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Pharmacologic Therapies for Non-Muscle Invasive Bladder Cancer: Current and Future Treatments

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Abstract

Bladder cancer is the sixth most common malignancy in the United States and 70% of cases are non-muscle invasive at the time of diagnosis. Effective treatment is crucial to prevent progression, which occurs in about 30% of patients. The American Urological Association (AUA) guidelines recommend treatment of non-muscle invasive bladder cancer (NMIBC) with intravesical Bacille Calmette-Guerin (BCG) and chemotherapy. However, ongoing shortages and high rates of BCG unresponsiveness creates a major need for novel therapies. In this narrative review, we discuss the evolving landscape of therapeutic options for NMIBC. Pembrolizumab, an anti-programmed cell death (PD)-1 antibody, was the first systemic therapy to be FDA-approved for BCG-unresponsive, high-risk disease. Promising new agents under investigation include various other checkpoint inhibitors and adenovirus-based therapies including CG0070 and nadofaragene firadenovec (rAd-IFNa/Syn3). Finally, new mechanisms of drug delivery are under investigation, including delivery with the GemRIS (TAR-200) device and delivery of intravesical chemotherapy at higher temperatures. With the promise of novel therapies on the horizon, we can expect the role of urologists in the management of NMIBC to evolve and expand.

Keywords: Urinary bladder neoplasms, Neoplasm invasiveness, Administration, Intravesical, Drug delivery systems, Salvage therapy, Immune checkpoint inhibitors

Introduction

Bladder cancer is the sixth most common cancer overall (fourth most common in men), and the second most frequently diagnosed genitourinary cancer in the United States. The American Cancer Society estimates 83,730 new cases of bladder cancer in 2021 [1]. Approximately 70% of bladder cancer is non-muscle invasive at the time of diagnosis, so treatment is crucial to prevent progression, which occurs in about 30% of patients [2]. The recurrence rate is estimated at 50-70% [3]. Largely because of the intensive surveillance required for high recurrence and progression rates in patients with non-muscle invasive bladder cancer (NMIBC), treatment for bladder cancer has the highest cost per patient from diagnosis to death of all cancers [4-6]. In this narrative review, we discuss the evolving landscape of intravesicular and systemic treatment options.

Methods

We performed a narrative review using PubMed, Google Scholar, Clinical Key, and Wiley Online Library of articles between the years of 1980 and 2021. Search terms included combinations of terms such as "non-muscle invasive bladder cancer," "guidelines," "pharmacotherapy," "salvage therapy," and "immunotherapies." Only original articles published in English were included. Editorials and media articles were not included.

For clinical trial information, we searched www.clinicaltrials.gov. This was accessed in September of 2021. We included Phase II-IV trials. This is not a comprehensive list of all trials for NMIBC. The search terms: "non-muscle invasive bladder

cancer" and "NMIBC" were used. Trials classified as "withdrawn" were excluded.

Review

Non-muscle invasive bladder cancer (NMIBC) risk stratification

NMIBC is a broad disease, which has led to a 3-group stratification system that refers to the risk of progression: low, intermediate, and high risk. The AUA stratification considers tumor grade, size, extent of invasion, focality, presence of lymphovascular invasion, variant histology, and response to prior therapy. Different organizations have minor variations on this classification system. AUA and European Urologic Association (EUA) guidelines are outlined in Table 1 [7-9].

The treatment algorithm differs by risk category. For low-risk and intermediate-risk NMIBC, transurethral resection of bladder tumor (TURBT) with a single dose of perioperative intravesical chemotherapy is recommended. For intermediate risk NMIBC, a six-week induction course of adjuvant intravesical therapy with chemotherapy or Bacille Calmette-Guerin (BCG) is recommended. For high-risk disease, an induction course of intravesical BCG therapy is recommended as first line treatment and has been shown to be superior to chemotherapy [10-12]. Depending on response to treatment, intermediate or high-

risk patients may then undergo maintenance therapy [13].

Intravesical therapy: BCG and chemotherapeutic agents

BCG first came into use in 1921 as a vaccine against tuberculosis (TB). It is a live-attenuated form of the mycobacterium that causes bovine TB. In 1976, Moralis et al. published a paper on the use of BCG for bladder cancer, launching its use as anti-tumor therapy [14]. The mechanism of action involves an infection of tumor cells with BCG through interaction with the extracellular glycoprotein fibronectin. BCG is internalized, activating the reticuloendothelial system though antigen presentation. Subsequently, a cell-mediated immune response occurs with release of cytokines; TNF-a, Interferon, and Interleukin (IL)-1, 6, 8, 10, and 12 have all been implicated [15]. There is also increasing evidence that a Th1 cell-mediated immune response involving neutrophils, macrophages, and dendritic cells is largely responsible for its antitumor activity [16].

Perioperative chemotherapy: There are a variety of chemotherapeutic agents used in the immediate post-operative period, within 24 hours of TURBT. Mitomycin c, gemcitabine, and anthracyclines such as epirubicin can be used as one-time doses following TURBT for low and intermediate-risk disease. In general, perioperative intravesical chemotherapy has been estimated to decrease recurrence

Table 1: Adapted from the AUA and EAU guidelines.		
	AUA	**EUA**
LOW-RISK TUMORS	LG solitary Ta ≤ 3cm	Primary, solitary, Ta G1 (Papillary urothelial neoplasm of low malignant potential), <3 cm, no CIS
	Papillary urothelial neoplasm of low malignant potential	
INTERMEDIATE-RISK TUMORS	Recurrence within a year, LG Ta	Tumors not defined by low-risk and high-risk categories
	Solitary LG Ta>3 cm	
	Multifocal LG Ta	
	HG TA, ≤ 3 cm	
	LG TA	
HIGH-RISK TUMORS	HG T1	Any of the following:
	Any recurrent HG Ta	T1 tumor
	HG TA, >3cm, or multifocal	G3 (HG) tumor
	Any CIS	CIS
	Any BCG failure in HG patient	Multiple, recurrent, and >3cm Ta G1G2 tumors
	Any variant histology	
	Any lymphovascular invasion	
	Any HG prostatic urethral involvement	
LG: Low Grade; HG: High Grade		

rates by approximately 35% [17]. In a phase III randomized clinical trial by Messing et al., intravesical gemcitabine was administered for an hour following TURBT for patients with low-risk NMIBC. Recurrence at 4 years was 35% compared to 47% in a group receiving intravesical saline largely supporting the use of gemcitabine in this setting [18].

Adjuvant intravesical therapy: In the seminal trial in 1980 by Lamm et al., patients with superficial bladder cancer were randomized to receive either TURBT or TURBT plus BCG, with BCG given intravesically and percutaneously at weekly instillations for 6 weeks at 1-2 weeks following TURBT. Those who received BCG had significantly reduced tumor recurrence at one year follow up [19]. The six-week induction course of intravesical BCG is now utilized for intermediate and high-risk disease, as mentioned above.

Both mitomycin and epirubicin have also been studied using multiple instillations as induction therapy following TURBT for multifocal/recurrent low-risk disease or for intermediate-risk disease [20]. Gemcitabine has recently been shown to have less toxicity than mitomycin with similar efficacy. A randomized phase III trial of patients with recurrent NMIBC found recurrence at 36 months in 28% receiving gemcitabine compared to 39% for patients treated with mitomycin. There were also significantly less irritative lower urinary tract symptoms, one of the most common adverse effects of mitomycin [21,22]. Finally, thiotepa, an alkylating agent, was the first FDA-approved intravesical chemotherapy. It has largely fallen out of favor due to its significant side effect profile, including lower tract irritant symptoms as well as myelosuppression [23].

Maintenance intravesical therapy: In patients who have an appropriate response to induction therapy, the AUA recommends at least a year of maintenance therapy for those with intermediate-risk disease. Three years of maintenance has been demonstrated to decrease recurrence rates for high-risk disease, but not intermediate-risk disease [24]. According to the AUA guidelines, standard therapy for BCG is induction with at least one year of maintenance for intermediate-risk disease, with three years of maintenance recommended for high-risk disease [13]. An EORTC clinical trial showed one year of maintenance therapy to be sufficient for intermediate-risk disease [25]. On the other hand, three years of therapy is the recommendation for high-risk disease as it is associated with a decreased risk of recurrence compared to one year [25]. Many institutions utilize the Lamm/Swog protocol consisting of BCG triplets at 3, 6, 12, 18, 24, 30 and 36 months [26].

BCG maintenance therapy has shown superiority to intravesical chemotherapy in terms of reducing recurrence rates. A large EORTC-GUCG meta-analysis found a 32% decrease in the risk of recurrence in patients with NMIBC treated with BCG maintenance compared to those receiving mitomycin [27]. There have been similar findings for epirubicin. The EORTC randomized phase III trial 30911 evaluated induction

and maintenance therapy of at least one year of BCG compared to epirubicin in patients with both intermediate and high-risk NMIBC. The risk of recurrence was significantly less in the BCG cohort compared to the epirubicin cohort (32.8% vs 52.7%) as was the risk of death from bladder cancer (6.8% vs 3.4%) through a median follow-up of 9.2 years. Overall, mortality from bladder cancer was 4.5% [28]. Likewise, for patients with carcinoma in situ (CIS), complete response was obtained in 34% patients on doxorubicin vs 70% for patients on BCG. BCG was superior for those with Ta and T1 tumors as well [29].

Beyond BCG

Intravesical BCG is the recommended therapy for patient with high-risk NMIBC. However, there has been an ongoing global shortage of BCG over the last few years, raising concern over allocation of this therapy. Shortages of BCG creates ethical dilemmas over the judicious allocation of resources. Ethical frameworks such as the accountability for reasonableness (A4R) are often utilized in the setting of shortages of oncologic drugs [30].

Dose reduction: For BCG, commonly used strategies include reducing the dose of maintenance therapy. A one-third dose-reduction was shown to be non-inferior in terms of progression and survival and seems to be the minimal effective dose with maintenance duration of one year [25,31]. Reducing frequency of therapy on the other hand was associated with shorter time to recurrence [25]. Restricting BCG use to only high-risk patients, cutting maintenance, and offering radical cystectomy for very high-risk disease are other strategies that have been posited [32].

Alternate strains: Using alternate strains of BCG is another way to combat shortages. Several strains of BCG exist but only the TICE strain is currently marketed in the U.S. Armond-Frappier and Connaught are also FDA approved, but not currently in production. Different BCG strains have been shown to vary in terms of immune alterations and reactions when given as a vaccine for TB. While some animal studies indicated superiority of certain strains of BCG in the treatment of NMIBC, a recent systematic review failed to identify any significant differences in recurrence across BCG strains – Tokyo, Pasteur, and TICE all showed significant decreases in recurrence compared to intravesical chemotherapy for stage Ta, T1, or CIS disease [33]. Multiple studies are currently investigating other BCG stains. The Phase III Swog1602 clinical trial is an ongoing trial comparing Tokyo-172 to TICE in patients with BCG-naïve high-grade NMIBC. Moreover, the NCT03982797 Phase II clinical trial is investigating the Moreau strain for high-risk disease. Depending on the outcome, therapy with new strains of BCG may be on the horizon, making this therapy more widely available.

Definitions of BCG failure: Approximately 40% of patients with NMIBC will ultimately fail BCG therapy [2]. Efforts have been made to clearly delineate categories of BCG failure. BCG refractory is defined as continued disease after 6 months of

maintenance or re-treatment at 3 months. BCG relapsing is disease recurrence after achieving a disease-free status at 6 months. BCG intolerant refers to disease recurrence in the setting of an inadequate treatment course due to symptom intolerance or serious adverse event requiring termination of treatment. Finally, BCG resistant refers to recurrent disease at 3 months after induction but at a lower stage or grade, followed by complete response at 6 months [34].

Recently, standard guideline definitions were put out to decrease discrepancy in clinical trial design. These definitions are predicated on the receipt of adequate BCG and define a population that will not benefit from further BCG. Adequate BCG therapy is defined as at least 2 courses of BCG. This includes 5/6 induction doses plus at least 2/3 doses of maintenance therapy or at least 2/6 doses of a second induction therapy. Should BCG shortages necessitate dosing and schedule changes, these definitions may need to be adjusted. BCG-unresponsive disease refers to patients who have high-grade recurrence following adequate BCG therapy. The term encompasses both BCG refractory and BCG relapsing. Interestingly, Li et al. found that there is an inherent difference in prognostic implications for patients with BCG-unresponsive disease. Comparing patients with recurrence after *adequate* BCG therapy to those with recurrence after only one induction course showed significantly lower cystectomy-free survival and rates of recurrent disease (77% vs 22% 5-year high grade recurrence) [35]. This elucidates the need for better alternatives for high-grade BCG-unresponsive disease.

Salvage treatment options for BCG-unresponsive NMIBC

In the case of BCG failure, cystectomy is the recommended therapy, but many patients are unable or unwilling to undergo this major procedure. The complication rate of this operation reaches 64% within 90 days post-surgery with mortality of about 4% [36]. Therefore, there is a need for alternative salvage therapy in this patient population.

Salvage intravesical chemotherapy: Salvage chemotherapy for patients with BCG- unresponsive disease has been difficult to evaluate given the previously non-standardized definitions of BCG-unresponsiveness and lack of prospective data. Currently, the only FDA-approved salvage intravesical therapy is valrubicin, a semisynthetic analogue of doxorubicin that is approved for BCG-refractory CIS [37,38]. Approval of valrubicin was based on a pivotal trial that showed complete response of 18% at 6 months. However, complete response rate was only 10% at 12 months. Moreover, 56% proceeded to radical cystectomy at a median follow-up of 30 months [37]. A major strength of this study was the strict entry criteria requiring patients to have to failed a minimum of two complete courses of intravesicular therapy. However, heterogeneity of the population was limited, as men represented 88% of the study population, and 98% of study participants were white. Mitomycin C has also been used as monotherapy, but recurrence- free survival is only about 19%

at three years despite decent outcomes within the first year [39,40]. Moreover, mitomycin C toxicity and cost has limited its usage and further investigational studies. Though not FDA-approved, gemcitabine has shown promise as a single agent, with an estimated recurrence-free survival at 2 years of 21% [41].

Combination chemotherapy has been under investigation over the last few years, though prospective data does not exist. Combination gemcitabine and docetaxel (GEM/DOCE) has shown promise in a multicenter, retrospective study of both treatment-naïve patients and those who had failed other regimens. The study revealed a recurrence-free survival rate for those with high-grade disease at the time of induction of 65% and 52% at one and two years, respectively. For those with BCG- unresponsive CIS specifically, recurrence free survival was 50% at 2 years. 15.6% of patients in the study underwent cystectomy at a median of 11.3 months from induction of therapy. Toxicity profile was favorable with the most common adverse effects being urinary frequency, urgency and dysuria [42]. This study, while the largest cohort to date, was limited in that it was retrospective in nature and that severity of symptoms was not reported.

Salvage systemic therapy: Pembrolizumab: Pembrolizumab is an anti- programmed cell death (PD)-1 antibody that has been used to treat a large variety of malignancies. PD-1 is expressed by T cells and acts as an immune checkpoint inhibitor. Programmed cell death ligand 1 (PD-L1) is induced by inflammatory signals, binding to PD-1 and leading to the destruction of T cells [43,44]. Carcinomas evade immune detection by upregulating PD-L1, making its inhibition a good drug target. In January of 2020, Pembrolizumab was approved for the treatment of BCG-unresponsive, high-risk NMIBC [45]. Approval was based on the Phase II clinical trial, KEYNOTE-057 (NCT02625961), a single arm study of 101 patients treated with Pembrolizumab [46]. Because it was a single arm study, the study is limited by a lack of a direct comparator group. Comparisons with other treatments were also limited by the historic lack of standardized BCG therapy and definitions for BCG failure. However, the study employed a rigorous disease evaluation protocol including independent review of all pathology and cytology to ensure consistency within the study itself. Ninety-six patients with high-risk CIS who were ineligible or unwilling to undergo radical cystectomy were included in the efficacy analysis. Patients received 200 mg of Pembrolizumab every three weeks and were assessed for complete clinical response rate. This was achieved in 39 (41%) patients at three months. Two-thirds of patients had adverse events related to treatment, most commonly diarrhea, fatigue, and pruritis, with 11 serious treatment-related adverse events. Twenty-two percent of patients had immune related adverse events, with hypothyroidism being most common [46].

Dr. Arjun Balar and colleagues presented an update of KEYNOTE-057 at the 2021 American Society of Clinical

Oncology (ASCO) Genitourinary (GU) Cancers Symposium based on an extended, minimum follow-up of 26.3 months. In the update, they explained that 13 of the 39 initial responders (33%) had maintained complete response greater than or equal to 2 years following the data cutoff date. Ultimately, 41.7% of patients underwent radical cystectomy following discontinuation of treatment for unacceptable toxicity or for disease recurrence, progression, or persistence [46,47].

New salvage therapies on the horizon

CG0070: CG0070 is a replication-selective adenovirus that has shown promise in high-risk BCG-unresponsive disease. It utilizes the E2F promotor, which is active in cells defective in the retinoblastoma (Rb) pathway. Approximately 80% of all cancers have disruptive Rb pathways [48]. A study by Miyamota et al. estimated Rb gene mutations in about 27% of bladder cancers [7]. Through E2F, CG0070 replicates and enhances granulocyte-macrophage colony-stimulating factor (GC-CSF), activating the immune system and destroying tumor cells. Promising results of this oncolytic therapy for NMIBC came from a phase I/II study by Burke et al. Complete response rates were 48.6% with a median duration of 10.4 months. They also found a positive correlation between response rates and higher Rb defective pathway expression [48]. Further studies are needed to quantify the degree of immune activation after therapy, and tissue samples should be examined to evaluate viral replication, tumor infection, and necrosis.

An ongoing phase II multicenter trial (NCT02365818) found a 47% complete response rate at 6 months for BCG unresponsive high-grade disease, with an even stronger response for those with CIS specifically [49]. A larger sample size and longer duration of follow-up should be assessed in future trials, as only 45 patients were assessed at 6 months. Side effect profiles in both of these studies were favorable, with transient local toxicities including dysuria, hematuria, and increased urinary frequency being most common without any Grade IV/V adverse events in either trial [48,49].

Ongoing clinical trials are further investigating oncolytic virus therapy with CG0070. The phase III trial ASCERTAIN (NCT04736394) is investigating CG0070 administration with a detergent, and the phase II NCT04387461 in combination with pembrolizumab.

Nadofaragene firadenovec: Intravesical nadofaragene firadenovec (rAd-IFNa/Syn3) is another novel therapy that has shown promise for high-risk NMIBC. It is composed of a non-replicating recombinant adenovirus vector that carries the human IFa-2b to the urothelium along with Syn3, a surfactant that enhances delivery [50,51]. In the recent, multicenter phase III trial (NCT02773849), complete response, defined as negative urine cytology and cystoscopy, was assessed. An objective pathology review was omitted and is a potential limitation. Complete response was demonstrated in 53.4% of patients with CIS. The median duration of response was

9.7 months and 45% of patients with CIS had maintained complete response at 12 months. The 12-month freedom from high-grade recurrence was 24.3%. Cystectomy was ultimately required in 26% of patients by 12 months. In total, 66% of patients experienced Grade I/II adverse effects, with discharge around catheter site being most common (25%) and fatigue being second most common (20%). Only 6% of patients experienced a Grade III adverse effect without any Grade IV/V.

Checkpoint inhibitors: Clinical trials are investigating other checkpoint inhibitor therapy, based off suggested utility in muscle-invasive bladder cancer. Atezolimub is another anti-PD-L1 monoclonal antibody that was at one point FDA-approved for muscle invasive and metastatic urothelial carcinoma. The phase II trial SWOG S1605 assessed atezolizumab in patients with BCG-unresponsive high-risk NMIBC. Preliminary data has shown similar efficacy to pembrolizumab. In a group of 73 patients with CIS, a complete response confirmed by biopsy was achieved in 41% of patients at 3 months and 26% at 6 months. Adverse events were experienced by 83% of the cohort, most commonly fatigue. Nine patients experienced grade 3-5 adverse events [52]. In the POTOMAC study, durvalumab, an anti-PD-1 immunoglobin combined with BCG is being investigated in over one thousand patients. Other checkpoint inhibitors under investigation include the PD-1 inhibitors nivolumab and sasanlimab in combination with BCG, as well as HX008, a humanized anti-PD1 monoclonal antibody [52].

Novel modes of drug delivery

The GemRIS (TAR-200) device was developed by Taris Biomedical and granted Fast Track Designation. It is currently being investigated in clinical trials for both muscle-invasive as well as low and intermediate NMIBC. Originally developed to deliver lidocaine for patients with interstitial cystitis, it is now being investigated as a means of delivering intravesical chemotherapy for bladder cancer. It consists of a 5 cm silicone tube that releases a dissolvable gemcitabine tablet over the course of a few weeks. Phase 1 trials have demonstrated an acceptable safety profile with minimal side effects. It has so far shown promise in clinical trials for muscle-invasive bladder cancer. A clinical trial (NCT02720367) was conducted on 12 NMIBC patients in the Netherlands, though data has not yet been reported [53].

Hyperthermic intravesical chemotherapy is another new mechanism of drug delivery. A recent meta-analysis comprised of 888 patients with NMIBC from 11 randomized control trials and one retrospective study, evaluated hyperthermic intravesical chemotherapy versus normal temperature intravesical chemotherapy. The rationale is that higher temperatures enhance drug absorption and malignant cell damage. Compared to normal temperature chemotherapy, there was a significantly lower recurrence rate with the use of thermal chemotherapy at 2-year follow-up (RR= 0.3, 95% CI: 0.21-0.43). Adverse events did not significantly differ

between the two groups, making this a viable option [54,55]. The analysis, however, was limited by the heterogeneity of chemotherapeutic agents and protocols utilized as well as varied risk levels amongst the study participants, which may bias direct comparisons.

The expanding role of urologists

While the development and administration of intravesical therapies has been pioneered by urologists, the role of the urologist becomes more ambiguous with novel systemic therapies on the horizon. This is not unique to bladder cancer. Immunotherapies, including pembrolizumab, are also being utilized in other urologic malignancies including metastatic renal cell carcinoma [56]. Inhibitors of MET, a tyrosine kinase receptor, are utilized for papillary renal cell carcinoma [57]. Similarly, for prostate cancer, androgen deprivation therapy is now being employed at earlier stages, via multiple modalities, and as both adjunctive and monotherapy [58]. A similar dilemma arises in the management of von Hippel-Lindau (vHL) disease, which has traditionally been managed by urologists, with the recent FDA breakthrough and orphan therapy designation of MK-6482, an oral Hypoxia Inducible Factor-2 (HIF2) [59].

The treatment landscape for patients with NMIBC is rapidly evolving. We have already seen the recent FDA approval of pembrolizumab in BCG-unresponsive NMIBC. Table 2 displays the wide array of phase II-IV clinical trials investigating novel therapies, drug combinations, and delivery modes. Physicians and surgeons managing NMIBC must be familiar with new mechanisms of drug delivery, including the promising GemRIS device which may soon be integrated in standard practice. An adept ability to recognize triggers for surgical intervention or adverse effects and their management is imperative. Urologists must decide what their role will be in this new age of immunotherapies. Will urology take a backseat to their medical oncology colleagues in this regard or take an active role as pioneers in the administration of these medications? Now is the time to decide.

Table 2: Trial data obtained from clinicaltrials.gov.					
Study	Phase	Agent (s)	Primary endpoint	Estimated Primary completion Date	Population (n)
NCT04859751	III	VB4-845 Injection in BCG unresponsive pts	Complete response rate	6/2022	53
NCT04165317	III	Sasanlimab + BCG vs BCG alone for induction (+/- maintenance) for high risk NMIBC	Event free survival	6/2024	999
NCT04490993	III	APL-1202 with Epirubicins hydrochloride vs Epirubicin hydrochloride alone in intermediate and high-risk chemo-refractory NMIBC	Event free survival	5/2022	359
NCT03982797	II	BCG Moreau strain (not currently authorized) in high risk NMIBC	Progression-free survival	4/2021	306
NCT03528694 (POTOMAC)	III	Durvalumab and Bacillus Calmette-Guerin Combination therapy in high risk NMIBC	Disease-free survival	11/2021	1019
NCT03022825	II/III	Comination BCG with ALT-803 (an IL-15 superagonist)for BCG Unresponsive High Grade NMIBC	Complete response, disease free rate	1/2023	180
NCT04387461	II	Comination CG0070 (engineered oncolytic adenovirus) + pembrolizumab for BCG unresponsive CIS	Complete response rate	12/2021	37
NCT04172675	II	Erdafitinib (fibroblast growth factor receptor 1-4 inhibitor) vs Intravesical Chemotherapy for high-risk BCG unresponsive pts with FGFR Mutations or Fusions	Recurrence-free survival	10/2022	280
NCT04738630	II	Efficacy and safety of HX008 (humanized anti-pd1 monoclonal ab) for BCG-unresponsive NMIBC	Complete response, disease free survival	12/2022	110

NCT03711032 (MK-3475-676/ KEYNOTE-676)	II/III	Efficacy and safety of pembrolizumab + BCG in high-risk NMIBC for BCG naïve or persistent/ recurrent post- BCG Induction	Complete response rate, event-free survival	5/2022	1525
NCT03799835 (ALBAN)	III	Efficacy of Atezolizumab + one year BCG in BCG-naive Patients With high risk NMIBC	Recurrence-free survival	4/2022	516
NCT02773849	III	High dose INSTILADRIN in BCG Unresponsive high-grade NMIBC	Complete response rate	5/2019	157
NCT03914794	II	Pemigatinib (fgf receptors 1, 2, and 3 inhibitor) before TURBT for pts with recurrent tumors and prior low or intermediate-risk NMIBC tumors. Enrolled patients will receive pemigatinib for 4-6 weeks prior to standard of care transurethral resection of bladder tumor (TURBT).	Complete response rate	5/2022	43
NCT03379909	II	3 months of oral metformin for low-grade NMIBC after TURBT	Overall response	1/2022	49
NCT04452591	III	CG0070 + n-dodecyl-B-D-maltoside (detergent) for BCG unresponsive CIS	Complete response rate	12/2022	110
NCT04736394 (ASCERTAIN)	III	Oral APL-1202 as single agent for intermediate-risk NMIBC	Event free survival	3/2025	800
NCT04386746 (GEMDOCE)	II/III	Combination intravesical Gemcitabine and Docetaxel for BCG naïve NMIBC	3-month complete response rate	8/2022	26
NCT04149574 (CheckMate 7G8)	III	Comination Nivolumab + BCG for high-risk BCG that is persistent or recurrent after BCG treatment	Event free survival	11/2022	700
NCT02371447	I/II	Safety and efficacy of intravesical instillation of VPM1002BC (recombinant BCG) for recurrent NMIBC after TURB (transurethral resection of the bladder) and standard BCG therapy	Dose-limiting toxicity, recurrence-free rate	10/2019	39
NCT03560479	I/II	Intravesicular alpha1H prior to transurethral surgery	Safety, efficacy, change in baseline characteristics	12/2021	52
NCT02449239	II/III	Vicinium (active ingredient VB4-845) for high risk NMIBC after BCG failure	Complete response rate	5/2022	134
NCT04179162	I/II	Combination intravesical Gemcitabine and BCG for BCG-relasping but responsive HG disease	Maximum tolerated dose, disease free survival	11/2022	68
NCT04640623	II	Tar200/gemcitabine (intracesicular drug delivery system) with or without Cetrelimab	Clinical response	10/2024	200
NCT04106115	I/II	durvalumab (PD-L1 immune checkpoint inhibitor) in combination with S-488210/S-488211 (a 5-peptide cancer vaccine).	Dose limiting toxicity/ Disease Free Survival Rate	8/2024	64
NCT04922047	I/II	Tislelizumab (PD-1 antibody) alone and with BCG for high risk NMIBC	Dose limiting toxicity	12/2021	6
NCT03081858	II/III/ IV	Proliposomal Intravesical Paclitaxel for Low-Grade NMIBC	Dose limiting toxicity/ Marker lesion response rate	8/2020	15

Summary

NMIBC is a challenging malignancy to treat due to its significant risk for recurrence and progression, and is associated with high health care costs. BCG is the current first-line standard of care therapy for both high-grade intermediate and high-risk disease. Ongoing shortages and high rates of unresponsiveness necessitate alternate options. A wide array of clinical trials is underway and offer promising alternatives for the future of NMIBC management.

Our narrative review has limitations. Since it is not systematic, there is a possibility of bias. Nevertheless, we intend to provide a comprehensive overview of current approved therapies while highlighting a multitude of new treatment options under investigation.

Conclusion

Options are limited for patients with BCG recurrent/refractory NMIBC. Radical cystectomy is curative, but associated with high morbidity. Moreover, many patients suffering from bladder cancer are elderly and have multiple comorbidities precluding surgery. Valrubicin and pembrolizumab are the sole FDA-approved subsequent-line therapies. However, even amongst initial responders, sustained benefit is limited. New drug delivery mechanisms are being investigated: hyperthermic and combination chemotherapy, as well as the GemRIS delivery system have shown benefit. Novel therapies on the horizon include adenovirus-based therapies like CG0070 and nadofaragene firadenovec as well as a variety of immune checkpoint inhibitors. This is an exciting time in the field of urology and an opportunity for urologists to expand their roles in the management of NMIBC.

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