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Intravesical Therapy for Non-muscle Invasive Bladder Cancer—Current and Future Options in the Age of Bacillus Calmette-Guerin Shortage

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Non-muscle invasive bladder cancer (NMIBC) is a common and burdensome malignancy. A substantial proportion of patients with intermediate- and high-risk disease will progress to invasive bladder cancer and are at a significant risk for metastasis and death. Bacillus Calmette-Guerin (BCG) therapy for selected cases has been the standard of care for nearly 40 years. Unfortunately, a world-wide shortage has made BCG challenging to obtain. Furthermore, recurrences and progressions do occur. With the US Food and Drug Administration creating a clear path to drug approval for novel treatments, many therapies have been tested, including intravesical cytotoxic chemotherapy, intravesical immunotherapy, systemic immunotherapy, and novel agents, such as gene therapy and targeted therapy. In this review, we highlight ongoing clinical trials.

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KEY WORDS

Bladder cancer • Intravesical treatment • Non-muscle invasive bladder cancer • Immunotherapy • BCG shortage

In the United States, there will be an estimated 81,000 new cases of bladder cancer in 2019, with >70% presenting as non-muscle invasive bladder (NMIBC).^{1,2} Although NMIBC usually carries

a favorable prognosis, there is a high risk of disease recurrence and a 10% to 20% risk of progression to muscle-invasive disease.³ The common treatment for intermediate- and high-risk patients is a transurethral

resection followed by intravesical therapy with bacillus Calmette-Guerin (BCG), a non-specific immunotherapy that has remained the gold standard for 40 years. This therapy, although shown to reduce tumor recurrence and progression, still has a 50% risk of failure.⁴ BCG failure has been variably defined in the literature and likely represents a heterogeneous group of patients. Nevertheless, these patients are at a high risk of progression to invasive and metastatic disease. The most definitive therapy with the greatest chance of cure is radical cystectomy with urinary diversion.⁵ However, there is a significant interest and need for organ-sparing treatments for this cohort of patients with limited non-invasive options.

New intravesical and systemic agents for all risk categories of NMIBC are now being evaluated in clinical trials. There has been an explosion in the number of early and late-phase clinical trials for patients who fail BCG. There are several reasons for this invigorated interest in the BCG failure space. First, only one drug, valrubicin—with admittedly low efficacy—is approved by the US Food and Drug Administration (FDA) for patients who fail BCG, making this a highly unmet medical need. Second, a worldwide shortage of BCG has limited the numbers of patients receiving adequate induction and maintenance, resulting in higher recurrence and failure rates. Finally, the FDA has underscored the urgency of this need and set a well-defined threshold for approval of novel therapies that does not require a randomized trial. Consequently, several drugs have shown promise in this space and will likely change the landscape of management of BCG failure.

Methodology

We conducted a literature search using clinicaltrials.gov, Ovid MEDLINE, and PubMed databases that included the following search terms: *non-muscle invasive bladder cancer, BCG failure, intravesical therapy, immunotherapy, targeted therapy*. We identified literature as recent as March 1, 2018. Recent abstracts from the American Urological Association (AUA), Society of Urologic Oncology (SUO), and the American Society of Clinical Oncology (ASCO) annual meetings were reviewed, and relevant abstracts from articles published in English were included.

Current Guideline-recommended Strategies

Initial Endoscopic Resection and Risk Stratification

The standard approach for initial treatment of NMIBC is a transurethral resection of a bladder tumor (TURBT). A visually complete TURBT provides critical staging information and surgeon experience is known to affect the rates of complete resection.⁶ The impact on treatment and overall prognosis is significant enough that both the AUA/SUO and European Association of Urology (EAU) guidelines recommend restaging TURBT in select patients.⁷ Several checklists and bladder maps are available and have been studied to help improve the quality of TURBT.⁷ Furthermore, a visually complete TURBT is known to aid the efficacy of future intravesical therapies. Therefore, the importance of the quality of TURBT cannot be overemphasized.

Although the definitions differ slightly, both the AUA/SUO and EAU guidelines recommend risk classifying patients into low, intermediate, and high risk at the time

of each endoscopic resection in order to guide further therapy and surveillance (Table 1).⁷ For low-risk patients, a single dose of intravesical chemotherapy within 24 hours is recommended. Traditionally, mitomycin-C (MMC) has been used. However, adherence to this recommendation has been notoriously poor.⁸ Recently, intravesical gemcitabine has been shown to improve recurrence-free survival to rates like those seen with MMC, although no randomized comparison data are available.⁹ For intermediate-risk disease, induction with either intravesical chemotherapy (eg, MMC) or immunotherapy (eg, BCG) and 1 year of maintenance therapy is recommended. For high-risk disease, guidelines recommend induction BCG followed by 1 to 3 years of maintenance BCG (EAU) or 3 years of maintenance BCG (AUA/SUO).

Adequate BCG Therapy and Definitions of Failure

BCG is debatably the most effective immunotherapy for any cancer. First used for bladder cancer over 40 years ago by Morales and colleagues, the mechanism of action is still incompletely characterized but functions via the innate and adaptive immune system to illicit a significant local inflammatory response, resulting in tumor-cell killing.¹⁰ The BCG treatment schedule consists of 6 weekly instillations, termed *induction therapy*, followed by 3 weekly instillations, termed *maintenance therapy*, at 3 and 6 months and then every 6 months thereafter for 3 years, totaling 27 instillations. BCG therapy results in complete response rates up to 66% in high-risk patients.¹¹ However, complete courses of BCG are rare, as only 16% of patients in the pivotal SWOG study were able to complete all 27 instillations and recent estimates suggest that the

TABLE 1

AUA NMIBC Risk Stratification		
Low Risk	Intermediate Risk	High Risk
Single low-grade Ta lesion ≤3 cm	Recurrence within 1 y; low-grade Ta	Any recurrent high-grade Ta
Papillary urothelial neoplasm of low malignant potential	Single low-grade Ta >3 cm	High-grade T1
	Low-grade Ta, multiple lesions	Carcinoma in situ
	High-grade Ta ≤3 cm	High-grade Ta >3 cm or multiple lesions
	Low-grade T1	BCG failures in high-grade patient
		Variant histology; lymphovascular invasion; high-grade prostatic urethral invasion

Adapted from Chang SS et al.⁷

AUA, American Urological Association; BCG, bacillus Calmette-Guerin; NMIBC, non-muscle invasive bladder cancer.

real-world number is significantly lower.¹² Therefore, adequate BCG therapy has been defined, which also aids in homogeneity for clinical trial purposes. Adequate BCG is at least 5 of 6 instillations of induction therapy and at least 2 of 3 maintenance instillations for at least 6 months.⁷

BCG failure has been variably defined in the literature and

contributes to some of the heterogeneity in outcomes seen with different therapies. Currently, BCG failure is subcategorized into refractory, relapsing, unresponsive, or intolerant disease (Table 2).^{13,14} *BCG refractory disease* is persistent high-grade disease at 6 months following adequate induction and maintenance, or any stage and/or grade progression at 3 months

following induction. *BCG relapsing disease* is high-grade disease after a disease-free interval of ≥6 months after adequate BCG therapy. *BCG unresponsive disease* is defined as BCG refractory and BCG relapsing disease. These patients are at the highest risk of progression. Finally, BCG intolerance includes any cessation of therapy secondary to side effects. Classification of BCG

TABLE 2

BCG Failure Definitions	
BCG Refractory Subcategories	Definition
BCG refractory	Persistent high-grade disease at 6 mo following adequate induction and maintenance, or any stage and/or grade progression at 3 mo following induction
BCG relapsing	High-grade disease after a disease-free interval of ≥6 mo after adequate BCG therapy
BCG unresponsive	BCG refractory and BCG relapsing disease; these patients are at the highest risk of progression
BCG intolerance	Includes any cessation of therapy secondary to side effects.

BCG, bacillus Calmette-Guerin.

failure is critically important to adequately understand the prognosis of disease and accurately characterize patient cohorts in clinical trials.

Ultimately, all BCG failures should seriously consider radical cystectomy as the most effective form of salvage therapy. However, many patients will opt for bladder-sparing treatment options and will sacrifice some efficacy to preserve their native bladders. Valrubicin is currently the only drug approved by the FDA for salvage intravesical therapy in patients who fail BCG with carcinoma in situ (CIS).¹⁵ This is despite data showing a meager 20% or less of patients remaining recurrence-free at 12 months and 8% of patients after 12 months.¹⁶

BCG Shortage and Its Implications

BCG is a live attenuated strain of *Mycobacterium bovis* initially used to vaccinate against tuberculosis but ultimately found its way as an intravesical immunotherapy for bladder cancer in the late 1970s. Despite its gold standard status and widespread success in the treatment of intermediate- and high-risk NMIBC, several controversies have arisen specifically regarding the economics of BCG. Currently there is a critical shortage of this life-saving treatment due in part to the lengthy and costly manufacturing process, a shrinking number of FDA-approved companies producing the drug, possible financial disincentives, and increased demand.

BCG is notoriously challenging to produce. The bacteria must be fermented in approved manufacturing laboratories and the process is almost unchanged since its inception in 1921.¹⁷ Production for a single batch can take up to 3 to 4 months. Furthermore, given this multistep

and often unpredictable process, irregularities can occur that affect the yield and quality of the bacteria. Finally, the sheer volume of BCG required for the treatment doses used in bladder cancer is astronomical compared with volumes used for vaccination doses.¹⁸ Compiled on top of this challenging production process, several manufacturing setbacks have created shortages over the past decade. In 2012, Sanofi Pasteur Limited discontinued production of ImmuCyst®—the Connaught substrain and the most commonly used strain of BCG in the United Kingdom and the United States—secondary to a flood in a manufacturing area in Toronto, Canada.¹⁹ Plagued by continued production issues, Sanofi had to completely shut down production of BCG by the middle of 2017. Subsequently, OncoTICE®, the Merck strain of BCG, became the most widely available form but met its own challenges with increased demand. Fast-forward to 2019 and we are on the precipice of another BCG shortage that again will have far-reaching consequences for patients with NMIBC.

In response to the current critical shortage, a joint statement from leading US-based urology associations was released in February 2019 that contained several proposed strategies to help minimize the impact of the BCG shortage on patients with NMIBC.²⁰ The strategies are presented in Table 3. Most importantly, these strategies are at the discretion of the treating physician and should be made on a case-by-case basis, tailored to the patient and their disease.

Therapeutic Options and Clinical Trials

Low-risk NMIBC

Perioperative Adjuvant Therapies.

Both AUA/SUO and EAU guidelines

recommend a single perioperative dose of intravesical chemotherapy, generally within 24 hours, following endoscopic resection of presumed low-risk papillary NMIBC. Based on the meta-analyses of several clinical trials, adjuvant chemotherapy has a relative risk reduction of approximately 0.50 and an absolute risk reduction of 10% to 15%.³ Multiple institutional and population-level studies have demonstrated poor compliance with this guideline recommendation.²¹ Attributed to relative contraindications for its use and the potential for serious side effects, MMC has largely fallen out of favor. Recently, a randomized trial compared perioperative intravesical gemcitabine with placebo and showed a relative and absolute risk reduction of recurrence like that seen with MMC.⁹ Other potential adjuvant therapies included apaziquone, an alkylating prodrug, that failed to demonstrate a significant improvement in recurrence-free survival in two phase 3 randomized trials.²² Currently, another trial using apaziquone is being conducted (NCT03224182) and results are forthcoming.²³

Primary Chemoablative Therapies.

An interesting novel area of research is primary chemoablation for low- and intermediate-risk NMIBC. Ablative therapies are ideal for patients who may otherwise be unable to tolerate in-office fulguration or more invasive procedures in the operating room secondary to medical comorbidities. A phase 2 (NCT02070120) and phase 3 (NCT03348969) trial are evaluating the role of MMC as a chemoablative agent. In the phase 2 CALIBER trial, preliminary results presented at the AUA Annual Meeting in 2018 demonstrate complete response in 37% of patients.²⁴ In the phase 3 trial, investigators

TABLE 3

Strategies to Minimize BCG Use During Shortages

- Avoid BCG in patients with low-risk disease.
- Intravesical chemotherapy is the first-line option for patients with intermediate-risk NMIBC.
- Utilize alternative intravesical chemotherapy rather than BCG for patients who would normally receive BCG as a second-line therapy for intermediate-risk NMIBC.
- For high-risk NMIBC, high-grade T1 and CIS patients undergoing induction therapy should be prioritized for full-strength BCG. If not available, then employ reduced 1/2 to 1/3 dose.
- If the BCG stocks available for maintenance therapy for NMIBC patients, attempt 1/3 dose BCG and limit doses to 1 year.
- During a BCG supply shortage, do not utilize maintenance therapy and limit induction BCG to BCG-naive patients with high-risk disease.
- If no BCG is available, then physicians should consider mitomycin for induction and maintenance up to 1 year. Other options include gemcitabine, valrubicin, epirubicin, docetaxel, sequential gemcitabine/docetaxel, and/or mitomycin.
- Patients with high-risk features who after shared decision making are not willing to accept alternative intravesical agents should be offered initial radical cystectomy.
- When a 1/2 to 1/3 dose is used, maximize resources by treating multiple patients in the same day to avoid wasting BCG; coordinate with pharmacy prior to split dosing.

BCG, bacillus Calmette-Guerin; CIA, carcinoma in situ; NMIBC, non-muscle invasive bladder cancer.

At the time of this writing, it is still unclear how split-vial dosing of BCG will be billed. The AUA is currently working with the Centers for Medicare & Medicaid Services (CMS) to determine the next step. Therefore, it is important for physicians to discuss with the insurance company prior to split dosing.

Adapted from American Urological Association.²⁰

are evaluating biomarkers of chemotherapeutic sensitivity in patients to guide further treatment. Results are forthcoming.²⁵ In data presented by our group at the AUA Annual Meeting in 2017, in collaboration with UroGen Pharma, a reverse thermosensitive hydrogel formulation of MMC was able to yield a complete response rate of 73% after a 6-week induction course and a 61% recurrence-free survival at 12 months without any maintenance therapy.²⁶ Currently, the OLYMPUS Phase II study is open for patients with intermediate-risk disease.

Intermediate- and High-risk NMIBC

Therapy for BCG-naive Patients. Currently, guidelines for intermedi-

ate- and low-risk patients for adjuvant therapy to prevent recurrence and progression clearly recommend induction BCG followed by 1 to 3 years of maintenance. Alternative strategies to curb the shortage of BCG as described above are exceptions. Nevertheless, novel therapies are needed to fill gaps left by a limited supply of BCG. First, additional strains of BCG used in other countries should be evaluated for potential approval by the FDA. To this end, SWOG S1602, led by Dr. Robert Svatek, seeks to evaluate the Japanese Tokyo strain against the TICE strain, as well as the effect of priming with intradermal BCG.²⁷ Approval of an additional strain could significantly curb the shortage.

Several systemic agents are making their way into the BCG-naive

space, although they are primarily being evaluated in the higher-risk cohort of patients who fail BCG. These clinical trials will evaluate pembrolizumab (NCT03504163,²⁸ NCT03167151²⁹) and durvalumab (NCT03528694³⁰). Novel agents in clinical trials for patients who fail include an intravesical typhoid vaccine call Ty21a (NCT03421236³¹), intravesical TSD-001 (NCT03081858³²), vesigenurtacel-L (NCT02010203³³), and tamoxifen citrate (NCT02197897³⁴).

Therapy for Patients Who Have Failed BCG

Patients who have failed BCG, particularly patients in the BCG unresponsive group, have the highest rates of disease progression and death from bladder cancer.

Furthermore, patients in this cohort have few additional options. Therefore, most clinical trials target this cohort of patients.

Intravesical Chemotherapy. Intravesical chemotherapy has been shown to have promising results in the treatment of NMIBC. However, combination intravesical therapy in patients who have failed BCG therapy has been shown to be even more fruitful. Initial preclinical studies used a genetically engineered mouse predisposed to progression from carcinoma in situ (CIS) to metastatic bladder cancer. In one study, they compared the results of instilling intravesical cisplatin, gemcitabine, and/or docetaxel alone or by combining two agents.³⁵ They found that gemcitabine (pyrimidine analog that inhibits cell growth and induces apoptosis) was the single most effective agent at preventing progression to invasive disease. However, a combination of two agents, especially those that included gemcitabine, was significantly more effective at reducing tumor burden. A multi-institutional study investigating the efficacy of sequential intravesical gemcitabine and docetaxel showed recurrence free rates of 48% at 1 year and approximately 40% at 2 years.³⁶ The successes observed in these studies was the impetus for a phase 1 trial investigating the safety profile of an intravesical triple agent salvage chemotherapy consisting of cabazitaxel (a taxane that inhibits microtubule polymerization), gemcitabine, and cisplatin. This regimen was used in patients who were BCG refractory or who had recurrent high-risk NMIBC who refused a cystectomy. Early results, published in 2017, showed a relatively benign safety profile in 8 patients with 4 patients experiencing only a grade 2 toxicity.³⁷ Importantly, all patients were able to complete 6 weeks of induction

therapy. At 6 weeks, 7 out of 8 patients had a complete response to treatment.

Systemic Immunotherapy. The realization that bladder cancer is highly sensitive to immune checkpoint inhibition (ICI) has revolutionized the treatment of advanced and metastatic disease. Sensitivity to immunotherapy, including ICI, stems from the high mutational burden of bladder cancer.³⁸ Utilization of these therapies has moved proximal from metastatic and advanced disease and are now being evaluated in NMIBC. Briefly, programmed cell death protein-1 (PD-1) is a checkpoint protein found on T cells that acts like an off switch to prevent immune cells from attacking other cells. PD-1 is activated when it attached to program death ligand-1 (PD-L1), which is found on both normal and malignant cells.³⁹ Therefore, malignant cells with high PD-L1 expression can evade the immune system. Specifically, in bladder cancer, higher levels of PD-L1 expression has been shown to correlate to higher grade tumors, worsened survival, and increased risk of recurrence.^{40,41} PD-L1 tumor cell expression was even associated with increased resistance to BCG therapy.⁴²

There are several clinical trials investigating the role of these checkpoint inhibitors for NMIBC, four of which are investigating the role of pembrolizumab in NMIBC. The first trial combines both intravesical pembrolizumab and BCG in patients with high-risk or BCG-refractory NMIBC.⁴³ This study is currently recruiting patients with an estimated enrollment of 27 and an estimated study completion date of February 2020. The second clinical trial compares intravenous and intravesical pembrolizumab in patients with intermediate-risk

recurrent NMIBC.²⁹ This clinical trial has an estimated enrollment of 36 patients and an estimated study completion date of August 2021. The third clinical trial, KEYNOTE 057, is a phase 2 trial for patients with high-risk NMIBC unresponsive to BCG.⁴⁴ In the first cohort to yield preliminary results, patients with CIS, with and without papillary disease, had a complete response rate of 40% at 3 months and 53% of these complete responders have a median duration of response of 12.7 months. Additionally, the adverse events in this cohort were manageable with only 12% to 15% of patients having a grade 3 or 4 adverse event.⁴⁵ There are currently 260 patients enrolled in this study with an estimated completion date of July 2023. Ongoing is a randomized, controlled phase 3 trial called KEYNOTE 676, which is testing pembrolizumab in combination with BCG versus BCG alone in patients refractory to BCG induction, which will further test this agent's role in high-risk BCG unresponsive NMIBC. There are currently 550 patients enrolled in this study with an estimated completion date of November 2024.⁴⁶

Other checkpoint inhibitor agents in clinical trials are atezolizumab and durvalumab. Two clinical trials investigate intravenous atezolizumab either in combination with BCG or alone for patients with recurrent BCG unresponsive NMIBC.⁴⁷ Only one of these trials (NCT02844816) is actively recruiting patients and has 162 patients enrolled and an estimated completion date of February 2020. The clinical trial investigating IV durvalumab is a phase 2 study for patients with BCG refractory urothelial CIS with 34 patients enrolled and a study completion date of December 2021.⁴⁸ Another clinical trial will evaluate the

use of intravesical durvalumab for patients with BCG-refractory NMIBC is actively recruiting patients.⁴⁹ Finally, POTOMAC is a phase 2, randomized, multicenter study investigating durvalumab either with BCG or alone in high-risk, BCG-naive NMIBC with 975 patients currently enrolled and an estimated completion date of November 2024.⁵⁰

ALT-803, a product of the Altor BioScience corporation, has a received Fast Track designation from the FDA. Interleukin-15 (IL-15) is a protein that induces the proliferation of natural killer cells and thereby enhances the anti-tumor immunity of cytotoxic T-cells.^{51,52} ALT-803 is a recombinant IL-15 superagonist complex found to have superior anti-tumor activity compared with the native IL-15 molecule.⁵³ This drug has been found in preclinical studies to have a rapid and durable responses against multiple malignancies and virally infected cells, allowing for a potential role in targeted treatments and vaccines.^{52,54} As a result of these successes, ALT-803 is being investigated in a phase 1b/2 trial in combination BCG in BCG-naive patients with high-grade NMIBC. A late-breaking abstract of the phase 2 registration study at the Society of Immunotherapy for Cancer showed significant response at 3 months.⁵⁵ A second phase 2 trial is studying intravesical ALT-803 in combination with BCG for BCG unresponsive NMIBC patients.⁵⁶

Gene Therapy. Nadfaragene firadenovec/Syn3 (rAD-IFN/Syn3; formerly instiladrin) is another agent that was recently awarded Fast Track designation by the FDA. Interferon (IFN) has been shown in several studies to have promising results in NMIBC; however, it was ineffective due to limited contact

with the bladder urothelium.⁵⁷ rAD-IFN/Syn3 is a recombinant adenovirus vector that results in INF expression. This recombinant adenovirus (rAd)-mediated IFN α 2b protein is co-administered with a polyamide surfactant, Syn3, that improves adenoviral transduction into the urothelial lining. Once inside the urothelial cells, the α 2b gene is translated by the cells' internal DNA machinery, resulting in the secretion of high quantities of interferon α 2b protein, thereby enhancing the body's natural cancer defense system. The initial phase 1 trial investigated this agent in NMIBC patients unresponsive to BCG therapy and showed that 43% of patients with IFN- α detectable in the urine had a complete remission at 3 months with durable response for 31 months.⁵⁸ Additionally, patients tolerated this agent well. The phase 2 studies showed that 35% of BCG non-responders were disease-free at 1 year.⁵⁸ There is currently a phase 3 study investigating the safety and efficacy of a high dose of rAD-IFN/Syn3 in the same patient population.⁵⁸

CG0070 is an oncolytic adenovirus that preferentially replicates in a deregulated retinoblastoma pathway found commonly in bladder tumor cells. The initial phase 1 study demonstrated a benign safety profile and patients who were BCG unresponsive or refused cystectomy had a complete response (CR) rate of 48.6% and a median duration of complete response of 10.4 months.⁴ The phase 2 study showed an overall CR rate at 6 months of 50% for patients with CIS.⁴ Additional interim analysis showed a CR of 30% at 12 months.⁵⁹

Targeted Therapy. Vicinium is recombinant fusion protein consisting of an epithelial cell adhesion molecule (EpCAM)-specific anti-

body fragment fused to a pseudomonas exotoxin. This drug targets the EpCAM antigen found to be overexpressed in urothelial tumor cells.⁶⁰ Once vicinium binds to the EpCAM antigen on the tumor cells, the drug is internalized and irreversibly blocks proteins synthesis, inducing cell death.⁶¹ This drug was evaluated for patients with high-grade, BCG-unresponsive NMIBC, in phase 1 and 2 studies and had an excellent safety profile.⁶² In CIS patients, the complete response rate at 3 months was 40% in a phase 2 trial.⁶² This trial is currently in phase 3 of evaluation with interim results showing a 42% complete response in CIS patients and only 4% of patients with a grade 3 or higher adverse event.⁶³ There is also a phase 1 clinical trial that is investigating the combination of durvalumab and vicinium for NMIBC patients intolerant or unresponsive to BCG.⁶⁴ Preclinical work with an earlier form of vicinium demonstrated an abscopal effect and synergy when used with an ICI, which was the impetus for this particular trial. There are currently 40 patients in this trial with an estimated study completion date of July 1, 2021.⁶⁴

Conclusions

NMIBC is a common and potentially lethal cancer. Unfortunately, the mainstay of treatment, BCG is in short supply with a dwindling number of producers. Several novel agents have made it to Fast Track status from the FDA and are pending approval. Novel agents include various other combinations of different cytotoxic therapies, systemic ICI, intravesical ICI, and other agents, such as gene therapy and targeted therapy. In the future, ideal treatments would be tailored to the specific somatic mutations present within the tumor. ■

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MAIN POINTS

- The current mainstay of treatment for non-muscle invasive bladder cancer, bacillus Calmette-Guerin (BCG), is in short supply with a dwindling number of producers. It is paramount to explore alternative therapies.
- Novel agents include various other combinations of different cytotoxic therapies, systemic immune checkpoint inhibition (ICI), intravesical ICI, and other agents, such as gene therapy and targeted therapy.
- In the future, ideal treatments would be tailored to the specific somatic mutations present within the tumor.

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