In cohort B, patients with papillary disease only (any grade T1 or high-grade Ta) received pembrolizumab for a maximum of 35 cycles with a median follow-up time of 45.4 months. The 12-month disease-free survival was 43.5% (95% CI: 34.9%-51.9%) with a 15% rate of serious TRAEs.[26] Importantly, PD-L1 expression did not predict response to pembrolizumab.

Other trials investigating the role of ICB in BCG-unresponsive disease demonstrate similar results. In a single-arm phase 2 trial, SWOG S1605 enrolled both BCG-unresponsive CIS (±Ta/T1) and Ta/T1 only patients to receive IV atezolizumab every 3 weeks for 1 year. CR at 3 and 6 months was achieved in 43% (95% CI: 32%-55%) and 27% (95% CI: 17%-38%) of patients, respectively; however, SWOGS1605 closed prematurely after failing to surpass the futility threshold.[27] Moreover, grades 3 to 5 TRAEs occurred in 16% of patients, including 3 (1.8%) treatment-related deaths (1.8%), highlighting the potential for significant systemic toxicity. Other clinical trials of ICB agents, such as camrelizumab (NCT04706598) and pucotenlimab (NCT04738630), are enrolling patients with BCG-unresponsive disease; however, the role of ICB monotherapy in NMIBC remains unclear.

Supported by preclinical data, combinations of ICB and BCG agents for NMIBC are currently being investigated as treatment options to overcome resistance patterns.[18,19,23] However, most studies

are in their preliminary phases and are single-arm designs with limited safety and efficacy results. In the BCG-unresponsive state, CR is variable with combination therapy. In a phase 1b/2 trial, atezolizumab with or without BCG was generally safe, with combination therapy favoring a longer DOR.[10] The ADAPT-BLADDER trial aimed to evaluate the safety and preliminary oncological efficacy of durvalumab combined with BCG or radiation in BCG-unresponsive patients. Compared with durvalumab monotherapy or durvalumab with radiation, durvalumab with BCG demonstrated the highest complete response rate (CRR) at 12 months, 73%, with lower rates of grade 3 or 4 toxicity, albeit not insignificant at 15%.[9] Changing the route of ICB delivery from systemic to intravesical has been hypothesized to reduce immune-related toxicities. Administration of intravesical pembrolizumab increased $CD8^+$ T cells and generated long-term immunity in an orthotopic mouse model of urothelial bladder cancer.[28] In the first in-human trial of intravesical ICB, BCG-unresponsive NMIBC patients received the combination of BCG and pembrolizumab but demonstrated a 22% recurrence-free survival (RFS) rate at 12 months.[7] Concerningly, the safety profile of intravesical ICB remains a critical question as 1 patient died from myasthenia gravis on this study. Despite the BCG-unresponsive designation within clinical trials, it is notable that combination with BCG tends to boost CRR and maintain durability of response. Although this observation reflects trials with small accrual sizes, these patients may still be able to generate a BCG-mediated antitumor immune response that synergizes with ICB or other immune-stimulating agents.

In the BCG-naïve NMIBC population, the results from the phase 3 CREST trial evaluating the role of sasanlimab, a subcutaneously administered PD-1 inhibitor, were recently reported. Patients were randomized to receive sasanlimab + BCG (induction + maintenance) (arm A), sasanlimab + BCG induction only (arm B), or BCG (induction + maintenance) alone (arm C). Although arm C demonstrated a 32% reduction in risk of disease-related events (HR 0.68, 95% CI: 0.49-0.94) compared with arm A, the absolute risk reduction was 7.3% at 3 years, driven primarily by a decrease in high grade noninvasive recurrences without improvement in rates of progression. Moreover, there was no difference in event-free survival between arm B compared with arm C, highlighting the need of maintenance BCG to evoke superior oncologic responses. Concerningly, grade $\geq$ 3 TRAEs occurred in 29.1% in arm A compared with 6.3% in arm C.[5] Two other phase 3 trials evaluated the addition of ICB to BCG. The POTOMAC trial met its primary end point, demonstrating a HR of 0.68 (95% CI: 0.50-0.93) for adding durvalumab to BCG (induction + maintenance)[12]; however, like CREST, the absolute improvement in disease-free survival (DFS) at 3 years was modest (4.4%). Interestingly, the ALBAN trial showed no significant benefit from adding atezolizumab to BCG (induction + maintenance).[13] Differences in trial design and definitions of treatment failure may have contributed to the discordant results. One notable distinction is that ALBAN excluded patients with prior BCG exposure, whereas CREST (>2 years since last BCG) and POTOMAC (>3 years since last BCG) included previously treated patients. Neither CREST nor POTOMAC has reported outcomes based on BCG-naïve vs BCG-experienced status. Such an analysis would be highly informative, as patients who recur after prior BCG monotherapy are potentially less likely to respond to BCG re-challenge alone and might derive greater benefit from the addition of ICB. This could explain the positive results seen in CREST and POTOMAC and warrants further investigation.

In both the CREST and POTOMAC trials, the patient subset which seem to benefit most for the addition of ICB to BCG are those with T1 disease. However, the patients at the highest risk for disease progression with BCG alone, those with HGT1 + CIS, appear to be underrepresented in these studies, accounting for 8% of patients in CREST. This explains the low progression rates seen in these trials and contributes to a lack of improvement in progression rates seen with the addition of ICB. Additional data for BCG + ICB is needed in patients with "very high-risk" T1 NMIBC where AUA and NCCN guidelines currently recommend immediate radical cystectomy over attempting BCG. To address this, our group is conducting a phase 2 single-arm trial of systemic pembrolizumab + BCG in patients with "very high-risk" T1 NMIBC, as defined by HGT1 + CIS plus at least 1 additional adverse feature (T1 on restaging biopsy, multiple recurrences, multifocality, $\geq$3 cm, T1b, lymphovascular invasion, variant histology, involvement of prostatic urethra) who are recommended for, but decline cystectomy (NCT03504163). As it is likely that ICB-associated toxicity is most justifiable in NMIBC patients with multiple high-risk features, data to support combination ICB + BCG as an alternative option to radical cystectomy is urgently needed.

### BCG + Cytokine Therapy

Interferon-alfa is a type-I IFN used for its antiviral properties and application in clinical oncology. Similar to BCG, interferon-alfa induces a nonspecific immune response, recruiting macrophages, $CD4^+$ T cells, and natural killer (NK) cells, and

the production of antitumor cytokines. In BCG-stimulated cells, interferon-alfa potentiates local cytotoxicity and antitumor activity.[29] The potential for synergistic activity of BCG + IFN in NMIBC provides the rationale for combination therapy in patients who do not respond to or tolerate standard-dose BCG therapy. The results from a nonrandomized multicenter phase 2 trial demonstrated that patients with prior BCG failure had a 2-year RFS rate of 45% after receiving reduced dose BCG + IFN.[30] However, in Cochrane pooled analyses comparing BCG + IFN vs BCG alone, there was no clear difference for recurrence (average risk ratio 0.76, 95% CI: 0.44-1.32) or for progression (average risk ratio 0.26, 95% CI: 0.04-1.87).[31] Given its comparable efficacy profile with BCG alone in patients with BCG failure, interferon-alfa has largely been abandoned in contemporary clinical practice.

However, cytokine therapy has again come to the forefront of NMIBC with the interleukin-15 superagonist nogapendekin alfa inbakicept (NAI). NAI is a fusion protein of a human IL-15 variant bound to dimeric human IL-15R$\alpha$ sushi domain/human IgG1 Fc. This immunostimulatory protein complex acts as a critical factor for the proliferation and activation of NK cells as well as memory and effector T cells; it is hypothesized that it may synergistically enhance BCG efficacy.[32,33] In an open-label, multicenter single-arm study, intravesical NAI + BCG was investigated in patients with BCG-unresponsive CIS ± papillary NMIBC.[8] A CR was achieved in 71% of patients, with a median DOR of 26.6 months. Of those with CR at 2 years, the estimated probability of cystectomy-free survival and of disease-specific survival (DSS) was 89.2% and 100%, respectively. By contrast, NAI monotherapy demonstrated a 20% CRR at 3 months and was discontinued for futility per protocol-defining stopping rules. In BCG-unresponsive papillary-only disease, NAI + BCG demonstrated a DFS of 55.4% at 12 months with a median DFS of 19.3 months. Most TRAEs were limited to grades 1 to 2 lower urinary tract symptoms. These results subsequently led to the 2024 Food and Drug Administration approval of NAI + BCG for BCG-unresponsive CIS ± papillary NMIBC. Moreover, in the BCG-naïve space, there is an ongoing phase 2b trial (QUILT 2.005) of NAI + BCG vs BCG, with a coprimary end point of 12-month CRR and 24-month DFS.

### BCG Priming Strategies

In recent years, the concept of BCG priming has re-emerged as a potential strategy to boost responses to BCG immunotherapy. Although it remains unsettled whether it is a tumor-specific T-cell response driving BCG outcomes, BCG priming is predicated on the hypothesis that prior BCG exposure (often through intradermal inoculation) can potentiate a BCG-antigen specific immune response to intravesical BCG.[34] This has been demonstrated in an orthotopic mouse model with improved antitumor response via T-cell infiltration into the bladder.[35]

Furthermore, NMIBC patients receiving a PPD (purified protein derivative) skin test before BCG treatment were found to have better 5-year RFS (66.6% vs 59.1%; $P = .048$) compared with those who did not receive PPD, although potentially with more BCG-related complications (24.1% vs 15.2%; $P = .02$).[35,36] The clinical role of "BCG priming," along with the comparison of different BCG strains, is now being tested with the SWOG PRIME trial (S1602), a 3-arm phase 3 randomized trial evaluating (1) intradermal BCG (Tokyo strain) 3 weeks before intravesical BCG (Tokyo strain), (2) intravesical only BCG (Tokyo strain), and (3) intravesical BCG TICE. Whether intradermal priming boosts sustained immune and clinical responses to intravesical BCG will provide critical insight into mechanisms behind response and failure to therapy.

## CHEMOTHERAPY COMBINATION STRATEGIES

An alternative promising treatment paradigm for NMIBC is chemoimmunotherapy. In meta-analyses comparing BCG and chemotherapy to BCG monotherapy, patients receiving combination therapy demonstrate improved RFS and DSS.[37] Furthermore, alternating chemotherapy with BCG may improve compliance by reducing toxicity levels without sacrificing treatment efficacy. Although poorly understood, it is hypothesized that the immunological response of BCG is potentiated by chemical disruption of the urothelium to promote BCG uptake, activation of immune effector cells, and the antitumor mechanism of chemotherapy. In a corollary fashion to other systemic forms of anticancer treatments, the rationale for combining intravesical therapies is based on reducing the emergence of tumor-resistant clones and improving clinical efficacy.

### Mitomycin C + BCG

Combination therapy with intravesical instillation of BCG and mitomycin C (MMC) has been investigated across multiple randomized controlled trials.[37] In pooled analyses, compared with BCG alone, combination therapy significantly improved RFS (HR 0.53, 95% CI: 0.43-0.66, $P < .01$), irrespective of treatment duration as well as in patients with and without CIS. Combination therapy also conferred longer DSS than BCG alone (HR 0.48, 95% CI: 0.29-0.80, $P = .005$) and improved overall survival (HR 0.66, 95% CI: 0.50-0.86, $P = .002$) without

**Table 3.** *Estimated 12-Month Pharmaceutical Costs of Contemporary Combination Regimens*

| Regimen | 12-mo treatment schedule | Cost of BCG at 12 mo ($) | Cost of combination therapy at 12 mo ($) | Combined cost at 12 mo[a] ($) | ≥Grade 3 TRAE (%) |
|---|---|---|---|---|---|
| BCG monotherapy | Induction + maintenance at 3, 6 mo | 1883 | — | 1883 | 6.3[5] |
| Intravesical gemcitabine + BCG | Gemcitabine 2000 mg twice weekly 1, 4, 7, 10 + BCG 50 mg 2, 3, 5, 6, 8, 9 wk + 3, 6 mo maintenance | 1883 | 692 | 2575 | 4.7[11] |
| Intravesical mitomycin + BCG (ANZUP 1301 protocol) | BCG (given wk 1, 2, 4, 5, 7, 8, and mo 4, 5, 7) plus 40 mg intravesical mitomycin (administered wk 3, 6, and 9, and mo 3, 6, and 9) | 1413 | 1843 | 3256 | 17.3[40] |
| IV durvalumab + BCG | Durvalumab 1500 mg every 4 wk for 1 y + BCG induction + maintenance with 3 weekly doses at 3, 6 mo | 1883 | 163,800 | 165,683 | 21.1[12] |
| IV atezolizumab + BCG | 1200 mg IV q3w + BCG induction + maintenance at 3 and 6 mo | 1883 | 182,364 | 184,247 | 22.7[13] |
| IV pembrolizumab + BCG | 200 mg pembrolizumab every 3 wk for 6 doses, with concurrent 6 weekly doses of BCG beginning at week 7 | 1883 | 201,787 | 203,670 | 31[6] |
| SubQ sasanlimab + BCG | Subcutaneous sasanlimab (300 mg) every 4 wk, with BCG induction + maintenance at 3 and 6 mo | 1883 | —[b] | —[b] | 29.1[5] |
| Intravesical pembrolizumab + BCG | 1-2 mg/kg intravesical pembrolizumab (2 wk prior to BCG induction), BCG (wk 0-5), and intravesical pembrolizumab (wk 0, 2, and 4), then intravesical pembrolizumab maintenance every 2 wk until wk 17, then every 4 wk until 1 y | 942 | 225,526 | 226,468 | 11.1[7] |
| IL-15 superagonist NAI + BCG | BCG plus NAI weekly for 6 consecutive wk + 3-wk maintenance course at mo 3, 6, 9 | 2354 | 567,486 | 569,840 | 21.1[8,c] |

Abbreviations: ANZUP, Australia and New Zealand Urogenital Prostate Cancer Trials Group; BCG, bacillus Calmette-Guérin; NAI, nogapendekin alfa inbakicept; q3w, every 3 weeks; SubQ, subcutaneous; TRAE, treatment-related adverse event.
Pricing of BCG and combination therapies sourced from Medicare Part B Average Sales Price.[50]
[a] Treatment cost does not include cost of immune-related adverse events.
[b] Sasanlimab pricing unavailable.
[c] This was a treatment-emergent adverse event rather than a TRAE.

significant heterogeneity in the analyzed studies. However, there was no difference in progression-free survival between combination therapy and BCG (HR 0.65, 95% CI: 0.25-1.68, $P = .38$). Despite the addition of an alkylating agent, combination chemoimmunotherapy was associated with a decreased rate of fevers, irritative lower urinary tract symptoms and hematuria without a difference in gastrointestinal symptoms.[37]

To improve the efficiency of uptake into the urothelium, studies have further examined electromotive drug administration (EMDA) of MMC. EMDA applies an electrical current to the bladder wall and improves drug absorption via iontophoresis, electrophoresis and electroporation. When compared with passive diffusion, EMDA is associated with 4 to 7 times greater increase in tissue uptake of MMC, with improved clinical response in high-risk NMIBC.[38] When comparing sequential BCG and electromotive mitomycin vs BCG alone in treatment-naïve high-grade patients, patients assigned combination therapy had improved DFS and lower rates of recurrence, progression, and overall mortality.[39] Despite promising results, adoption and implementation of EMDA-MMC is not widespread, likely due to a lack of prospective data and challenges with delivery. Contemporary efforts are now underway to evaluate the oncological outcomes of adding intravesical chemotherapy to BCG as adjuvant therapy. ANZUP 1301 is an open-label phase 3 trial that randomized 500 high-risk BCG-naïve NMIBC patients (high-grade Ta, T1, ±CIS; CIS alone excluded) in a 1:1 fashion to receive standard BCG therapy vs BCG + MMC. The 2 treatment arms use the same regimen of chemoimmunotherapy regimen as in Di Stasi's trial, with the exception of electromotive delivery of MMC.[39] Analyses of all oncological end points (2-year DFS, 3-month CR, time-to-recurrence, time-to-progression, and overall survival) demonstrated similar efficacy in both treatment arms.[40] However, subgroup analysis for DFS suggests a potential role for BCG + MMC in patients with higher risk (T1 and/or any CIS) NMIBC (HR 0.69, 95% CI: 0.48-0.99, $P = .043$). ANZUP 1301 also demonstrated that BCG + MMC regimen can reduce the number of vials of BCG without a detrimental effect on oncologic outcomes; however, with the BCG shortage likely being resolved soon, it is unclear if this is beneficial. Future efforts need to focus on combination strategies that provide improvements in oncologic outcomes without substantially increasing toxicity and costs.

## Gemcitabine + BCG

Although MMC historically has been the intravesical chemotherapy of choice for NMIBC, it is a known vesicant associated with substantial irritative voiding symptoms. By contrast, gemcitabine is selectively cytotoxic to bladder cancer cells yet may reduce urinary symptoms. In a randomized trial for recurrent NMIBC after prior BCG, intravesical gemcitabine had better efficacy (18-month RFS ~58% vs ~38%, $P = .049$) and half the urinary and overall toxicity compared with

MMC.[41] As described above, an increase in protumorigenic, immunosuppressive cells such as MDSCs, tumor-associated macrophages, and Tregs within the TME is a common mechanism of BCG immunotherapy resistance.[15-17] Gemcitabine has been shown to reduce the level of Tregs and MDSCs within the TME without significant reductions in $CD4^+$/$CD8^+$ T cells, NK cells, or B cells.[42,43] These effects are particularly compelling for combination with BCG, as the ratio of effector cytotoxic immune cells to immunosuppressive cells in the pretreatment TME is a potential determinant of BCG response.[16,17] Gemcitabine also increases the antitumor activity of $CD8^+$ T cells and activated NK cells, which results in increased expression of interferon (IFN)-$\gamma$[44] and HLA-I,[45] and enhanced cytotoxicity of $\gamma\delta$ T cells against urothelial cells in vitro and in vivo,[46] all of which are critical for BCG efficacy. Furthermore, gemcitabine may lead to immunogenic cell death, resulting in release of immunostimulatory damage-associated molecular patterns and presentation of tumor neoantigens that may enhance response to BCG immunotherapy.[47] There is also a substantial body of evidence suggesting that gemcitabine may yield synergistic antitumor effects if combined with BCG, and preclinical studies in mice demonstrate that combination gemcitabine and BCG is more effective than either agent alone.[48]

Despite being better tolerated, more effective, and less expensive than MMC (Table 3), no previous studies have combined intravesical gemcitabine with BCG until recent efforts. In a phase 1 trial (NCT04179162) of intravesical gemcitabine and BCG (GemBCG) for patients with BCG-exposed high-grade NMIBC, a total of 25 patients (Ta/T1 $\pm$ CIS) that recurred within 24 months of BCG therapy were enrolled with at least 12-month follow-up. CR at 6 and 12 months were 96% and 92%, respectively, without progression to muscle-invasive bladder cancer or radical cystectomy.[49] GemBCG was well tolerated, without dose-limiting toxicity, and with no patients experiencing grades 3 to 5 TRAEs. Moreover, GemBCG was found to favorably modulate the immune system based on changes in urinary cytokines. The phase 2 trial finished accrual in October 2024 and preliminary results demonstrated a CRR of 94% and 81% at 6 and 12 months, respectively.[11] Based on these promising results, there is now an ongoing randomized phase 3 study comparing GemBCG against the current standard of care, retreatment with BCG, in patients with BCG-exposed NMIBC (NCT07000084). This trial is open nationally through the National Clinical Trial Network and will be enrolling patients through 2028.

## CONCLUSIONS

Over the past 2 decades, the armamentarium for bladder-sparing treatment options has expanded in NMIBC. Many ongoing clinical trials attempt to overcome resistance to BCG yet are hampered by limited durability of response. Recently, advances in the understanding of the molecular biology of mechanisms of resistance to BCG demonstrate the importance of combination therapy. Chemoimmunotherapy represents an opportunity to enhance the effectiveness of BCG and induce long-lasting effects. However, extensive limitations pertain to previous study design as combinations are endless, and most trials are early phase and single arm without a comparator group. In addition, challenges for widespread adoption of chemoimmunotherapy include overlapping mechanisms of resistance in combination therapy, adverse events associated with systemic therapy, and financial toxicity. Innovative cost-effective approaches with favorable risk-to-benefit ratio are thus critical in NMIBC. Development of predictive biomarkers from translational correlative studies is integral to understand how to select patients for combination treatment approaches and how to potentially sequence therapies.

## REFERENCES


1. Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin.* 2025;75(1):10-45. doi:10.3322/caac.21871
2. Chou R, Selph S, Buckley DI, et al. Intravesical therapy for the treatment of nonmuscle invasive bladder cancer: a systematic review and meta-analysis. *J Urol.* 2017;197(5):1189-1199. doi:10.1016/j.juro.2016.12.090
3. Packiam VT, Johnson SC, Steinberg GD. Non-muscle-invasive bladder cancer: intravesical treatments beyond bacille Calmette-Guérin. *Cancer.* 2017;123(3):390-400. doi:10.1002/cncr.30392
4. Brausi M, Oddens J, Sylvester R, et al. Side effects of bacillus Calmette-Guérin (BCG) in the treatment of intermediate- and high-risk Ta, T1 papillary carcinoma of the bladder: results of the EORTC genito-urinary cancers group randomised phase 3 study comparing one-third dose with full dose and 1 year with 3 years of maintenance BCG. *Eur Urol.* 2014;65:69-76. doi:10.1016/j.eururo.2013.07.021
5. Shore ND, Powles TB, Bedke J, et al. Sasanlimab plus BCG in BCG-naive, high-risk non-muscle invasive bladder cancer: the randomized phase 3 CREST trial. *Nat Med.* 2025;31(8):2806-2814. doi:10.1038/s41591-025-03738-z
6. Alanee S, Sana S, El-Zawahry A, et al. Phase I trial of intravesical bacillus Calmette-Guérin combined with intravenous pembrolizumab in recurrent or persistent high-grade non-muscle-invasive bladder cancer after previous bacillus Calmette-Guérin treatment. *World J Urol.* 2021;39(10):3807-3813. doi:10.1007/s00345-021-03716-3
7. Meghani K, Cooley LF, Choy B, et al. First-in-human intravesical delivery of pembrolizumab identifies immune activation in bladder cancer unresponsive to bacillus Calmette-Guérin. *Eur Urol.* 2022;82(6):602-610. doi:10.1016/j.eururo.2022.08.004
8 Chamie K, Chang SS, Kramolowsky E, et al. IL-15 superagonist NAI in BCG-unresponsive non-muscle-invasive bladder cancer. *NEJM Evid.* 2023;2(1):EVIDoa2200167. doi:10.1056/EVIDoa2200167
9. Hahn NM, O'Donnell MA, Efstathiou JA, et al. A phase 1 trial of durvalumab in combination with bacillus Calmette-Guerin (BCG) or external beam radiation therapy in patients with BCG-unresponsive

non-muscle-invasive bladder cancer: the Hoosier Cancer Research Network GU16-243 ADAPT-BLADDER study. *Eur Urol.* 2023;83(6):486-494. doi:10.1016/j.eururo.2023.01.017

10. Inman BA, Hahn NM, Stratton K, et al. A phase 1b/2 study of atezolizumab with or without bacille Calmette-Guérin in patients with high-risk non-muscle-invasive bladder cancer. *Eur Urol Oncol.* 2023;6(3):313-320. doi:10.1016/j.euo.2023.01.013

11. Wald G, Gaffney C, Alam SM, et al. Initial results of a multicenter phase II trial of intravesical gemcitabine and BCG for patients with BCG-exposed non-muscle invasive bladder cancer (NCT04179162). Abstract presented at: 25th Annual Meeting of the Society of Urologic Oncology; December 4-6, 2024; Dallas, Texas.

12. De Santis M, Palou Redorta J, Nishiyama H, et al; POTOMAC Investigators. Durvalumab in combination with BCG for BCG-naive, high-risk, non-muscle-invasive bladder cancer (POTOMAC): final analysis of a randomised, open-label, phase 3 trial. *Lancet.* 2025;406(10516):2221-2234. doi:10.1016/S0140-6736(25)01897-5

13. Roupret M, Bertaut A, Pignot G, et al. Alban (GETUG-AFU 37): a phase 3, randomized, open-label, international trial of intravenous atezolizumab and intravesical bacillus Calmette-Guérin (BCG) versus BCG alone in BCG-naive high-risk, non-muscle invasive bladder cancer (NMIBC). *Ann Oncol.* Published online October 17, 2025. doi:10.1016/j.annonc.2025.09.017

14. Damrauer JS, Roell KR, Smith MA, et al. Identification of a novel inflamed tumor microenvironment signature as a predictive biomarker of bacillus Calmette-Guérin immunotherapy in non-muscle-invasive bladder cancer. *Clin Cancer Res.* 2021;27(16):4599-4609. doi:10.1158/1078-0432.CCR-21-0205

15. Spranger S. Mechanisms of tumor escape in the context of the T-cell-inflamed and the non-T-cell-inflamed tumor microenvironment. *Int Immunol.* 2016;28(8):383-391. doi:10.1093/intimm/dxw014

16. Chevalier MF, Trabanelli S, Racle J, et al. ILC2-modulated T cell-to-MDSC balance is associated with bladder cancer recurrence. *J Clin Invest.* 2017;127(8):2916-2929. doi:10.1172/JCI89717

17. Takayama H, Nishimura K, Tsujimura A, et al. Increased infiltration of tumor associated macrophages is associated with poor prognosis of bladder carcinoma in situ after intravesical bacillus Calmette-Guerin instillation. *J Urol.* 2009;181(4):1894-1900. doi:10.1016/j.juro.2008.11.090

18. Kates M, Matoso A, Choi W, et al. Adaptive immune resistance to intravesical BCG in non-muscle invasive bladder cancer: implications for prospective BCG-unresponsive trials. *Clin Cancer Res.* 2020;26(4):882-891. doi:10.1158/1078-0432.CCR-19-1920

19. Inman BA, Sebo TJ, Frigola X, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer.* 2007;109(8):1499-1505. doi:10.1002/cncr.22588

20. Kates M, Nirschl T, Sopko NA, et al. Intravesical BCG induces $CD4^+$ T-cell expansion in an immune competent model of bladder cancer. *Cancer Immunol Res.* 2017;5(7):594-603. doi:10.1158/2326-6066.CIR-16-0267

21. Chevalier MF, Schneider AK, Cesson V, et al. Conventional and PD-L1-expressing regulatory T cells are enriched during BCG therapy and may limit its efficacy. *Eur Urol.* 2018;74(5):540-544. doi:10.1016/j.eururo.2018.06.045

22. Rouanne M, Adam J, Radulescu C, et al. BCG therapy downregulates HLA-I on malignant cells to subvert antitumor immune responses in bladder cancer. *J Clin Invest.* 2022;132(12):e145666. doi:10.1172/JCI145666

23. Gerald T, Woldu SL, Halstuch D, et al. Impact of baseline PD-L1 status in BCG naive nonmuscle invasive bladder cancer on outcomes and changes after BCG exposure. *Urol Oncol.* 2025;43(6):391.e1-391.e10. doi:10.1016/j.urolonc.2025.01.015

24. Copland A, Sparrow A, Hart P, et al. Bacillus Calmette-Guérin induces PD-L1 expression on antigen-presenting cells via autocrine and paracrine interleukin-STAT3 circuits. *Sci Rep.* 2019;9(1):3655. doi:10.1038/s41598-019-40145-0

25. Balar AV, Kamat AM, Kulkarni GS, et al. Pembrolizumab 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. *Lancet Oncol.* 2021;22(7):919-930. doi:10.1016/S1470-2045(21)00147-9

26. Necchi A, Roumiguié M, Kamat AM, et al. Pembrolizumab 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. *Lancet Oncol.* 2024;25(6):720-730. doi:10.1016/S1470-2045(24)00178-5

27. Black PC, Tangen CM, Singh P, et al. Phase 2 trial of atezolizumab in bacillus Calmette-Guérin-unresponsive high-risk non-muscle-invasive bladder cancer: SWOG S1605. *Eur Urol.* 2023;84(6):536-544. doi:10.1016/j.eururo.2023.08.004

28. Kirschner AN, Wang J, Rajkumar-Calkins A, Neuzil KE, Chang SS. Intravesical anti-PD-1 immune checkpoint inhibition treats urothelial bladder cancer in a mouse model. *J Urol.* 2021;205(5):1336-1343. doi:10.1097/JU.0000000000001576

29. Zhang Y, Khoo HE, Esuvaranathan K. Effects of bacillus Calmette-Guérin and interferon alpha-2B on cytokine production in human bladder cancer cell lines. *J Urol.* 1999;161(3):977-983. doi:10.1016/s0022-5347(01)61832-9

30. Joudi FN, Smith BJ, O'Donnell MA; National BCG-Interferon Phase 2 Investigator Group. Final results from a national multicenter phase II trial of combination bacillus Calmette-Guérin plus interferon alpha-2B for reducing recurrence of superficial bladder cancer. *Urol Oncol.* 2006;24(4):344-348. doi:10.1016/j.urolonc.2005.11.026

31. Shepherd AR, Shepherd E, Brook NR. Intravesical bacillus Calmette-Guérin with interferon-alpha versus intravesical bacillus Calmette-Guérin for treating non-muscle-invasive bladder cancer. *Cochrane Database Syst Rev.* 2017;3:CD012112. doi:10.1002/14651858.CD012112.pub2

32. Li Z, Wrangle J, He K, Sprent J, Rubinstein MP. IL-15: from discovery to FDA approval. *J Hematol Oncol.* 2025;18(1):19. doi:10.1186/s13045-025-01664-8

33. van Puffelen JH, Keating ST, Oosterwijk E, et al. Trained immunity as a molecular mechanism for BCG immunotherapy in bladder cancer. *Nat Rev Urol.* 2020;17(9):513-525. doi:10.1038/s41585-020-0346-4

34. Antonelli AC, Binyamin A, Hohl TM, Glickman MS, Redelman-Sidi G. Bacterial immunotherapy for cancer induces CD4-dependent tumor-specific immunity through tumor-intrinsic interferon-$\gamma$ signaling. *Proc Natl Acad Sci USA.* 2020;117(31):18627-18637. doi:10.1073/pnas.2004421117

35. Biot C, Rentsch CA, Gsponer JR, et al. Preexisting BCG-specific T cells improve intravesical immunotherapy for bladder cancer. *Sci Transl Med.* 2012;4(137):137ra72. doi:10.1126/scitranslmed.3003586

36. Niwa N, Kikuchi E, Matsumoto K, Kosaka T, Mizuno R, Oya M. Purified protein derivative skin test prior to bacillus Calmette-Guérin therapy may have therapeutic impact in patients with nonmuscle invasive bladder cancer. *J Urol.* 2018;199(6):1446-1451. doi:10.1016/j.juro.2017.12.057

37. Huang D, Jin YH, Weng H, Huang Q, Zeng XT, Wang XH. Combination of intravesical bacille Calmette-Guérin and chemotherapy vs. bacille Calmette-Guérin alone in non-muscle invasive bladder cancer: a meta-analysis. *Front Oncol.* 2019;9:121. doi:10.3389/fonc.2019.00121

38. Di Stasi SM, Giannantoni A, Stephen RL, et al. Intravesical electromotive mitomycin C versus passive transport mitomycin C for high risk superficial bladder cancer: a prospective randomized study. *J Urol.* 2003;170(3):777-782. doi:10.1097/01.ju.0000080568.91703.18

39. Di Stasi SM, Giannantoni A, Giurioli A, et al. Sequential BCG and electromotive mitomycin versus BCG alone for high-risk superficial bladder cancer: a randomised controlled trial. *Lancet Oncol.* 2006;7(1):43-51. doi:10.1016/S1470-2045(05)70472-1

40. Hayne D, Zhang AY, Thomas H, et al. Mitomycin plus BCG as adjuvant intravesical therapy for high-risk, non-muscle-invasive bladder cancer: a randomized phase 3 trial (ANZUP 1301). *J Clin Oncol.* 2025;43(17_suppl I). doi:10.1200/jco.2025.43.17_suppl.lba4504

41. Addeo R, Caraglia M, Bellini S, et al. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer: evaluation of efficacy and tolerance. *J Clin Oncol.* 2010;28(4):543-548. doi:10.1200/JCO.2008.20.8199

42. Nowak AK, Robinson BWS, Lake RA. Gemcitabine exerts a selective effect on the humoral immune response: implications for combination chemo-

immunotherapy. *Cancer Res.* 2002;62(8):2353-2358.

43. Gujar SA, Clements D, Dielschneider R, Helson E, Marcato P, Lee PWK. Gemcitabine enhances the efficacy of reovirus-based oncotherapy through anti-tumour immunological mechanisms. *Br J Cancer.* 2014;110(1):83-93. doi:10.1038/bjc.2013.695

44. Le HK, Graham L, Cha E, Morales JK, Manjili MH, Bear HD. Gemcitabine directly inhibits myeloid derived suppressor cells in BALB/c mice bearing 4T1 mammary carcinoma and augments expansion of T cells from tumor-bearing mice. *Int Immunopharmacol.* 2009;9(7-8):900-909. doi:10.1016/j.intimp.2009.03.015

45. Liu WM, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. *Br J Cancer.* 2010;102(1):115-123. doi:10.1038/sj.bjc.6605465

46. Shimizu T, Tomogane M, Miyashita M, Ukimura O, Ashihara E. Low dose gemcitabine increases the cytotoxicity of human Vγ9Vδ2 T cells in bladder cancer cells in vitro and in an orthotopic xenograft model. *Oncoimmunology.* 2018;7(5):e1424671. doi:10.1080/2162402X.2018.1424671

47. Hayashi K, Nikolos F, Lee YC, et al. Tipping the immunostimulatory and inhibitory DAMP balance to harness immunogenic cell death. *Nat Commun.* 2020;11(1):6299. doi:10.1038/s41467-020-19970-9

48. Horinaga M, Fukuyama R, Iida M, et al. Enhanced antitumor effect of coincident intravesical gemcitabine plus BCG therapy in an orthotopic bladder cancer model. *Urology.* 2010;76(5):1267.e1-1267.e6. doi:10.1016/j.urology.2010.03.028

49. Alam SM, Gaffney CD, Lavery J, et al. Abstract PR005: Final results from a phase I trial of intravesical chemoimmunotherapy with gemcitabine and bacillus Calmette-Guérin (BCG) for patients with BCG-exposed high-grade non-muscle invasive bladder cancer. *Clin Cancer Res.* 2024;30(10_suppl):PR005. doi:10.1158/1557-3265.bladder24-pr005

50. Centers for Medicare & Medicaid Services. *Medicare Part B Drug Average Sales Price.* Accessed June 22, 2025. https://www.cms.gov/medicare/payment/fee-for-service-providers/part-b-drugs/average-drug-sales-price

## EDITORIAL COMMENTS

I once heard an early mentor James McKiernan argue that medical oncologists learned more than 30 years ago that combination chemotherapy outperforms single-agent therapy. Yet in urology, we still administer single-agent intravesical chemotherapy for NMIBC and expect comparable results. Through the early leadership of McKiernan and Mike O'Donnell at the University of Iowa, urologists gradually began testing and evaluating rational combinations in NMIBC.

Any combination regimen must, by definition, improve on each component alone—and must do so without imposing significant additional toxicity. These 2 principles, although intuitive, are seldom rigorously tested. GemDoce provides a clear example: no prospective trial has evaluated gemcitabine vs docetaxel vs GemDoce head-to-head in high-risk NMIBC. This absence of randomized data is not specific to GemDoce; no intravesical combination in our field has been studied this way, largely due to feasibility barriers related to cost, trial size, and accrual. We are therefore left with assumptions and untested hypotheses about the additive value of combination regimens.

A second consideration is overtreatment. Wald et al[1] highlight this tension by focusing on BCG-naïve disease and the recent wave of combination IO–BCG trials. POTOMAC and CREST achieved their event-free survival primary end points, whereas ALBAN did not.[2-4] Even if one considers the 7.3% absolute risk reduction at 3 years (largely driven by decreases in high-grade noninvasive recurrences without reductions in progression) clinically meaningful, it remains true that many patients may be unnecessarily exposed to immune-related toxicity. In CREST, 15.7% of patients experienced grade $\geq$ 3 autoimmune adverse events, and 19.7% required corticosteroids, underscoring the real risks associated with systemic immunotherapy layered onto intravesical therapy.

Ultimately, combination therapy should be viewed as a promising strategy—but only when chosen wisely. Urologists must balance incremental oncologic benefit against the meaningful toxicity and potential overtreatment that some combinations introduce.

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## REFERENCES

1. Wald G, Lang J, Alkazemi H, et al. Combination strategies to enhance bacillus Calmette-Guérin efficacy nonmuscle-invasive bladder cancer. *J Urol.* 2026;215(3):264-275. doi:10.1097/JU.0000000000004848

2. De Santis M, Palou Redorta J, Nishiyama H, et al; POTOMAC Investigators. Durvalumab in combination with BCG for BCG–naïve, high-risk, non–muscle-invasive bladder cancer (POTOMAC): final analysis of a randomised, open-label, phase 3 trial. *Lancet.* 2025;406(10516):2221-2234. doi:10.1016/S0140-6736(25)01897-5

3. Shore ND, Powles TB, Bedke J, et al; for the CREST Investigators. Sasanlimab plus BCG in BCG-naïve, high-risk non-muscle-invasive bladder cancer: the randomized phase 3 CREST trial. *Nat Med.* 2025;31(8):2806-2814. doi:10.1038/s41591-025-03738-z

4. Roupret M, Bertaut A, Pignot G, et al. ALBAN (GETUG-AFU 37): a phase 3 randomized open-label trial of atezolizumab plus BCG vs BCG alone in BCG-naïve high-risk NMIBC. *Ann Oncol.* 2025;36(5):507-517. doi:10.1016/j.annonc.2025.04.087

High-risk, NMIBC remains an area of active investigation, increasing interest, and needed scrutiny. Guidelines recommend Bacillus Calmette-Guerin (BCG) intravesical therapy as the standard of care to reduce recurrence and progression rates.[1] However, BCG may not be effective in 20% to 40% of these patients, and up to 20% may discontinue due to intolerance.[2] These limitations, in addition to an inconsistent BCG supply, have driven efforts to develop novel agents and combination therapies for patients with BCG-unresponsive or intolerant disease.

Wald et al[3] present a narrative review synthesizing the proposed mechanism of BCG, resistance based on the tumor microenvironment (TME) and emerging treatment strategies. Studies indicate a "noninflamed" immunosuppressive TME, the ratio of antitumor cytotoxic T cells vs protumor suppressive T cells, and downregulation of human leukocyte antigen class I in the development of inadequate BCG response. This suggests that effectiveness may be biologically predetermined and enhanced through combinatorial approaches.

Recent studies have evaluated the combination of BCG and immune checkpoint blockade, delivered intravesical or systemically, and have demonstrated improved complete response, recurrence-free, and event-free survival, although benefits may decrease overtime. Furthermore, treatment-related adverse effects remain a concern. Cytokine therapy, such as BCG and interleukin-15 superagonist, demonstrated a complete response of 71% in BCG-unresponsive carcinoma in situ with or without papillary disease. This finding underscores the importance of potentiating the antitumor effect in the TME. Similarly, a combination chemoimmunotherapy strategy, for example Gemcitabine with BCG, may prove a promising alternative to BCG alone with increased antitumor effects.

As the therapeutic options expand for NMIBC, ongoing clinical trials to evaluate the long-term durability and cost-effectiveness are essential. Understanding the mechanism of BCG failure is a promising step toward personalized approaches that will need to investigate tumor risk, therapeutic efficacy and safety, as well as social and financial cost.

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## REFERENCES

1. Holzbeierlein JM, Bixler BR, Buckley DI, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline: 2024 amendment. *J Urol.* 2024;211(4):533-538. doi:10.1097/JU.0000000000003846
2. Witjes JA. Management of BCG failures in superficial bladder cancer: a review. *Eur Urol.* 2006;49(5):790-797. doi:10.1016/j.eururo.2006.01.017
3. Wald G, Lang J, Alkazemi H, et al. Combination strategies to enhance bacillus Calmette-Guérin efficacy for nonmuscle-invasive bladder cancer. *J Urol.* 2026;215(3):264-275. doi:10.1097/JU.0000000000004848