

Advancing Care in Non-Muscle-Invasive Bladder Cancer

FACULTY

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GOAL

The goal of this program is to improve clinical decision-making and patient-centered care in non-muscle-invasive bladder cancer (NMIBC) by educating health care professionals (HCPs) on the role of novel intravesical gene therapies, evidence-based treatment pathways, and multidisciplinary strategies in addressing the needs of patients with BCG-unresponsive disease.

INTENDED AUDIENCE

This educational initiative is designed for US-based urologists, oncologists, hospital pharmacists, Veterans Health Administration pharmacists, and other HCPs involved in the care of patients with bladder cancer.

EDUCATIONAL OBJECTIVES

At the completion of the activity, participants will be better able to:

1. Review the clinical burden and unmet needs associated with to Bacillus Calmette-Guérin (BCG)-unresponsive NMIBC.
2. Discuss the current treatment landscape in BCG-unresponsive NMIBC.
3. Evaluate the mechanism of action, safety, efficacy, and clinical use criteria for an approved intravesical gene therapy in NMIBC.
4. Outline how to incorporate patient-centered communication, shared decision-making, and health system navigation strategies to improve outcomes for patients with NMIBC.

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INTRODUCTION

The management of non-muscle-invasive bladder cancer (NMIBC) can represent a significant clinical challenge. High-risk patients and those unresponsive to first-line standard-of-care (SOC) treatment face a substantial risk for disease progression, recurrence, and bladder loss, which can adversely affect their quality of life (QoL) and survival. Recent years have witnessed a shift in the management of these cases, with the emergence of new bladder-sparing options. Understanding the epidemiology, evolving diagnostic and risk stratification tools, mechanisms of therapeutic resistance, and positioning of new treatments is central to improving patient outcomes in this complex disease state.

EPIDEMIOLOGY AND DISEASE BURDEN

Bladder cancer poses a significant public health challenge in the United States. In 2025, it is expected to be the 6th most commonly diagnosed cancer overall, with about 84,870 new cases, and the 10th leading cause of cancer death, responsible for an estimated 17,420 deaths.¹ Incidence is notably higher in men, who are diagnosed nearly 4 times as often as women, making bladder cancer the 4th most common cancer in men and the 11th in women.¹⁻³ More than 593,000 individuals currently live with bladder cancer in the United States.⁴

The disease predominantly affects older adults, with a median age at diagnosis of 73 years, and more than 90% of cases occurring in individuals aged 55 or older. Incidence peaks between ages 70 and 80, reflecting a strong age-dependent risk.² During the past decade, both incidence and mortality have declined by approximately 1% per year, likely owing to reductions in cigarette smoking, advances in early detection, and modern treatment approaches.^{1,2} Despite these improvements, outcomes remain closely tied to disease stage at diagnosis. The overall 5-year survival rate for bladder cancer is about 78%. However, this decreases to 40% for patients with lymph node involvement and 9% to 29% for those with distant metastasis.¹ These statistics underscore the critical need for prevention and timely intervention.

Geographic trends demonstrate a higher incidence of bladder cancer in industrialized and urban areas, likely influenced by occupational exposure to carcinogenic chemicals.¹ Racial and ethnic disparities persist: White men have the highest incidence, whereas Black and Hispanic patients often present at more advanced disease stages and experience worse outcomes.^{2,5,6} Black patients are also more likely to be diagnosed with variant histology, which is generally considered a high-risk feature that limits treatment options.^{5,6}

Histologically, approximately 90% of bladder cancers diagnosed in the United States are urothelial (transitional cell) carcinomas, originating in the transitional epithelium. The remainder are squamous cell carcinomas (2%-7%) and

adenocarcinomas (2%).^{3,7} Tumors are further classified morphologically as either sessile (flat) or papillary, and by grade as low- or high-grade.³ From a clinical perspective, distinguishing between muscle-invasive and non-muscle-invasive disease is crucial for determining management strategy. At diagnosis, approximately 75% of cases are non-muscle-invasive.⁸

NMIBC remains uniquely challenging due to its high rates of recurrence and progression. One-year recurrence rates range from 15% to 61%, and by 5 years, as many as 78% of patients experience a recurrence. This makes NMIBC the most recurrent malignancy among common solid tumors.⁹ These high recurrence rates generate a substantial economic burden, as the costs of treating NMIBC, including surveillance and repeated interventions, make up the majority of bladder cancer-related health care expenditures.¹⁰ For patients who do not respond to initial treatment and require radical cystectomy, costs increase significantly.

RISK FACTORS FOR BLADDER CANCER

The single most significant modifiable risk factor for bladder cancer is tobacco use, accounting for nearly 50% of all new cases. Carcinogenic chemicals from smoking are filtered and concentrated in the urine, prolonging exposure to the bladder lining and increasing mutational risk.^{1,3} Other

important risk factors include male sex, age older than 55 years, chronic bladder inflammation (from infections or long-term catheter use), prior pelvic radiation, and prior exposure to chemotherapeutic agents such as cyclophosphamide.^{1,3}

Occupational exposure to aromatic amines—chemicals used in dyes, rubber, leather, petroleum, and various manufacturing industries—also represents a prominent risk factor. Chronic exposure to these compounds is strongly associated with bladder cancer, especially among workers in high-risk occupations.^{1,3}

Military service also confers elevated risk. Bladder cancer is the fourth most common cancer among US veterans, with about 3200 new cases diagnosed annually. Veterans are 2 to 3 times more likely than the general public to be diagnosed with bladder cancer, a disparity attributed to toxic exposures (eg, Agent Orange, dioxins, depleted uranium), the demographic predominance of men, higher rates of smoking, and occupational hazards encountered during service.¹¹⁻¹³ Diagnosis may be delayed in veterans due to subtle symptoms that may be downplayed, overlooked, or misattributed to other issues such as post-traumatic stress disorder (PTSD), the presence of complex comorbidities, and a reduced willingness to seek medical attention or cope with a cancer diagnosis.^{12,13}

Table 1. Diagnostic Modalities in Bladder Cancer.¹⁵⁻²²

Test	Sensitivity, %	Specificity, %	Clinical role	Comments
Cystoscopy	~85-90	~87-100	First-line tool for detecting visible lesions	Gold standard; limited in detecting flat lesions like CIS ¹⁵
Blue light cystoscopy	~93-96	~46	Adjunct to standard cystoscopy	Detects additional lesions, particularly CIS; improves detection, lowers recurrence and progression; requires HAL agent and special equipment ^{17,18}
Urine cytology	~20-40 overall; up to 80-90 for CIS	~90-98	Adjunctive tool, especially for high-grade disease	Poor sensitivity for low-grade tumors; widely available ¹⁹
FISH (eg, UroVysion)	~60-80	~65-80	Detects chromosomal abnormalities in voided urine	Useful for ambiguous cytology; higher cost ²⁰
NMP22 (nuclear matrix protein)	~55-70	~60-85	Urine-based tumor marker	Higher false positives in inflammation or infection ²¹
Bladder tumor antigen (BTA-TRAK/Stat)	~50-70	~60-80	Antibody-based ELISA	Poor specificity in benign urologic conditions ²²
CT urography	~80-85 (for upper tract)	~90	Excludes upper tract urothelial carcinoma	Less helpful for primary NMIBC; exposes to radiation and contrast ¹⁶

CIS, carcinoma in situ; **CT**, computed tomography; **ELISA**, enzyme-linked immunosorbent assay; **FISH**, fluorescence in situ hybridization; **HAL**, hexaminolevulinate; **NMIBC**, non-muscle-invasive bladder cancer.

CLINICAL PRESENTATION AND DIAGNOSTIC PATHWAYS

NMIBC presents with a broad spectrum of symptoms. The most common presenting feature is hematuria, either gross or microscopic, seen in up to 85% of patients. Hematuria is typically painless and may be intermittent, which can contribute to diagnostic delays. Irritative voiding symptoms such as urinary frequency, urgency, and dysuria are less common but may signal carcinoma in situ (CIS), and are frequently mistaken for urinary tract infection (UTI) or benign prostatic hyperplasia, especially in older adults.^{14,15} A significant minority of patients remain asymptomatic. In some cases, NMIBC is detected during evaluation for persistent microscopic hematuria or recurrent infection or is incidentally identified on imaging for unrelated indications.¹⁶

The diagnosis of NMIBC is complicated by the absence of validated noninvasive screening tools and limitations in the sensitivity of available adjunct tests (Table 1).¹⁵⁻²² Thus, many cases are diagnosed at advanced stages.²³ Cystoscopy remains the gold standard, offering high sensitivity (approximately 85%-90%) and specificity (87%-100%) for visible urothelial lesions. It is routinely performed in the office setting and permits direct visualization, biopsy, and resection when needed. Flat lesions, such as CIS, may be missed, underscoring the importance of both operator experience and the use of ancillary testing.^{15,16}

Blue light cystoscopy is an advanced diagnostic technique that uses hexaminolevulinate, a photosensitizing agent, which causes cancerous cells to fluoresce under blue light, making them more readily distinguishable from normal tissue.¹⁷ When illuminated by blue light (380-450 nm), cancerous cells emit red fluorescence, whereas normal cells appear blue.¹⁷ This technique can significantly increase sensitivity for detection, particularly of flat CIS or papillary tumors, and has been shown to improve clinical outcomes by reducing recurrence and progression rates compared with conventional (white light) cystoscopy.²⁴

Urine cytology, which is widely accessible, has high specificity and is most sensitive for detecting high-grade lesions or CIS (60%-70%) but demonstrates poor sensitivity for low-grade tumors. Thus, it functions primarily as an adjunct tool for high-risk patients and during surveillance.^{15,19}

Molecular assays, such as fluorescence in situ hybridization (UroVysion), NMP22, and the BTA-TRAK or BTA-Stat test, provide moderate sensitivity (usually 50%-80%) and are not routinely used. The utility of these assays is limited by higher cost, lower specificity (with false positives frequently resulting from benign conditions such as inflammation or UTI), and inconsistent insurance reimbursement.²⁰⁻²² Advanced molecular diagnostics are less accessible in rural or resource-limited environments.²² Computed tomography (CT) urography is

Table 2. Drawbacks to BCG in Non-Muscle-Invasive Bladder Cancer³⁷⁻³⁹

Drawback	Description/Examples
High rate of AEs	>70% of patients experience some side effects, including irritative urinary symptoms, cystitis, hematuria, and fever
Serious AEs leading to discontinuation	Approximately 8%-10% of patients must stop BCG due to toxicity, including severe bladder complications or sepsis
Reduced tolerance with full dose or maintenance	Full-dose and longer maintenance increase side effects vs lower-dose or combination therapy
Incomplete treatment adherence	Toxicity and AEs result in low completion rates; only 16% in some studies complete full induction plus maintenance therapy
Risk for failure (non-responsiveness)	≤40% of patients may not respond, requiring alternative therapy or radical cystectomy, especially for high-risk disease
Systemic complications	Rare but serious risks include BCG sepsis, prostatitis, joint pain, rash, malaise, and incontinence
Exacerbated by comorbidities or infections	Urinary tract infections or bladder trauma can worsen or contraindicate BCG use
Global shortages	Supply issues have interrupted care, increasing the need for alternatives

AE, adverse event; BCG, Bacillus Calmette-Guérin.

primarily used to exclude upper tract involvement in patients with hematuria but plays a limited role in primary NMIBC diagnosis.¹⁶

The most typical scenario is diagnosis of stage Ta low-grade NMIBC following evaluation for painless hematuria. However, 40% to 50% of new cases already present with high-grade disease—most notably those with CIS or persistent/recurrent symptoms—and these patients require prompt risk stratification and aggressive management.^{14-16,19,25}

TRANSURETHRAL RESECTION OF BLADDER TUMOR

Transurethral resection of bladder tumor (TURBT) is the initial and definitive diagnostic and therapeutic procedure for patients with suspected bladder neoplasms. It remains the gold standard for establishing a pathologic diagnosis, assessing tumor stage and grade, and providing the majority of patients with their first therapeutic intervention. TURBT is typically performed under regional or general anesthesia using a resectoscope passed through the urethra. The main objective is complete gross tumor resection and representative sampling of the underlying and adjacent bladder wall for staging and grading.¹⁵

The completeness of initial TURBT is crucial. Removal of all visible tumor tissue, along with adequate sampling of underlying detrusor muscle, is necessary to distinguish non-muscle-invasive from muscle-invasive disease and to avoid understaging. Under-sampling or incomplete resection may result in missed identification of T1 or T2 disease and thus, suboptimal treatment stratification. For high-risk lesions—particularly T1 tumors, high-grade disease, or specimens lacking muscle tissue—a repeat TURBT is recommended within 2 to

6 weeks to ensure accurate staging and reduce the risk for progression.¹⁴⁻¹⁶

In addition to establishing diagnosis and primary management, TURBT enables the identification of CIS, which can appear as a flat erythematous lesion or in regions distant from the primary tumor. Advanced imaging techniques, such as narrow-band imaging, may improve the detection of CIS and completeness of initial resection, especially in high-risk patients. However, this technology may have limited availability, particularly in community or under-resourced settings.¹⁴⁻¹⁶

Complications from TURBT are relatively infrequent but can include bleeding, bladder perforation, and infection. Rare but important risks include obturator reflex with resultant bladder wall injury and, in patients with deep resection near the ureteral orifices, risk for ureteric injury or stricture.

PATHOLOGIC STAGING AND GRADING OF NMIBC

The diagnosis and risk stratification of NMIBC relies on a combination of tumor stage—based on the American Joint Committee on Cancer (AJCC)/TNM system—and tumor grade, typically using the World Health Organization (WHO) 2004/2016 grading system.^{15,26}

- **Stage Ta tumors** are noninvasive papillary lesions confined to the urothelium.
- **Stage T1 tumors** invade the lamina propria but not the muscularis propria.
- **CIS** is, by definition, a flat, high-grade, noninvasive lesion limited to the urothelium, frequently multifocal, and prone to rapid progression if not promptly managed.^{15,16}

Table 3. Defining BCG-Unresponsive NMIBC⁴⁵

Subcategory	Definition	Key Features
BCG-refractory	Persistent high-grade disease at 6 mo (or at 3 mo with worsening disease) despite adequate BCG	Indicates primary failure; unlikely to respond to further BCG
BCG-relapsing (early)	Recurrence of high-grade tumor within 6-12 mo after a CR to adequate BCG	High risk for progression; often treated as unresponsive
BCG intolerance	Inability to complete BCG due to severe adverse events	May be considered unresponsive if recurrence occurs
BCG-resistant (less commonly used term)	High-grade recurrence after initial response but after 12 mo	May still be eligible for retreatment depending on timing

BCG, Bacillus Calmette-Guérin; CR, complete response.

Tumor grade is a major prognostic factor and determinant of therapy. The 2004/2016 WHO grading system designates tumors as low-grade or high-grade, superseding the older 3-tiered system (G1-G3). Low-grade tumors display fewer mitotic features and a more orderly architecture, whereas high-grade tumors are pleomorphic and more aggressive.^{15,26}

Multiple tumors, large size (>3 cm), multifocality, frequent recurrences, concomitant CIS, deep lamina propria invasion (T1), and lympho-vascular invasion are all features associated with higher risk for progression and recurrence. The presence of subtype histology or divergent differentiation (eg, micropapillary, plasmacytoid) also signals a higher risk and may warrant aggressive management.¹⁴⁻¹⁶

Careful annotation of tumor number, size, site, and the presence or absence of muscle in the resected specimen should be included in the pathology report to optimally inform treatment planning.^{15,16,25}

RISK STRATIFICATION AND TREATMENT PLANNING

After complete TURBT and pathologic confirmation, patients with NMIBC must be stratified into risk categories to guide further management. Contemporary guidelines from the American Urological Association (AUA), the European Association of Urology (EAU), and the National Comprehensive Cancer Network (NCCN) recommend classifying patients as low-, intermediate-, or high-risk for recurrence and progression based on an integrated assessment of stage, grade, tumor size, focality, presence of CIS, and other adverse features.^{14-16,27}

Low-risk NMIBC refers to solitary, low-grade Ta papillary tumors that are 3 cm or smaller, without evidence of CIS, and no prior recurrences. Patients with low-risk NMIBC have an excellent prognosis, with management strategies designed to maximize effectiveness while minimizing overtreatment.¹⁵ Complete TURBT may be sufficient in many cases; however, guidelines recommend a single immediate postoperative intravesical chemotherapy instillation

within 24 hours of TURBT.^{16,28} This practice reduces the risk for recurrence by approximately 35%, based on high-level evidence from multiple randomized trials and meta-analyses.²⁸

Both gemcitabine and mitomycin C are cytotoxic agents originally approved for intravenous administration in the treatment of various solid tumors; their intravesical use in NMIBC is off-label, but it is endorsed by the NCCN and EAU guidelines. Notably, intravesical administration enables direct, localized drug activity within the bladder while minimizing systemic absorption and associated toxicity.^{15,16} Gemcitabine was first approved by the FDA in 1996, and has since become widely used in bladder cancer; mitomycin C, FDA-approved in 1974, has been used off-label for intravesical therapy since the late 1980s and has become an internationally accepted SOC in this context.^{15,28}

After TURBT and a single perioperative dose of chemotherapy, no further intravesical therapy is required in most low-risk cases. The risk for recurrence is low, and the expected risk for disease progression is essentially zero. Ongoing management focuses on careful surveillance involving periodic cystoscopy to detect new tumors at an early, easily curable stage.^{15,16}

Intermediate-risk NMIBC encompasses patients with multiple and/or large low-grade Ta lesions, early recurrences, or some but not all high-risk features. This includes recurrent or multifocal low-grade Ta tumors, as well as solitary low-grade Ta lesions larger than 3 cm.¹⁵ The primary goal for this cohort is to reduce the risk for recurrence, prolong disease-free intervals, and minimize overtreatment.

The backbone of management for intermediate-risk NMIBC is complete TURBT followed by a 6-week course of an intravesical agent such as gemcitabine or mitomycin C.^{15,16} Maintenance chemotherapy may be considered for up to 1 year in patients with higher recurrence risk or significant tumor burden; this approach has been shown to extend recurrence-free survival and diminish the need for repeat interventions in carefully selected populations.^{15,29}

UGN-102

A notable new option for intermediate-risk disease is UGN-102, a reverse thermal gel formulation of mitomycin C approved by the FDA in August 2025 and intended for patients with recurrent low-grade intermediate-risk NMIBC who are poor candidates for surgical resection.³⁰⁻³² The drug is administered via a urinary catheter once weekly for 5 consecutive weeks. Unlike traditional aqueous mitomycin C, which is difficult to retain for more than 1 to 2 hours, UGN-102 is instilled as a liquid and gels at body temperature, remaining in the bladder for 4 to 6 hours to promote consistent mucosal exposure.^{30,32}

Approval was based primarily on the single-arm, open-label phase 3 ENVISION trial, which included patients with recurrent low-grade intermediate-risk NMIBC. In this study, 78% of patients achieved a complete response (CR) at 3 months, and 82.3% maintained that response for at least 12 months.^{30,31} Adverse events (AEs) were typically mild and included dysuria (25%), urinary urgency (20%), hematuria (15%), and fatigue (12%).

In contrast, the phase 3 ATLAS trial was a randomized, controlled study comparing UGN-102 as monotherapy to standard TURBT in patients with either newly diagnosed or recurrent low-grade intermediate-risk NMIBC. UGN-102 demonstrated a 3-month CR rate of 63.6%, similar to that seen with TURBT (64.8%); at 12 months post-treatment, 79.7% and 67.7% of patients remained disease-free after UGN-102 and TURBT, respectively. The hazard ratio for duration of response (DoR; 0.46) favored UGN-102, indicating a lower risk for recurrence compared with surgery alone. Dysuria was slightly more common in ATLAS (30.4%) vs ENVISION (22.5%).³³

High-risk NMIBC is defined by the presence of any of the following features: high-grade Ta, T1, CIS, multiple and large tumors, variant histology, or lympho-vascular invasion.^{15,16} These cases require aggressive management, typically with induction and maintenance Bacillus Calmette-Guérin (BCG) therapy, rigorous surveillance including upper-tract imaging, and prompt re-resection if high-risk features are confirmed.¹⁴⁻¹⁶ Therapies for high-risk disease are summarized in the next section.

BCG IN HIGH-RISK NMIBC

BCG is the foundational, guideline-endorsed therapy for patients with high-risk NMIBC, including with CIS, high-grade Ta, and T1 tumors after complete TURBT.³⁴ BCG consists of a live, attenuated strain of *Mycobacterium bovis*, originally developed as a tuberculosis vaccine and approved for bladder cancer treatment in 1990 based on its ability to stimulate a robust, localized immune response against residual and microinvasive urothelial cancer cells.³⁴ Following instillation directly into the bladder via catheter, BCG attaches to urothelial cells, is internalized, and triggers a cascade

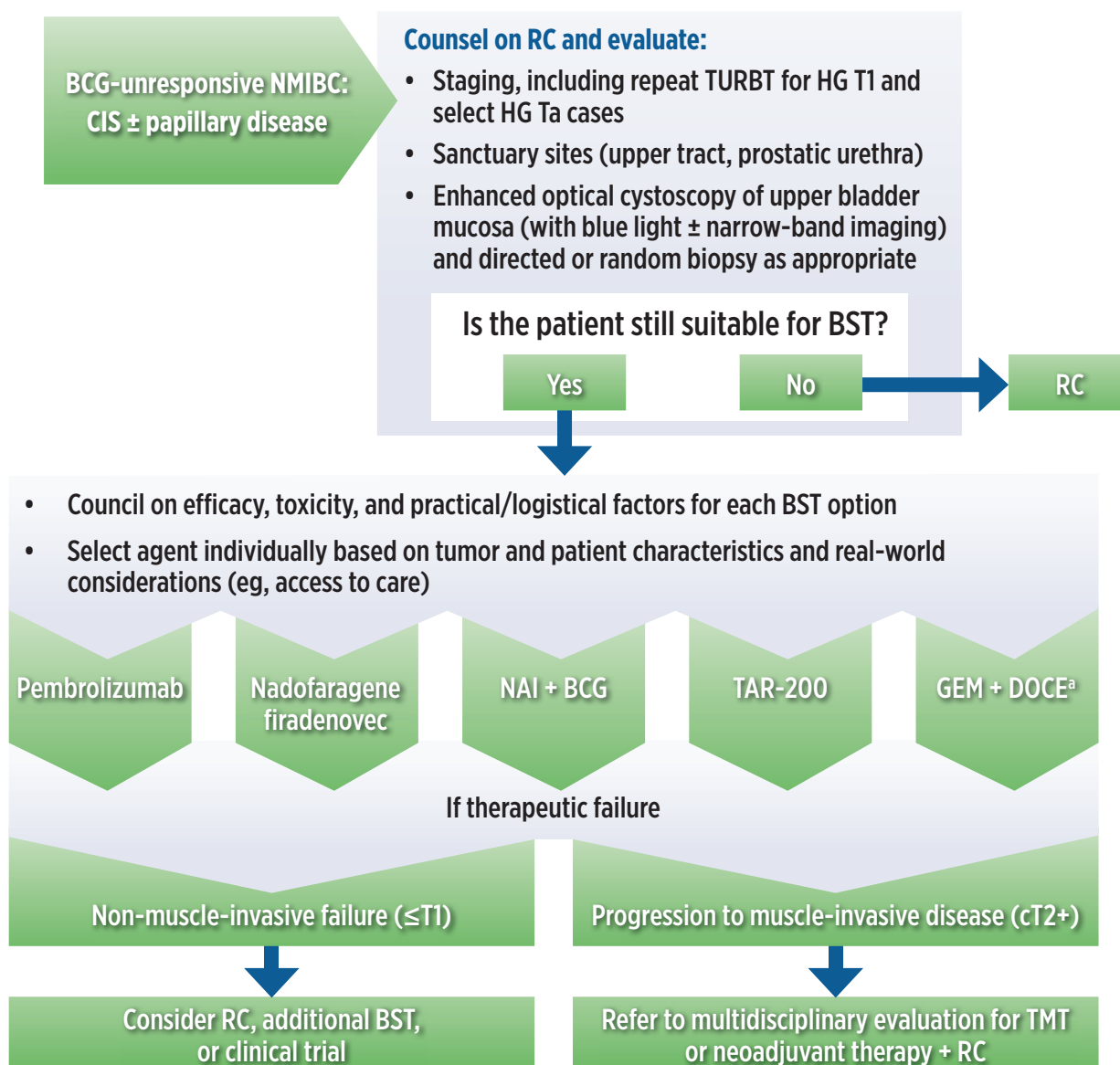


Figure 1. Algorithm for BST in patients with BCG-unresponsive NMIBC who are ineligible for or refuse RC.

^a Not specifically approved for this use but may be considered based on available evidence.

BCG, Bacillus Calmette-Guérin; **BST**, bladder-sparing treatment; **CIS**, carcinoma in situ; **GEM + DOCE**, gemcitabine + docetaxel; **HG**, high grade; **NAI**, nogapendekin alfa inbakicept; **NMIBC**, non-muscle-invasive bladder cancer; **RC**, radical cystectomy; **TAR-200**, gemcitabine intravesical system; **TUR**, transurethral resection of bladder tumor; **TMT**, trimodal therapy.

Adapted from reference 46.

of immunologic processes. The mechanism involves activation of resident macrophages and dendritic cells, leading to the recruitment of cytotoxic CD4⁺ and CD8⁺ T cells. This interferon (IFN)- and cytokine-enriched environment, particularly involving T-helper 1 cytokines like interleukin-2 (IL-2) and IFN- γ , results in the direct lysis and clearance of malignant cells.^{35,36}

Standard BCG induction consists of once-weekly intravesical instillations for 6 consecutive weeks, delivered after grossly complete TURBT. Maintenance therapy is then recommended at 3, 6, and 12 months, and may be extended up to

3 years in patients with continued high-risk features or CIS, as validated in randomized trials and major guideline recommendations.^{15,16,34} BCG provides high efficacy for NMIBC: CR rates in CIS approach 70%, and long-term randomized and pooled data confirm significant reductions in both recurrence and progression for patients receiving both induction and maintenance therapy.³⁶ These results have anchored BCG as the international SOC for more than 3 decades.

Despite its history of success, BCG is associated with several drawbacks (Table 2), including a spectrum of AEs.³⁷⁻³⁹ The most common

AEs are localized and include dysuria, increased urinary urgency or frequency, mild fever, and self-limited hematuria. Most are mild to moderate, but rare and clinically significant complications—including systemic BCG infection (BCG sepsis), fever exceeding 38.5°C, or disseminated granulomatous disease—can occur, especially if mucosal integrity is compromised or the bladder wall is traumatized during catheterization.³⁴ Important contraindications include immunosuppression (related to HIV/AIDS, leukemia, lymphoma, or chronic corticosteroid use); active UTI; febrile illness; gross hematuria;

Table 4. Key Bladder-Sparing Therapies for BCG-Unresponsive High-Risk NMIBC⁵⁸⁻⁷⁰

Drug	Pembrolizumab	Nadofaragene fircidenovec	Nogapendekin alfa inbakicept + BCG	Gemcitabine intravesical system	Gemcitabine + docetaxel
Mechanism of action	Anti-PD-1 monoclonal antibody—restores immune activity by blocking PD-1/PD-L1 axis	Nonreplicating adenoviral vector delivers IFN- α 2b gene to urothelial cells, producing local interferon and immune activation	IL-15 receptor superagonist—stimulates NK cells and CD8 ⁺ T cells, synergizes with BCG	Inhibition of DNA synthesis; sustained-release (device)	Gemcitabine inhibits DNA synthesis; docetaxel induces mitotic arrest and apoptosis
Indication	BCG-unresponsive high-risk NMIBC with CIS $\pm$ papillary tumors when cystectomy refused/ineligible ⁵⁸	BCG-unresponsive high-risk NMIBC with CIS $\pm$ papillary tumors ⁶⁰	BCG-unresponsive with CIS $\pm$ papillary tumors, given with BCG ⁶³	BCG-unresponsive NMIBC with CIS $\pm$ papillary tumors ⁶⁵	Used off-label for BCG-unresponsive NMIBC; recurrent intermediate-/high-risk disease ^{16,27}
Administration and dosing	200 mg IV every 3 wk for ≤ 24 mo	75 mL instilled every 3 mo	Weekly $\times 6$ (induction), then weekly for 3 wk at months 4, 7, 10, 13, and 19 (maintenance), with BCG	225 mg; device inserted into bladder; replaced every 3 wk $\times 6$ cycles (induction) then every 12 wk (maintenance) for ≤ 24 mo	1 g gemcitabine, followed by 37.5 mg docetaxel weekly $\times 6$ (induction), then monthly for ≤ 24 mo (maintenance)
Key trial(s)	KEYNOTE-057 (phase 2)	NCT02773849 (phase 3)	QUILT 3.032 (phase 2/3)	SunRISe-1 (phase 2b)	NCT02202772, NCT01619363, multi-institutional studies
Key efficacy outcomes	41% CR at 3 mo; median DoR 16.2 mo; 46% maintained at 12 mo ⁵⁹	51% CR at 3 mo; 45% maintained at 12 mo; median DoR 9.7 mo; 24-mo RFS 17%; 75% cystectomy-free at 12 mo ⁶¹	71% CR; 45% at 12 mo; 91% cystectomy-free at 24 mo in CIS cohort ⁶⁴	82% CR; 46% maintained at 12 mo; median DoR 25.8 mo ⁶⁶	48%-54% RFS at 2 y; 75% bladder preservation at 5 y; comparable/superior to BCG salvage in multicenter 2025 study ⁶⁷⁻⁷⁰
Common AEs	Fatigue, pruritus, diarrhea, immune-related AEs (colitis, pneumonitis, endocrinopathies) ^{58,59}	Fatigue (23%), bladder spasm (18%), urgency (17%), hematuria (12%); nearly all grade 1-2 ^{61,62}	Dysuria (36%), fatigue (25%), frequency (20%), nocturia (18%); some grade 3 hematuria, UTI, immune events, rare grade 5 ⁶⁴	Pollakiuria (44%), dysuria (40%), micturition urgency (25%), UTI (21%); grade ≥ 3 AEs, 12%; serious AEs, 5.9% ⁶⁶	Dysuria, frequency, mild local cystitis ^{67,70}
FDA approval	2020	2022	2024	2025	Not FDA-approved for this use but guideline-supported ^{16,27}

AE, adverse event; **BCG**, Bacillus Calmette-Guérin; **CIS**, carcinoma in situ; **CR**, complete response; **DoR**, duration of response; **IFN**, interferon; **IL**, interleukin; **IV**, intravenous; **NK**, natural killer; **NMIBC**, non-muscle-invasive bladder cancer; **PD**, programmed death; **RFS**, recurrence-free survival; **UTI**, urinary tract infection.

or recent bladder instrumentation, biopsy, or surgery within the past 7 to 14 days.³⁴

A current challenge in clinical practice is the ongoing shortage of BCG, which has disrupted treatment protocols worldwide. Clinicians have often been forced to use reduced dosing regimens (ie, one-third of the standard dose) or to ration full-dose BCG, prioritizing patients with the highest-risk disease.⁴⁰⁻⁴² These shortages affect the availability of both induction and maintenance courses, occasionally necessitating alternative intravesical therapies or enrollment in clinical trials.

Furthermore, up to 40% of patients will not respond to BCG or will experience disease recurrence (BCG failure), even after completing an adequate course of treatment.^{14,43,44} These cases present the greatest risk for progression and have represented a major clinical dilemma. However, the recent development of alternative and gene therapies offers new hope for these patients.

BCG-UNRESPONSIVE NMIBC

Precisely defining BCG unresponsiveness is crucial for clinical decision-making, regulatory clarity, and trial eligibility. Consensus definitions from the FDA, AUA, and EAU, as well as current NCCN guidelines, define BCG-unresponsive NMIBC as shown in [Table 3](#).^{14-16,45}

Adequate BCG is characterized as the receipt of at least 5 of 6 induction doses and at least 2 of 3 maintenance doses (or a second induction course). If patients have not received this full regimen, they are often labeled “BCG-exposed” and may still be eligible for re-induction rather than being considered truly unresponsive.^{14,16}

A designation of BCG-unresponsive carries important regulatory and clinical implications, as it defines eligibility for subsequently approved or experimental therapies. Patients with high-risk NMIBC, especially those with CIS, T1, or persistent/recurrent high-grade lesions after adequate BCG,

face a substantial risk for disease progression to muscle-invasive disease and metastasis. In this group, timely identification and a frank discussion of treatment options—including radical cystectomy as the gold standard therapy, and newer FDA-approved and guideline-supported bladder-sparing approaches ([Figure 1](#))⁴⁶—is paramount for optimizing survival while supporting patient preferences for bladder preservation.¹⁶

RADICAL CYSTECTOMY: INDICATIONS, OUTCOMES, AND PATIENT CONSIDERATIONS

For patients who do not respond to BCG therapy, the next traditional treatment option is radical cystectomy. This procedure entails complete surgical removal of the bladder along with adjacent organs (the prostate and seminal vesicles in men; uterus and anterior vaginal wall in women); pelvic lymphadenectomy; and urinary diversion

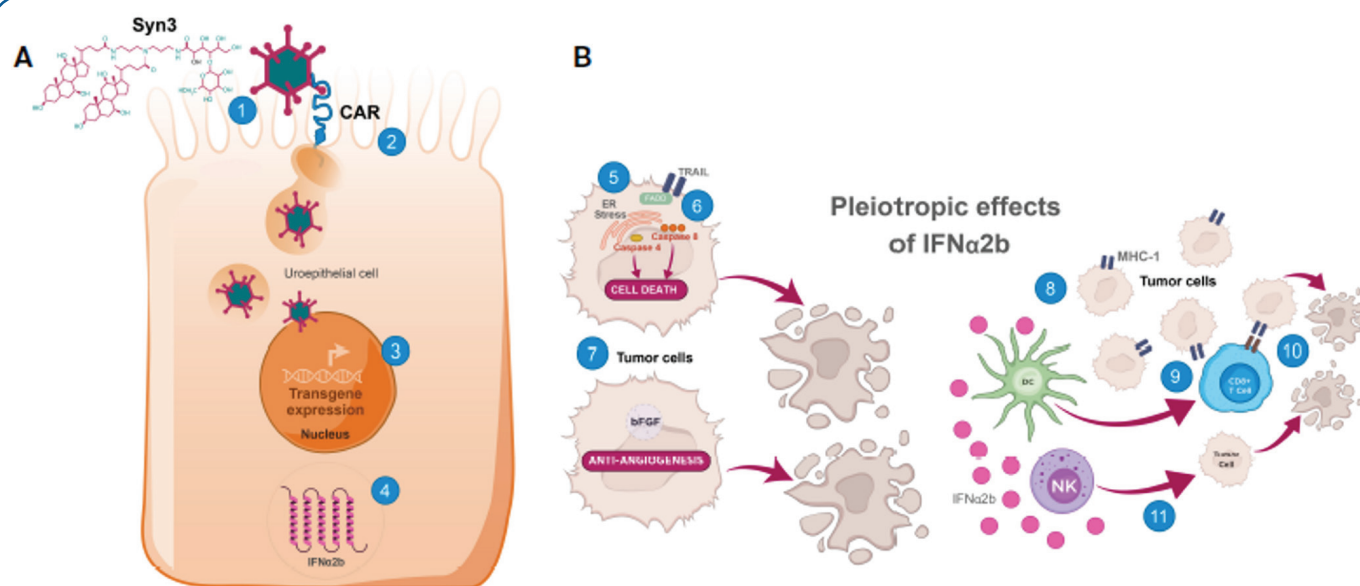


Figure 2. Mechanism of action for nadofaragene firadenovec.⁷³

A. Internalization of adenoviral vector into uroepithelial cells and transcription/translation of IFNa2b. (1) Syn3 promotes adenoviral vector access to uroepithelial cells; (2) After CAR-mediated endocytosis into the uroepithelial cell and escape from endosomes, the adenoviral capsid translocates to the nuclear envelope where it disassembles, and the human IFNa2b transgene is imported into the nucleus; (3) After import into the nucleus, IFNa2b cDNA is transcribed into mRNA; (4) IFNa2b mRNA is translated, leading to sustained production of IFNa2b.

B. IFNa2b exerts pleiotropic antitumor effects directly and indirectly in the tumor microenvironment. Direct cytotoxic effects include (5) induced ER stress in bladder cancer cells, leading to caspase 4 activation and cell death, (6) increased expression of TRAIL, leading to caspase 8 activation and cell death, and (7) antiangiogenic effects through downregulation of growth factors including bFGF, leading to tumor hypoxia and central necrosis. Direct immunomodulatory effects are elicited through (8) upregulation of the presentation of surface tumor-associated antigens via augmentation of MHC-I class molecules, increasing the immunogenicity of tumor cells. Indirect immunomodulatory effects occur through (9) stimulation of DC priming of cytotoxic CD8+ T cells, which (10) kill MHC-I+ tumors, and (11) increased antitumor activity of NK cells, which preferentially kill BCa cells lacking MHC-I (downregulation or loss of MHC-I is common in BCa cells).

BCa, bladder cancer; **bFGF**, basic fibroblast growth factor; **CAR**, coxsackievirus and adenovirus receptor; **CD**, cluster of differentiation; **cDNA**, complementary deoxyribonucleic acid; **DC**, dendritic cell; **ER**, endoplasmic reticulum; **FADD**, Fas-associated protein with death domain; **IFNa2b**, interferon a2b; **MHC-I**, major histocompatibility complex class I; **mRNA**, messenger ribonucleic acid; **NK**, natural killer; **TRAIL**, tumor necrosis factor-related apoptosis-inducing ligand.

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via an ileal conduit, continent cutaneous reservoir, or orthotopic neobladder.¹⁵ When performed early for high-risk NMIBC, radical cystectomy is associated with greater than 90% cancer-specific survival at 5 years.¹⁴

Nevertheless, radical cystectomy is a major surgery with a high risk for complications. Data from the United States Radical Cystectomy Consortium reflect a 90-day overall complication rate of 64%, with 13% classified as major (Clavien grade III-V) and 51% as minor (Clavien I-II). Other studies report complication rates between 30% and 50%, especially in older patients, those with comorbidities, and at lower-volume centers.⁴⁷⁻⁴⁹ Complications include bowel obstruction, anastomotic leak, UTI, sepsis, and venous thromboembolism.^{43,50-52}

QoL may be profoundly affected. Patients must adjust to altered body image, daily routines centered on stoma or pouch/appliance care (for ileal conduits or continent reservoirs), and learn new techniques for continence control or intermittent self-catheterization.⁵³ Long-term challenges include stomal complications, incontinence,

and “right-time” catheterization. Sexual dysfunction is common. Up to 80% of men may experience erectile dysfunction due to nerve damage, and loss of ejaculation is widespread. Women may face vaginal shortening, dyspareunia, and surgical menopause.^{54,55} Psychosocial burdens, such as anxiety, depression, and social withdrawal related to appliance concerns or body image, are well documented.⁵⁶

Despite these challenges, QoL after cystectomy may compare favorably to bladder-sparing therapies, which can help patients facing difficult treatment decisions.⁵⁷

BLADDER-SPARING THERAPIES IN BCG-UNRESPONSIVE HIGH-RISK NMIBC

Recently, a shift toward bladder-sparing, non-surgical treatments has transformed the management landscape for BCG-unresponsive NMIBC—a setting where, until very recently, radical cystectomy or experimental regimens were the only alternatives. **Table 4** provides summaries of key bladder-sparing treatment options for

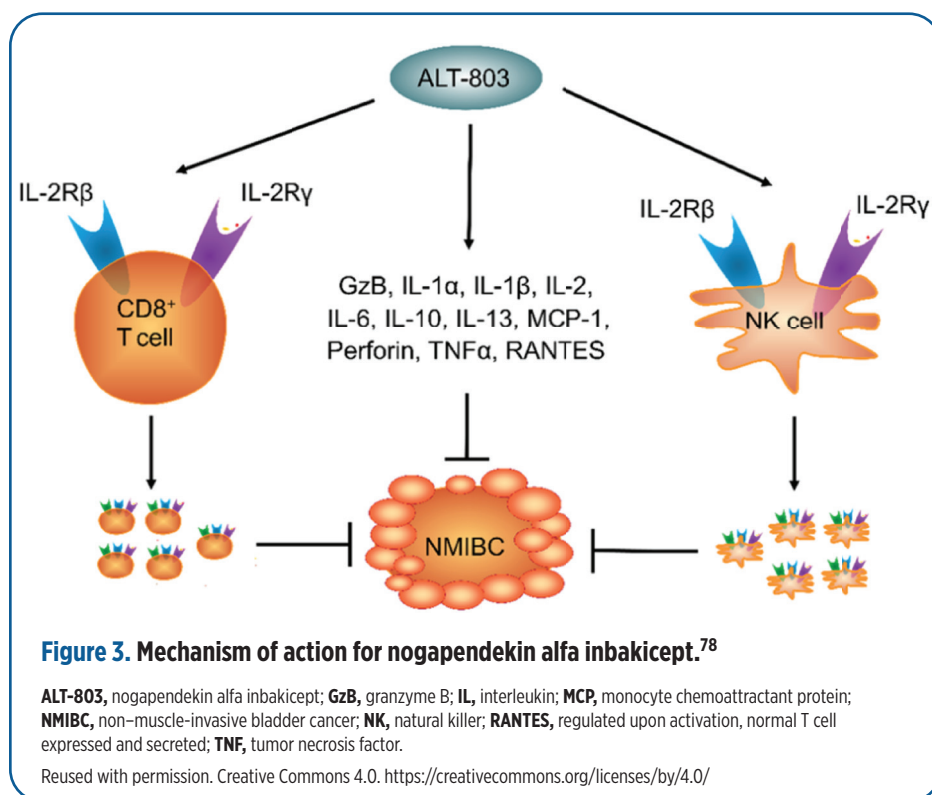
BCG-unresponsive high-risk NMIBC.⁵⁸⁻⁷⁰

PEMBROLIZUMAB

Pembrolizumab is an immune checkpoint inhibitor targeting the programmed death (PD)-1 protein that promotes immune-mediated clearance of tumor cells. The FDA approved pembrolizumab in 2020 for patients with BCG-unresponsive, high-risk NMIBC with CIS, who are either ineligible for or decline cystectomy.⁵⁸ Its use remains off-label for papillary disease or for use in combination regimens outside this indication.

In the pivotal KEYNOTE-057 phase 2 trial, single-agent pembrolizumab achieved a 40.6% CR rate at 3 months, with a median DoR of 16.2 months.⁵⁹ Among responders, only about one-third maintained response at 18 months and 23% at 24 months.

Treatment is administered intravenously at 200 mg every 3 weeks, for up to 2 years. Because pembrolizumab is administered systemically, it necessitates collaboration between urology and medical oncology providers and carries risks for



immune-related AEs, including colitis, pneumonitis, and endocrinopathy, which can require high-dose steroids or multidisciplinary management.⁵⁸ The need for frequent infusions also imposes time and logistical burdens on patients and care teams.⁷¹

NADOFARAGENE FIRADENOVEC

With FDA approval in 2022, nadofaragene firadenovec is the first intravesical gene therapy for BCG-unresponsive NMIBC. Specifically, it is indicated for adult patients with CIS with or without concomitant papillary tumors who have failed adequate BCG therapy.^{60,72}

The mechanism of action of nadofaragene firadenovec involves the use of a nonreplicating adenoviral vector to deliver the human IFN- α 2b gene directly to the urothelium (Figure 2).⁷³ This leads to the local production of IFN and stimulation of both innate and adaptive anti-tumor immune responses, including recruitment of cytotoxic T cells and the release of key cytokines such as IL-2 and IFN- γ .^{73,74}

Nadofaragene firadenovec is administered as a 75-mL intravesical instillation every 3 months in the urologist's office.⁶⁰

In the pivotal phase 3 trial (NCT02773849), which enrolled 157 heavily pretreated patients (50% with ≥ 3 prior BCG courses), 53.4% of the CIS cohort achieved a CR within 12 months of their first dose, with all responses observed by month 3. Among responders, 45.5% maintained response at 12 months.⁶¹ The median DoR was 9.7 months, and the 24-month recurrence-free survival (RFS) rate was approximately 17%. For those with high-grade Ta or T1 tumors, 72.9% were high-grade recurrence-free at

month 3 and 60% at 12 months, with a median high-grade RFS of 12.35 months. Notably, 75% of patients were cystectomy-free at 12 months.⁶¹

The safety profile for nadofaragene firadenovec has been favorable: most AEs were low-grade (catheter site discharge, fatigue, bladder spasms, urgency), grade 3 events were rare, and no grade 4 or 5 treatment-related events were observed.^{60,61} Five-year follow-up confirmed an RFS rate of 13% at 57 months in the CIS cohort and 33% in the Ta/T1 cohort, alongside 49% cystectomy-free survival at 60 months and no severe AEs.⁶²

Early real-world data support the pivotal trial. For example, a 2025 Mayo Clinic study demonstrated CR rates of 79% at 3 months and 84% at 7.3 months, with safety consistent with earlier reports.⁷⁵ The ABLE-41 phase 4 observational study is underway and will report on real-world use, treatment patterns, and long-term outcomes when completed in December 2025.⁷⁶

Practical considerations with nadofaragene firadenovec involve cold-chain shipping and gene therapy-specific handling protocols. This agent should not be administered in cases of gross hematuria, catheter trauma, or within 14 days of bladder surgery, to minimize risk for systemic exposure.⁶⁰

Based on phase 3 efficacy data (CR $\geq 50\%$) and favorable long-term safety, nadofaragene firadenovec has been included in updated guidance from the NCCN, AUA, and the Society of Urologic Oncology, which together support its role as the preferred gene therapy for eligible BCG-unresponsive NMIBC patients.^{16,27,77}

NOGAPENDEKIN ALFA INBAKICEPT

Nogapendekin alfa inbakicept is a recombinant IL-15 receptor immunotherapy approved by the FDA in 2024 for use in combination with BCG for patients with BCG-unresponsive NMIBC with CIS, with or without papillary tumors.⁶³ It is a recombinant fusion protein engineered as an IL-15 receptor superagonist, which works synergistically with BCG to drive immune-mediated tumor clearance. Specifically, nogapendekin alfa inbakicept binds to and signals through the IL2R β/γ receptor complex on immune effector cells—including natural killer cells and CD8⁺ cytotoxic T lymphocytes—resulting in sustained cytotoxic activity within the bladder wall. The end result is amplification of antitumor responses originally triggered by BCG, enhancing cytokine release and tumor infiltration by immune effector cells (Figure 3).^{64,78}

Nogapendekin alfa inbakicept is administered via intravesical instillation as 6 weekly induction doses (given with standard BCG instillations) followed by monthly maintenance for up to 12 months in patients who derive benefit or until recurrence or progression.⁶³

Efficacy and safety were reported in the QUILT 3.032 phase 2/3 open-label study, for which the main efficacy population included 82 patients with CIS (with or without papillary tumors) and 77 patients with high-grade papillary (Ta/T1) NMIBC.⁶⁴ CR was seen in 71% of patients with CIS, with a median DoR of 26.6 months, and 45% of initial responders remaining disease-free at 12 months. In the high-grade papillary group, the median disease-free survival was 19.3 months. The most common AEs were urinary in nature or immune-related and were generally manageable and consistent with the effects of other intravesical immunotherapies.

Treatment-emergent adverse events (TEAEs) were mostly lower urinary tract symptoms, including dysuria, pollakiuria (frequent urination), and hematuria.⁶⁴ Grade 3 TEAEs included 4 cases of hematuria, 3 of UTI, 3 immune-related events, and 1 each of dysuria and pollakiuria. One grade 5 event (fatal cardiac arrest) was attributed to underlying comorbidity rather than drug toxicity, according to investigators. The final readout of the phase 3 QUILT 3.032 study is anticipated in March 2029.

There are several practical considerations for nogapendekin alfa inbakicept/BCG therapy. Due to its mechanism and the need for synergy, nogapendekin alfa inbakicept is not approved as monotherapy and should not be used without concurrent BCG; consequently, therapy is limited by BCG availability and ongoing international supply constraints. Although generally well tolerated, IL-15 superagonists can produce systemic immune symptoms, such as fever and fatigue, at higher rates than BCG alone and may require supportive management. As a biologic, nogapendekin alfa inbakicept must be ordered through a specialty pharmacy, and

initial treatment coordination can be affected by pharmacy logistics and delivery timelines.^{63,64}

GEMCITABINE INTRAVESICAL SYSTEM

The most recent approval, TAR-200, is an intravesical delivery system that uses osmotic minitables to provide continuous local release of gemcitabine over several weeks, at a dose of 225 mg.⁶⁵

Approval was based on the phase 2b SunRISe-1 trial, which enrolled patients with BCG-unresponsive high-risk NMIBC with CIS with or without papillary disease. In the monotherapy cohort (n=85), the CR rate was 82.4%, with 45.9% of patients maintaining response at 12 months, and the median DoR was 25.8 months.⁶⁶ AEs were mostly low-grade and included pollakiuria, dysuria, micturition urgency, and UTI.

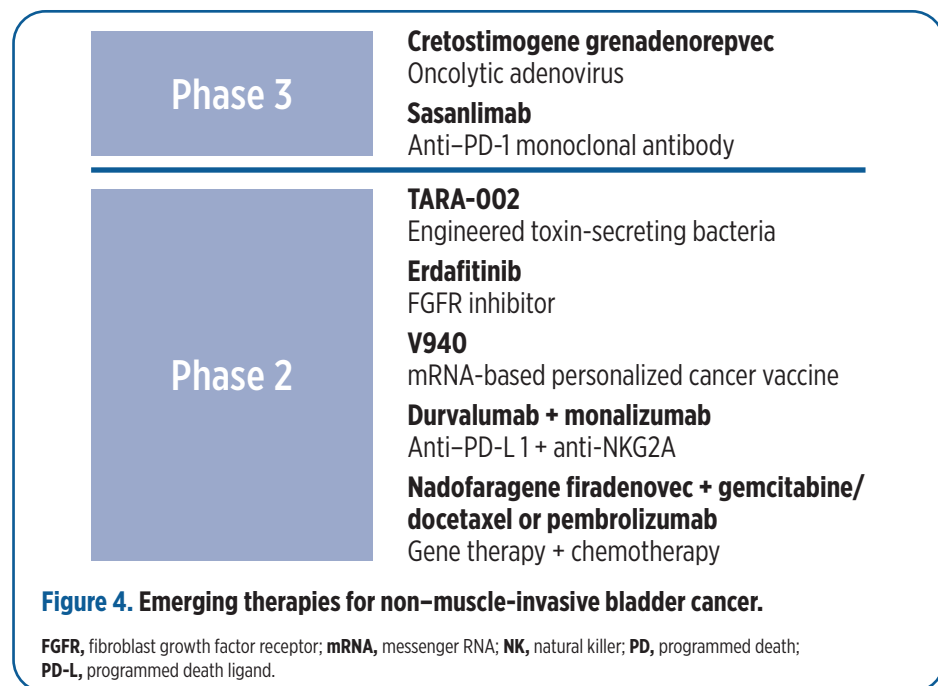
The gemcitabine intravesical system is inserted once every 3 weeks for up to 6 months (8 doses), followed by once every 12 weeks for up to 18 months (6 doses), or until the development of persistent or recurrent high-grade NMIBC, disease progression, or unacceptable toxicity.⁶⁵ Contraindications include bladder perforation and prior hypersensitivity reaction to gemcitabine.⁷

GEMCITABINE ± DOCETAXEL

The combination of intravesical gemcitabine (a nucleoside analog that inhibits DNA synthesis) and docetaxel (a microtubule stabilizer preventing mitosis) is not FDA-approved for use in NMIBC but is widely used off-label for patients with BCG-unresponsive or recurrent intermediate/high-risk disease, especially if gene therapies or immunotherapy are unavailable. This sequential regimen is listed in both AUA and NCCN guidelines.^{16,27}

The clinical evidence base for this use has evolved over 2 decades. Initial single-center data in heavily pretreated, BCG-unresponsive NMIBC showed high-grade RFS of 34% at 2 years,⁷⁹ and subsequent multi-institutional studies confirmed 2-year high-grade RFS rates around 46%.⁶⁷ Long-term follow-up of these cohorts demonstrated a 5-year bladder preservation rate of 75% and a cancer-specific survival rate of 91%.⁸⁰ More recent retrospective and comparative studies, including multicenter studies, have shown 3-month CR rates as high as 92% for treatment-naïve patients, multi-institutional 2-year RFS rates between 46% and 54%, and 5-year bladder preservation rates consistently exceeding 70%.^{69,70,80} A recent international comparative analysis found that sequential gemcitabine-docetaxel provided significantly higher rates of progression-free, cystectomy-free, and cancer-specific survival than additional BCG in BCG-unresponsive disease, with similar overall survival and favorable tolerability.⁷⁰

This drug combination is being studied in the BRIDGE trial, the first randomized phase 3 study directly comparing intravesical gemcitabine + docetaxel with intravesical BCG in BCG-naïve high-grade NMIBC.⁸¹ This is the first large trial to test for



noninferiority to BCG in event-free survival (EFS) in the frontline setting.

For most patients, intravesical gemcitabine/docetaxel is administered via weekly induction instillations for 6 weeks, with monthly maintenance as appropriate. Side effects are typically mild and localized, such as dysuria or urinary frequency, and the regimen is well tolerated even in elderly or comorbid populations.^{67,70,79}

PIPELINE AND EMERGING THERAPIES IN NMIBC

Multiple novel agents and platforms are now in advanced clinical development for patients with NMIBC—particularly those who are unresponsive to or ineligible for BCG (Figure 4). These new therapies focus on enhancing response durability, minimizing recurrence risk, and providing alternatives to surgery.

- **Cretostimogene grenadenorepvec (CG0070)** is a tumor-selective oncolytic adenovirus engineered to replicate in cells with defective retinoblastoma pathway function and locally express granulocyte-macrophage colony-stimulating factor to amplify anti-tumor immunity. In the pivotal phase 3 BOND-003 trial (N=110, high-risk, BCG-unresponsive NMIBC), an interim CR rate of 75.7% was reported, with high durability at 3 and 6 months and a favorable tolerability profile.⁸² Updated AUA 2024 data confirmed a 75.2% CR, 96.7% 12-month progression-free survival, and no severe TRAEs.⁸³ Ongoing studies are evaluating CG0070 in intermediate-risk disease (PIVOT-006) and in combination with pembrolizumab (CORE-001).
- **Sasanlimab** is a subcutaneously administered anti-PD-1 monoclonal antibody. In the phase

3 CREST trial (N=1055; high-risk, BCG-naïve NMIBC), sasanlimab plus SOC BCG resulted in a meaningful improvement in EFS, with a hazard ratio of 0.68 and a 36-month EFS of 82.1% vs 74.8% with BCG alone. Benefits were consistent across CIS, Ta, and T1 subgroups and regardless of PD-L1 status. Safety findings were consistent with known BCG and checkpoint inhibitor profiles.^{84,85}

- **TARA-002** is a purified, inactivated strain of *Streptococcus pyogenes* that elicits a local immune response. Interim analysis of the phase 2 ADVANCED-2 study showed encouraging activity in patients with CIS who were BCG-unresponsive or -naïve.⁸⁶
- **Erdafitinib** is an oral pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor, already approved in metastatic urothelial carcinoma, now in evaluation for FGFR-mutated NMIBC. A phase 2 trial is comparing erdafitinib with intravesical chemotherapy in patients who have FGFR-altered high-risk NMIBC (NCT04172675). Erdafitinib is also the active agent used in TAR-210, a novel drug-releasing intravesical delivery system designed to provide sustained local release directly into the bladder over a 3-month period. This therapy showed high CR rates and safety in FGFR3-altered intermediate-risk tumors in early study.⁸⁷ The Moonrise-1 phase 3 study is now evaluating device against standard intravesical therapies for patients with FGFR-altered intermediate-risk NMIBC, and results will further clarify its role in clinical practice.⁸⁸
- **V940 (mRNA neoantigen vaccine)** is a personalized mRNA vaccine encoding patient-specific tumor neoantigens, designed to stimulate anti-tumor T-cell responses. A phase 2

study is evaluating V940 co-administered with BCG in high-risk NMIBC (NCT06833073).

- **Durvalumab + monalizumab** combines anti-PD-L1 (durvalumab) plus anti-NKG2A (monalizumab) mechanisms and is intended to enhance both adaptive and innate anti-tumor immunity. The phase 2 ENHANCE study is assessing efficacy in BCG-exposed CIS or papillary NMIBC (NCT02671435).
- **Nadofaragene firadenovec + gemcitabine/docetaxel or pembrolizumab** represents another multimodal regimen seeking to improve outcomes beyond current monotherapy approaches. The ABLE-22 randomized phase 2 trial is examining this combination in high-grade, BCG-unresponsive NMIBC (NCT06545955). The protocol allows re-induction for patients without CR at 3 months, assessing for delayed response at 6 months. The design was presented at the ASCO GU Cancers Symposium, but as of mid-2025, no efficacy or safety data have been released; topline results are expected in July 2028.⁸⁹

INCORPORATING PATIENT-CENTERED COMMUNICATION, SHARED DECISION-MAKING, AND HEALTH SYSTEM NAVIGATION IN NMIBC CARE

Effective management of NMIBC demands more than technical proficiency; it requires that clinicians facilitate patient understanding, empower shared decision-making, and actively address health system barriers. These elements become especially urgent given the complexity and emotional toll of NMIBC treatment decisions. Most patients are elderly, medically complex, and face difficult choices between emerging bladder-sparing therapies and radical cystectomy. The burden of lifelong surveillance, unfamiliarity with cancer risk, and misunderstandings about trade-offs among therapies heighten anxiety and threaten adherence to follow-up. Emotional stress, including fear of recurrence and “scanxiety,” can adversely affect QoL and even outcomes, underscoring the need for empathetic, proactive communication at every stage of care.^{2,14,90}

Patient-centered communication begins by soliciting patients’ values, concerns, and goals. Clinicians should strive to explain diagnosis, prognosis, and therapeutic choices in plain language, adapting explanation to the individual’s background and health literacy. Rather than relying exclusively on technical language, physicians are encouraged to use conversational approaches—asking patients to describe in their own words what they understand about their disease and treatment options, and correcting misunderstandings as needed. It is especially important to normalize the emotional effects of an NMIBC diagnosis, discuss anticipated follow-up requirements,

and offer referrals for psychosocial support when distress is reported.⁹⁰

When presenting treatment options, including gene therapies, immunotherapy, or surgery, clinicians should neutrally describe the anticipated benefits, risks, frequency of administration, and monitoring needs for each approach. Discussing logistics and safety monitoring for novel agents can demystify treatment and foster adherence. Where appropriate, evidence-based decision aids and visual summaries can be provided to help patients weigh choices. Validated tools (eg, risk calculators or institutional treatment algorithm charts) facilitate clearer discussion of recurrence and progression risk in the context of patient values. Involving family or caregivers and inviting questions further strengthens patient engagement.^{47,91,92}

Health system navigation is an essential complement to effective communication and shared decision-making. New therapies, such as nadofaragene firadenovec (J-code: J9355) or nogapendekin alfa inbakicept (J-code: J9028), may require specialist pharmacy handling, prior authorizations, and coordination among multiple departments. Anticipating insurance or formulary barriers, financial counseling, and assistance from dedicated nurse navigators or administrative staff can minimize delays and patient frustration. Institutional protocols for biosafety, product storage, and staff training must be followed for gene therapies, with clear

explanation to patients about scheduling and procedural requirements.

For veterans or patients navigating large health systems, clinicians should proactively clarify local access pathways and help patients connect with resources unique to their care setting. Patients in the Veterans Health Administration and similar systems may benefit from early engagement with patient advocates, social workers, or resource navigators who can facilitate access to care, resolve logistical hurdles, and provide tailored information about benefits and entitlements. The efficacy of patient navigation programs in improving cancer treatment adherence, outcomes, and patient satisfaction is well-supported by systematic reviews.⁹³ Engagement with peer support groups—either veteran-specific or general cancer support networks—has also been shown to improve coping skills and satisfaction with care.^{94,95}

Because financial stress and out-of-pocket costs can lead patients to delay or forego necessary cancer care, open, nonjudgmental dialogue around drug costs, insurance coverage, travel expenses, and other financial concerns is crucial. This risk, commonly termed “financial toxicity,” has been widely recognized as a critical component of modern cancer care. Proactive communication and referral to financial counselors or navigators can help patients anticipate, mitigate, and manage these burdens, which

Patient Case: A Veteran’s Experience With Bladder-Sparing Gene Therapy



John is a 68-year-old retired US Navy veteran living in rural Virginia. His medical history includes hypertension, PTSD managed by the VA, a 45 pack-year history of cigarette smoking, and exposure to industrial solvents during active duty.

He presents to the VA primary care clinic reporting intermittent painless hematuria. Urinalysis and urine cytology are abnormal. Referral to urology and subsequent cystoscopy reveal multiple papillary lesions and CIS. John undergoes complete TURBT. Staging confirms high-risk NMIBC CIS with associated high-grade Ta lesions, no invasion into the lamina propria, and negative upper-tract imaging.

He starts standard induction BCG therapy (6 weekly instillations) and a 3-month maintenance course. However, at his 6-month surveillance cystoscopy, persistent CIS and positive cytology are observed. He is now classified as having BCG-unresponsive NMIBC.

Radical cystectomy is discussed as a guideline-recommended option; however, John declines surgery due to concerns about QoL and PTSD-related anxiety. Instead, after a multidisciplinary discussion including the urology team, oncology nurse navigator, and mental health support, John opts for bladder-sparing therapy with nadofaragene firadenovec, administered as 75-mL intravesical instillations every 3 months.

At 3 and 6 months post-treatment, John is recurrence-free with negative cystoscopy, cytology, and bladder biopsies. Mild urinary urgency is observed, but no serious AEs occur. By 12 months, John is still cancer-free, has resumed part-time volunteering at a military museum, and reports improved emotional well-being. He credits the availability of an effective nonsurgical option with maintaining his physical health and managing his PTSD.

Key Points

- John’s case exemplifies the veteran population’s unique exposures and comorbidities influencing both disease risk and treatment preferences.
- For BCG-unresponsive high-risk NMIBC, gene therapy with nadofaragene firadenovec offers a bladder-sparing alternative when radical cystectomy is not feasible or desired, particularly in patients with significant surgical risk or mental health considerations.
- Collaborative, patient-centered decision-making and engagement with VA navigation resources optimized John’s clinical outcome and QoL.

may be particularly significant for those on fixed incomes, facing multiple comorbidities, or transitioning from military to civilian insurance coverage.^{94,96,97}

A structured approach to these challenges might include:

- Conducting scheduled, uninterrupted counseling sessions dedicated to decision-making
- Summarizing follow-up and treatment pathways in both written and visual forms
- Documenting the use of shared decision-making aids and patient preferences in the medical record
- Coordinating with multidisciplinary teams (including nursing, pharmacy, navigation support, and advocacy organizations) throughout the care continuum
- Referring patients to key resources such as Cancer Care's dedicated veteran guide⁹⁵ and NCI's financial navigation resources, which offer practical support for addressing access and affordability issues⁹⁶

By intentionally centering the patient in all aspects of NMIBC management and anticipating both personal and health system barriers, clinicians can optimize outcomes—ensuring equitable access to innovative therapies, improving adherence, and maximizing quality of life throughout the cancer journey.

CONCLUSION

NMIBC remains a burdensome malignancy for patients, clinicians, and the health care system due to its high rates of recurrence, progression, and the psychosocial consequences of both treatment and surveillance. Although BCG has served as the backbone of therapy for decades, the persistent challenge of BCG-unresponsive disease has driven innovation in the field. The emergence of intravesical gene therapies and novel immunomodulatory regimens now offers patients meaningful, bladder-sparing options that are supported by clinical trial data and growing real-world experience. Individualized risk stratification grounded in current staging and grading paradigms guides the use of such therapies and ensures that patients receive optimal, evidence-based care.

Success in NMIBC management now requires not only mastery of evolving treatment pathways and multidisciplinary decision-making, but also the intentional application of patient-centered communication, shared decision-making, and effective health system navigation. By staying updated on therapeutic advancements and proactively addressing patient values, logistical barriers, and disparities in access, clinicians can help maximize cure rates, QoL, and long-term outcomes for all individuals confronting NMIBC.

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