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Emerging treatments for bacillus Calmette–Guérin-unresponsive non-muscle-invasive bladder cancer

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Intravesical bacillus Calmette–Guérin (BCG) immunotherapy has been the gold standard adjuvant treatment for intermediate- and high-risk non-muscle-invasive bladder cancer (NMIBC) after transurethral resection of bladder tumor (TURBT). BCG immunotherapy prevents disease recurrence and progression to muscle-invasive disease following TURBT. Although most patients initially respond well to intravesical BCG, considerable concern has been raised for patients with BCG failure who are refractory or recur in 6 months after their last BCG, which implies 'BCG-unresponsiveness'. Based on current clinical guidelines, early radical cystectomy (RC) is recommended to treat BCG-unresponsive NMIBC. However, due to the high risk of morbidity and mortality of RC and patients' desire to preserve their own bladder, there is a critical unmet need for alternative conservative treatments as bladder-sparing strategies in BCG-unresponsive patients. Trials for effective bladder-sparing treatments are ongoing, and several novel agents have been recently tested in the NMIBC setting. The goal of this review is to introduce and summarize recently reported novel and emerging drugs and ongoing clinical trials for BCG-unresponsive NMIBC.

Keywords: Antibody-drug conjugate; Bacillus Calmette-Guerin; Immune checkpoint inhibitors; Oncolytic virotherapy; Urinary bladder neoplasms

INTRODUCTION

Urothelial carcinoma (UC) is the fifth most prevalent cancer worldwide. Globally, 549,393 new cases and 199,922 deaths from bladder cancer were reported in 2018 [1]. The National Cancer Institute estimated that over 79,000 new cases of UC were diagnosed in 2017, of which more than 16,000 people died in the United States alone. Based on the Korea Central Cancer Registry, 4,379 new cases were diagnosed in 2017 in Korea [1,2].

UC of the bladder can be categorized as non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic bladder cancer according to stage. NMIBC constitutes 75% of primary diagnoses and is characterized by frequent recurrence and progression to MIBC. Of bladder cancer patients, 20% are classified with

MIBC at diagnosis, and the condition is potentially lethal in approximately 50% of patients despite radical cystectomy (RC) [3,4]. International guidelines recommend treatment methods based on classification of NMIBC into low-, intermediate-, and high-risk groups according to the probability of recurrence and progression (Table 1) [5-7]. The current gold standard for intermediate- and high-risk NMIBC is transurethral resection of bladder tumor (TURBT) followed by intravesical bacillus Calmette–Guérin (BCG) instillation. The mycobacterium strain to which BCG belongs is being improved. For instance, *Mycobacterium smegmatis* is less pathogenic than *Mycobacterium bovis* but easier to cultivate in the laboratory owing to its rapid reproduction [8]. Further, the antitumor immune effect of *M. smegmatis* can be increased using genetic engineering [9,10]. BCG is a live, attenuated *M. bovis*, which induces a nonspecific anti-tumor immune response in the bladder mucosa, although the exact mechanism of BCG is not completely understood [11]. Intravesical BCG after TURBT has been reported to reduce risk of recurrence by 20% to 65% at 5 years [12,13]. BCG may also reduce disease progression. A meta-analysis and several large studies have indicated a reduction in risk of progression by 30% to 50% when compared to TURBT alone [12-14]. Bladder preservation and time to RC were also improved by BCG in the adjuvant setting [15].

In particular, carcinoma *in situ* (CIS) is a type of NMIBC that exhibits high-grade features and increases the risk of recurrence and progression [16,17]. Generally, 40% to 60% of untreated CIS patients develop MIBC with an average risk of progression of 54% within 5 years of diagnosis [16,17]. The complete resolution rate of CIS after intravesical BCG treatment was 60% to 70% and 30% with a median disease-free survival of 4 and 10 years, respectively [18].

Nevertheless, 20% to 50% of NMIBC patients may recur or progress to MIBC despite sufficient intravesical BCG therapy; these patients are considered as 'BCG failure' [19,20]. Given that BCG failure is associated with an increased risk of progression to muscle-invasive disease and substantial risk of death, both the European Association of Urology (EAU) and American Urological Association (AUA) have recommended early RC as a standard treatment option for BCG-refractory NMIBC patients [5,6]. However, RC is associated with morbidity and mortality rates of 28% to 94% and 2% to 5%, respectively. Further, many patients either have comorbidities precluding surgical intervention or refuse cystectomy due to concerns about decreased quality of life [21]. Additionally, the global BCG supply is becoming more tenuous, which has substantially impacted patient treatment options.

Table 1. Risk group stratification by the international guidelines and risk-based treatment strategies in NMIBC

Risk group	EAU	AUA	NCCN	Treatment recommendation
Low-risk	Primary, solitary, Ta, LG/G1, <3 cm, no CIS	Small volume, LG Ta	LG Ta	TURBT+single immediate instillation of intravesical chemotherapy
Intermediate-risk	All tumors not defined in the two adjacent categories (between the category of low and high risk)	Multifocal and/or large volume LG Ta (high risk of recurrence, low risk of progression)	HG Ta	TURBT+single immediate instillation of intravesical chemotherapy±either intravesical chemotherapy for a maximum of 1 year or 1-year full-dose BCG
High-risk	Any of the following: • T1 tumor • HG/G3 tumor • CIS • Multiple and recurrent and large (≥3 cm) Ta, G1, G2 tumors	HG Ta, all T1, CIS	All T1 (CIS listed separately)	TURBT±re-staging TURBT+intravesical full-dose BCG instillation for 1–3 years (induction and maintenance course) or cystectomy

NMIBC, non-muscle-invasive bladder cancer; EAU, European Association of Urology; AUA, American Urological Association; NCCN, National Comprehensive Cancer Network; LG, low grade; TURBT, transurethral resection of bladder tumor; HG, high grade; BCG, bacillus Calmette–Guérin; CIS, carcinoma *in situ*.

Additional intravesical therapy with non-BCG agents has been extensively evaluated in both front-line and post-BCG settings [22]. Valrubicin is the only agent approved by the U.S. Food and Drug Administration (FDA) for patients with BCG-failed CIS who are not medically eligible for or refuse cystectomy. Several studies on intravesical valrubicin demonstrated a complete response (CR) rate of 18% to 21% at 6 months and an estimated CR rate of 16.4% at 12 months [23-25]. Several intravesical chemotherapeutic agents have been evaluated in BCG-failed NMIBC but have demonstrated variable efficacy because heterogeneous groups of patients were included, and they do not provide a satisfactory oncologic efficacy profile [23,26-31]. Systemic immunotherapy using pembrolizumab has recently received approval from the FDA for the treatment of patients with BCG-unresponsive high-risk NMIBC with CIS who are ineligible for or decline RC. Furthermore, several clinical trials investigating the efficacy of novel agents in BCG-unresponsive disease are in progress.

In this paper, we clarified the concept of BCG unresponsive NMIBC who will not benefit from additional BCG courses anymore and summarized salvage treatment options at the frontier of therapeutic approaches for BCG-failure NMIBC. We also provide an overview of novel and emerging drugs, including immune check point inhibitors, viral gene therapy as GC0070 or nadofaragene firadenovec, and antibody-drug-conjugate as oportuzumab monatox in BCG-unresponsive NMIBC by discussing the available data and ongoing relevant clinical trials.

DEFINITION OF BCG UNRESPONSIVENESS

The prognosis of patients with a recurred tumor after optimal BCG therapy differs to that of patients with recurrence following suboptimal or inadequate treatment. Therefore, a precise definition of BCG failure is crucial when assessing patients with tumor recurrence after BCG immunotherapy. Similarly, the prognosis of patients with recurrence of a low-grade tumor or more than 1 year after the last dose of BCG is clearly more favorable than that of patients presenting with a high-grade and/or T1 tumor recurrence or less than 1 year [32], which affects subsequent clinical management. Therefore, several principles should be considered when managing recurrent NMIBC patients. First, maintenance therapy following BCG induction may be considered sufficient BCG immunotherapy, particularly in high-risk NMIBC groups. Studies have demonstrated that a 6-week induction course of BCG followed by maintenance BCG instillations at regular intervals is important for pre-

venting recurrence and tumor progression [33-36]. The typical intravesical BCG course includes a six-times weekly induction course followed by three-times weekly maintenance intravesical instillations at 3, 6, 12, 18, 24, 30, and 36 months, termed the SWOG 6+3 regimen [33,37]. Current guidelines recommend 1 to 3 years of maintenance with three weekly instillations based on the risk of tumor recurrence and progression [3-5]. For clinical trial design, sufficient intravesical BCG therapy can be defined as the performance of at least five-times weekly induction course followed by one maintenance or reinduction course at least two-times instillations [15,38]. Second, various terminology has been used to define the different types of BCG failure (Table 2). The term "BCG-intolerant" implies a situation whereby a patient cannot receive BCG due to a serious adverse events (AEs) or symptomatic intolerance [4,5]. "BCG-refractory" indicates the presence of persistent high-risk NMIBC at 6 months after the start of induction therapy or progression of disease stage or grade at 3 months after the start of induction therapy [4,5]. "BCG-relapsing" refers to tumor recurrence after achieving a disease-free status by 6 months after adequate BCG treatment [4,5]. Among patients experiencing BCG relapse, those with recurrent high-risk NMIBC within 6 months or CIS recurrence within 12 months from the last BCG exposure are likely to have poor prognosis, similar to BCG-refractory patients. Consequently, both BCG-refractory and BCG-relapsing patients who recur within 6 months or present with CIS recurrence within 12 months after their last BCG exposure are combined into the "BCG-unresponsive" category [15]. The term "BCG-unresponsive" indicates patients at high risk of disease recurrence and progression, who have failed intravesical BCG therapy and who will no longer benefit from additional BCG courses.

SALVAGE TREATMENTS FOR BCG FAILURE NMIBC

RC is recommended as the standard of care in BCG-unresponsive NMIBC by various guidelines and expert panels, i.e. EAU and AUA guidelines [5,6]. A retrospective study demonstrated that disease-specific survival was improved in NMIBC patients experiencing disease recurrence or progression after BCG who underwent early RC (92% within 2 years of initial BCG) compared to that in patients who underwent delayed RC (56% after 2 years of initial BCG) [39]. In another retrospective study of patients with T1 recurrence after BCG, patients who underwent RC exhibited a decreased incidence of death from cancer (31%) when compared to those who were treated with repeat TURBT and

Table 2. Types of BCG failure in NMIBC

Type	Definition
BCG intolerance	Tumor recurs after less than an adequate course of therapy due to a BCG related adverse event
BCG refractory	1) Increase in tumor stage, grade, or disease extent at 3 months after iBCG 2) Persistent high-risk disease at 6 months (failure to achieve a disease-free status by 6 months) despite adequate BCG (iBCG+mBCG) treatment
BCG relapsing	Recurrence of high-risk disease after achieving a disease-free status by 6 months after adequate BCG (iBCG+mBCG) treatment (early <12 months, immediate 12–24 months, and late <24 months)
BCG unresponsive	BCG refractory or BCG relapse with high-risk tumor within 6 months or CIS development within 12 months from last BCG exposure

BCG, bacillus Calmette–Guérin; NMIBC, non-muscle-invasive bladder cancer; iBCG, induction BCG; mBCG, maintenance BCG.

intravesical BCG (48%) [40]. Furthermore, tumor progression to muscle-invasive disease in patients initially presenting with NMIBC portends a poorer prognosis compared to that of patients with initial T2 disease presentation [41,42]. However, the decision to perform RC should be determined carefully given the morbidity and mortality rates of 20% to 94% and 2% to 5%, respectively, as well as the detrimental impact on patients' quality of life associated with the procedure [21,43,44]. Moreover, with the aging of the population, a substantial number of patients are unsuitable for radical treatment owing to their comorbidities and frailty. These factors have led clinicians to seek bladder preserving treatment options that are less invasive in BCG-unresponsive NMIBC.

1. Intravesical chemotherapy

Several intravesical chemotherapeutic agents have been assessed for BCG failure NMIBC, either alone or in combination. Valrubicin is the only FDA-approved agent for intravesical use in CIS patients with BCG failure when RC is not an option. A pivotal single-arm study, which included 90 BCG failure patients treated with intravesical valrubicin (six or nine weekly doses of 800 mg in 75 mL saline), reported that the CR rate was 21% at 6 months [23]. The majority of AEs were classified as local bladder symptoms, and 81 patients (90%) had at least one AE during treatment. The most common AEs included urinary frequency (66%), urinary urgency (63%), and dysuria (60%); however, most AEs were mild to moderately severe and none were life threatening [23]. Updated results from both this study and another phase II/III trial (A9303 study), which enrolled 80 patients with BCG-refractory/recurrent CIS containing NMIBC, revealed that the 6-month CR rate was lower (18%) [24]. Of the 80 patients, 69 (86%) experienced at least one local bladder symptom during treatment and 36 (45%) during follow-up. However, the majority of symptoms were mild to moderately severe (73% [45/62] during treatment; 75% [15/20] during follow-up) [24]. The most common local bladder symptoms were urinary frequency, urinary urgency, and dysuria [24]. A multi-institutional retrospective analysis for 113 NMIBC patients who failed previous intravesical treatments, including BCG and/or chemotherapy, demonstrated that the 12-month CR rate to intravesical valrubicin was even lower (16.4%) [25]. Treatment-related local bladder symptoms and serious AEs were reported in 56 (49.6%) and 7 (6.2%) patients, respectively [25]. The most common local bladder symptoms were hematuria (17.7%), pollakiuria (17.7%), micturition urgency (15.9%), bladder spasm (14.2%), and dysuria (13.3%) [25]. In total, 4.4% (5/113) of patients discontinued valrubicin owing to AEs [25]. These data suggest that intravesical valrubicin is a suboptimal

salvage treatment in terms of efficacy in BCG-unresponsive settings.

Traditionally, gemcitabine has been systemically used in neoadjuvant and/or adjuvant settings of MIBC and palliative settings of locally advanced or metastatic UC (mUC). However, gemcitabine has been extensively investigated as a salvage intravesical agent in BCG failure NMIBC. In a phase II trial of 30 patients treated with intravesical gemcitabine after BCG failure, the CR rate at 12 months was 21%, with median follow-up duration of 19 months [45]. Three patients showed grade 2 dysuria defined by occasional pain or difficulty urinating, and six patients had grade 3 dysuria defined by continuous difficulty urinating with pain and frequency [45]. One patient developed a rash on the glans penis, and one patient who was receiving immunosuppressants for a renal transplantation developed cellulitis of the leg and required intravenous antibiotics [45]. A multi-institutional phase II study (SWOG S0353 trial) of 58 patients treated with intravesical gemcitabine (2,000 mg/100 mL normal saline six times weekly, and then monthly for 12 months) after at least two prior BCG courses demonstrated that a CR rates were 28% and 21% at 12 months and 24 months, respectively [46]. A total of 34 patients (62%) showed grade 1–2 toxicity, primarily dysuria and urinary frequency, whereas 3 showed grade 3 toxicity (dysuria, frequency, and neutropenia). No patients had grade 4 or 5 toxicity. One patient discontinued treatment 4 weeks after starting treatment because of personal reasons and another 5 weeks after because of grade 2 dysuria [46]. Although the efficacy of gemcitabine in true BCG-unresponsive NMIBC is unknown, several trials have reported that intravesical gemcitabine has superior efficacy and safety profiles when compared to repeat BCG in NMIBC patients failing one course of BCG [28]. Further, patients with high-grade recurrence after BCG exhibit better disease-free survival and lower toxicity when treated with gemcitabine as opposed to mitomycin (MMC) [27]. Despite these promising results, the long-term efficacy of gemcitabine in BCG unresponsive NMIBC for preventing disease progression remains unknown [28].

Taxanes have been investigated for intravesical use in BCG failure NMIBC. A phase I study of 18 NMIBC patients treated with intravesical docetaxel after at least one course of BCG demonstrated that 1-year CR rate was approximately 50%, and 22% of patients maintained disease-free status at 4 years [47]. None of the patients experienced any delayed toxicities [47]. Updated results from an expanded cohort (54 patients) revealed that 1- and 3-year recurrence-free survival rates for the entire cohort treated with intravesical docetaxel (maximum dose of 75 mg/100 mL; six weekly

and monthly instillations for maximum of a 9 maintenance) were 40% and 25%, respectively [48]. In a similar patient population, nanoparticle albumin-bound paclitaxel as salvage intravesical chemotherapeutic agent resulted in a 36% disease-free rate at 1 year in 28 BCG-failed NMIBC patients [49]. Treatment-related AEs were observed in nine patients (32.1%) and were limited to grade 1 (four patients, 14%) or 2 (five patients, 18%), with no grade 3 or higher, toxicities [49]. Grade 1 or 2 AEs included fatigue, urinary frequency and urgency, hematuria, and urinary tract infection. There was no treatment discontinuation due to treatment-related AEs [49].

Based on mechanisms of action, chemotherapy combinations have evolved around sequential intravesical gemcitabine followed by intravesical docetaxel or MMC. In a retrospective analysis, 27 patients with recurrent NMIBC after BCG therapy received intravesical gemcitabine (1 g/50 mL for 90 min weekly for 6–8 weeks) followed by intravesical MMC (40 mg/20 mL for 90 min weekly for 6–8 weeks) [30]. The median disease-free survival of all patients was 15.2 (range, 1.7–39.3) months, and 10 patients (37%) demonstrated recurrence-free at a median follow-up duration of 22 months [30]. AEs were observed in eight patients (29.6%), and the most common side effect was irritative voiding and bladder spasm (22%), which occurred in six patients [30]. Anemia, thought to be secondary to systemic absorption of gemcitabine, occurred in two patients (7%), and one patient (4%) developed acute renal failure during treatment [30]. Four patients, one with acute renal failure and three with secondary irritative voiding symptoms, received incomplete courses of therapy [30]. A recent multi-institutional, retrospective study reported that the use of sequential intravesical gemcitabine (1 g/50 mL for 60 min weekly for 6 weeks) and docetaxel (37.5 mg/50 mL for 60 min weekly for 6 weeks) in 276 NMIBC patients who recurred after BCG treatment resulted in 1-year and 2-year recurrence-free survival rates of 60% and 46%, respectively, with manageable tolerability [50]. Further large prospective studies are required to verify these preliminary results.

2. Device-assisted treatments

Device-assisted treatments have been applied with the purpose of improving the efficacy of intravesical chemotherapy by increasing its permeability through the bladder wall. Among these approaches, chemohyperthermia (CHT), electromotive drug administration (EMDA), and photodynamic therapy (PDT) have been extensively studied [51].

CHT therapy aims to attain a bladder wall temperature >41°C for at least two sessions of 20 minutes each, while

circulating a solution of MMC. The use of combined CHT and intravesical MMC in NMIBC patients has been investigated extensively. A retrospective analysis of 111 BCG failure NMIBC patients reported that CHT+MMC yielded 1- and 2-year disease-free survival rates of 85% and 56%, respectively, and the progression rate was 3% for all patients, with a median follow-up period of 16 months (range, 2–72 months) [52]. AEs occurred in 45% of patients, of which most were mild (grade 1 or 2) and transient. The most common AEs were bladder spasm (30.6%) and pain (27.0%) during treatment sessions, followed by hematuria (18.9%), dysuria (16.2%), and transient incontinence (9.9%) [52]. In a randomized controlled trial comparing CHT+MMC with BCG in 190 intermediate- and high-risk NMIBC patients, 24 month recurrence-free survival rates were 78.1% and 64.8% in the CHT+MMC group and BCG group, respectively [53]. Progression was observed in less than 2% of patients in both groups. In the CHT+MMC group, the most common AEs during treatment sessions were bladder spasms (14.4%) and bladder pain (14.1%). The most common AEs after treatment were dysuria (11.7%), nocturia (10.3%), and urinary frequency (9.9%) [53]. Although encouraging, these results should be cautiously interpreted in terms of their applicability to BCG-unresponsive patients, because a large proportion of tumors were not high grade, and prior BCG treatment within 48 months was an exclusion criterion of the study. Indeed, 95% of patients in this trial were BCG-naïve [53].

EMDA enhances the penetration of chemotherapeutics across the bladder urothelium and stroma via iontophoresis [54]. In a randomized trial comparing BCG alone with sequential BCG+EMDA MMC in treatment-naïve T1 bladder cancer patients, the sequential BCG+EMDA MMC group exhibited a longer disease-free interval (69 months) when compared to the BCG alone group (21 months). Other secondary end-points, including recurrence rate (41.9% vs. 57.9%), progression (9.3% vs. 21.9%), overall mortality (21.5% vs. 32.4%), and disease-specific mortality (5.6% vs. 16.2%) were more favorable in the sequential BCG+EMDA MMC group [55]. Neither the frequency nor severity of AEs differed between both groups. In the BCG+EMDA MMC group, AEs were mainly localized in the bladder, including macroscopic hematuria (64/107), dysuria (54/107), and drug-induced cystitis (49/107) [55]. Three patients from each group withdrew from the study because of severe AEs [55]. To date, only one study has evaluated the efficacy of EMDA in BCG failure settings [56]. This prospective phase II trial enrolled 26 patients with recurrent high-grade NMIBC after BCG therapy. The high-grade recurrence-free survival was 61.5%, with a median follow-up duration of 36 months [56]. Of patients, 10 were finally treated with RC due to persistent high-grade disease (six patients, 23.1%) or progression to muscle-invasive stage (four patients, 15.4%) [56]. Three patients (11.5%) showed severe adverse systemic events of hypersensitivity to MMC with a hand-foot reaction, which caused treatment discontinuation. Six patients (23.1%) had local AEs, namely dysuria (15.4%), pain (11.5%), bladder spasms (11.5%), and frequency/urgency (11.5%) [56]. Although emerging evidence suggests that EMDA may be a useful tool against NMIBC, its specific role in BCG-unresponsive settings requires elucidation in additional well-designed prospective trials.

PDT acts via the activation of a photosensitizer agent that is selectively absorbed by cancer cells following the administration of specific wavelengths of an intravesical light. To date, several PDT-related studies involving small populations have been conducted in NMIBC [57-59]. Although PDT is effective for BCG-refractory NMIBC, the wide use of PDT in bladder cancer is limited due to high levels of toxicity (i.e., detrusor scarring, skin hypersensitivity, reduction and loss in bladder capacity, and storage LUTS such as frequency and urgency) [60]. However, novel agents with more effective therapeutic indices and less toxicity are being explored and may offer an effective salvage option for BCG-unresponsive NMIBC.

EMERGING THERAPIES IN BCG-UNRESPONSIVE NMIBC

The current search for effective bladder-sparing approaches for BCG-unresponsive patients is ongoing and represents one of the most relevant unmet needs in the field of urologic oncology. Growing evidence suggests that immune checkpoint inhibitors (ICIs), oncolytic adenoviruses, recombinant interferon-α2b protein, and antibody-drug conjugates (ADCs) exhibit promising responses with tolerable toxicity profiles and are potential salvage treatment options for BCG-unresponsive NMIBC [61]. Further, several relevant clinical trials are underway in this setting.

1. Immune checkpoint inhibitors
ICIs block programmed cell death 1 protein (PD-1) and/or the programmed cell death 1 protein ligand (PD-L1)-mediated pathways, and have been mainly assessed in mUC settings. To date, five ICIs blocking PD-1 (pembrolizumab and nivolumab) or PD-L1 (atezolizumab, durvalumab, and avelumab) have been approved by the FDA for first- or second-line use in mUC [62]. In a small study of NMIBC patients, at least 30% of patients expressed PD-1, with an association noted between PD-1 expression and prior BCG therapy [63].

Another study demonstrated marked expression of PD-L1 in 69% of post-BCG relapsed urothelial cancer tumors compared to 19% of BCG-naïve tumors from the same patients [64]. These data implicate the PD-1/PD-L1 pathway as a key resistance mechanism to traditional BCG therapy in NMIBC. Recently, the PD-1 inhibitor pembrolizumab has gained FDA approval for the treatment of patients with BCG-unresponsive high-risk NMIBC with CIS who are ineligible for or decline RC. This approval was based on preliminary results of the KEYNOTE-057 (NCT02625961) phase II trial [65]. This study enrolled 96 patients with BCG-unresponsive high-risk NMIBC with CIS to receive intravenous administration of 200 mg pembrolizumab every 3 weeks until unacceptable toxicity, persistent or recurrent high-risk NMIBC, or disease progression. Primary end point was CR rate with absence of high grade NMIBC and secondary end point was duration of response. At a median follow-up duration of 28 months, the CR rate was 41.2%. Among the 39 patients who achieved a CR, the median duration of response was 16.2 months, and 46% exhibited a response of 12 months or longer (Table 3) [65]. As the treatment was proceeded, no patient developed muscle-invasive or metastatic disease while receiving pembrolizumab. Of the 39 CR patients, 22 experienced recurrence, and 40% of them had cystectomy. Fifty-seven patients showed failure to CR, 47 percent of whom had cystectomy. Of the 36 patients who received cytectomy after pembrolizumab, only 3 cases who are non-responders to pembrolizumab progressed to muscle invasive bladder cancer. 66% of patients experienced treatment-related side effects, although side effects above grade 3 occurred in 13% of patients, which is similar to previous reports of pembrolizumab monotherapy. Nine percent of patients discontinued treatment due to treatment-related side effects. Immune-related side effects occurred in a total of 21 people, and grade 3–4 side effects occurred in 3 patients. The most common side effects were thyroid-related side effects in 13 patients. Pneumonitis was the most common adverse reaction that led to permanent discontinuation of pembrolizumab.

The PD-L1 inhibitor atezolizumab is also being investigated in BCG unresponsive NMIBC. The results of the SWOG S1605 phase II trial (NCT02844816) were recently presented in the 2020 American Society of Clinical Oncology Virtual Annual Meeting [66]. The study enrolled 75 patients with BCG unresponsive CIS (with or without concomitant Ta/T1) to receive an intravenous administration of 1,200 mg atezolizumab every 3 weeks for 1 year. The primary end point was the 6-month pathological CR rate as defined by mandatory biopsy, and the secondary end points included the 3-month CR rate and safety profiles. A CR was observed in 30 patients (41.1%) at 3 months and in 19 (26.0%) at 6 months. Possibly-treatment-related AEs were observed in 61 patients (83.6%) [66]. The most frequent AEs were fatigue (49.3%), pruritus (11.0%), hypothyroidism (11.0%), and nausea (11.0%). Grade 3–5 AEs occurred in nine patients (12.3%), and there was one treatment-related death (myasthenia gravis with respiratory failure and sepsis) [66].

The response to these ICIs in UC can be predicted using molecular subtype classifications and immune markers. A series of studies demonstrated that the "genomically unstable" Lund subtype classification was associated with the best response to atezolizumab [67]. Additionally, the neuronal subtype in the Cancer Genome Atlas cohort, which features low levels of transforming growth factor-beta expression and high mutation/neoantigen burden, may be significantly responsive to ICIs in progressive UC [67,68]. Several immune markers, including high CD3 and PD-L1 expression, may predict favorable response to ICIs in UC [69]. Therefore, in a situation in which ICIs are used in BCG-unresponsive NMIBC, these molecular subtypes and immune markers may provide therapeutic guidance.

Several PD-1 and PD-L1 inhibitors are currently being investigated for NMIBC, including BCG-unresponsive disease (Table 4).

2. Viral gene therapy (CG0070 and instiladrin/nadofaragene firadenovec)

Intravesical viral gene therapy occupies another frontier of immunotherapy for BCG-unresponsive NMIBC. Oncolytic immunotherapy employs viruses that are designed to preferentially replicate in and lyse cancer cells, and trigger anti-tumor immunity in this process. Following the first description of a virus engineered to replicate selectively in cancer cells over 20 years ago, the field of oncolytic immunotherapy has expanded substantially [61]. CG0070 is an oncolytic adenovirus modified to include a human granulocyte-macrophage colony-stimulating factor (GM-CSF) gene. CG0070 selectively replicates in retinoblastoma (Rb)-deficient cells, induces lysis and release of tumor-specific antigens, and induces local GM-CSF expression. This produces long-lasting antitumor immunity by activating antigen-presenting cells and, consequently, acting as an 'in situ' vaccine. In a phase I study of 35 patients with BCG-unresponsive disease, CG0070 therapy was correlated with a 48.6% response rate at a median duration of 10.4 months; patients with Rb-deficient tumors were likely to exhibit even higher response rates [70]. A recent interim analysis from the phase II BOND2 trial (NCT02365818), which included 45 patients with high-grade BCG-unresponsive disease who refused RC, reported that

Table 3. Comparison of emerging novel drugs in BCG unresponsive NMIBC (with CIS)

Drug	Pembrolizumab	Atezolizumab	CG0070	Instiladrin (nadofaragene firadenovec)	Vicinium (oportuzumab monatox)
Relevant clinical trial	KEYNOTE-057 (NCT02625961) phase II, single-arm [62]	SWOG S1605 (NCT02844816) phase II, single-arm [63]	BOND2 (NCT02365818) phase II, single arm [71]	NCT02773849 phase III, single-arm [74,75]	VISTA (NCT02449239) phase III, single-arm [78]
Mode of administration	Intravenous	Intravenous	Intravesical	Intravesical	Intravesical
Treatment dose & interval	200 mg every 3 weeks for up to 24 months	1,200 mg every 3 weeks for one year	Induction course=weekly×6 ($1×10^{12}$ vp/mL) Second induction course=weekly×6 at month 3 ($1×10^{12}$ vp/mL) Maintenance courses=weekly×6 at month 6 ($1×10^{12}$ vp/mL), every 6 months	$3×10^{11}$ vp/mL (75 mL) once every 3 months (for up 4 doses in the inital 12 months)	Induction: 30 mg in 50 mL saline twice weekly for 6weeks followed by once weekly for 6 weeks, for a total of 12 weeks Maintenance: 30 mg in 50 mL saline once weekly every other week for up to 104 weeks
No. of enrolled patients	96	75	45	103	89
Primary end-point	CR rate (up to 3 years)	CR rate (at 6 months)	CR rate (at 6 months)	CR rate (at 3 months)	CR rate (up to 24 months)
CR rate (%)					
At 3 months	40.6	41.1		53.4	40.0
At 6 months		26.0	50.0	40.8	28.0
At 9 months				35.0	
At 12 months	23.6		29.0	24.3	17.0
At 15 months	20.9				
At 18 months	17.0				11.0
Duration of CR (mo)	16.2	Not reported	Not reported	Not reported	9.4
Treatment related grade 3–5 adverse events (%)	12.7	12.3	none	3.8	4.0

BCG, bacillus Calmette–Guérin; NMIBC, non-muscle-invasive bladder cancer; CIS, carcinoma *in situ*; CR, complete response.

Table 4. Ongoing clinical trials in BCG unresponsive NMIBC

Clinical trial number	Interventions	Population enrollment	Study design	Phase	Measured endpoints (primary/secondary)	Study completion
NCT02625961 (KEYNOTE-057) [62]	Pembrolizumab (intravenous)	260	Single-arm trial	II	CRR, DFS/DoR	July 30, 2023
NCT02808143 [82]	Pembrolizumab (intravesical)+BCG solution	9	Single-arm trial	I	MTD/DLTs, TRAE	February 2022
NCT04387461 (CORE1) [83]	Pembrolizumab (intravenous)+CG0070 (intravesical)	37	Single-arm trial	II	CRR/TRAE, median DoR, OS, PFS	June 2022
NCT03258593 [84]	Durvalumab (intravenous)+vicinium (intravesical)	40	Single-arm trial	I	Safety and tolerability/efficacy, response rate, immune parameters, urinary EpCAM, PD-L1 and PD-1 levels	December 30, 2022
NCT03317158 [85]	Durvalumab (intravenous)±EBRT±BCG	186	Randomized, multi-arm, multi-cohort trial <Phase 1> Cohort 1: durvalumab alone Cohort 2a: durvalumab+BCG Cohort 2b: durvalumab+EBRT <Phase 2> Cohort 2a: durvalumab+BCG Cohort 2b: durvalumab+EBRT BCG re-treatment: cross-over durvalumab monotherapy	I/II	<Phase 1> MTD/RFS, TRAE <Phase 2> RFS/TRAE	March 1, 2023
NCT03759496 [86]	Durvalumab (intravesical)	39	Single-arm trial	II	MTD, high-grade recurrence free rate/high-grade progression-free rate, PD-L1 and VEGF expression	December 31, 2021
NCT03950362 [87]	Avelumab (intravenous)+radiotherapy	67	Single-arm trial	II	High-risk RFS	June 15, 2024
NCT02844816 (SWOG S1605) [63,88]	Atezolizumab (intravenous)	202	Single-arm trial	II	CRR, EFS/PFS, cystectomy-free survival, bladder cancer specific survival, OS, TRAE	April 1, 2021
NCT03519256 [89]	Nivolumab (intravenous)±BMS-986205 (intravenous)±BCG	358	Randomized, multi-arm trial Arm 1: nivolumab alone Arm 2: nivolumab+BCG Arm 3: nivolumab+BMS-986205 Arm 4: nivolumab+BMS-986205+BCG	II	CRR, DoR/RFS, TRAE	September 15, 2024

Table 4. Continued

Clinical trial number	Interventions	Population enrollment	Study design	Phase	Measured endpoints (primary/secondary)	Study completion
NCT02202772 [90]	Intravesical cabazitaxel, gemcitabine, and cisplatin	19	Randomized, multi-arm trial Arm 1: gemcitabine+low dose cabazitaxel Arm 2: gemcitabine+high dose cabazitaxel Arm 3: gemcitabine+high dose cabazitaxel+low dose cisplatin Arm 4: gemcitabine+high dose cabazitaxel+moderate dose cisplatin Arm 5: gemcitabine+high dose cabazitaxel+high dose cisplatin	I	TRAE/CRR	December 1, 2020
NCT03945162 [91]	TLD-1433 (photosensitizer, intravesical)+photodynamic therapy	125	Single-arm trial	II	CRR/TRAE	May 2022
NCT04179162 [92]	BCG+gemcitabine (intravesical)	68	Single-arm trial	I/II	MTD, CRR	November 2022
NCT04172675 [81]	Erdafitinib (oral)	280	Randomized, multi-cohort trial Cohort 1 (experimental): erdafitinib in high-risk NMIBC without CIS Cohort 1 (active comparator): intravesical chemotherapy (gemcitabine or MMC) in high-risk NMIBC without CIS Cohort 2: erdafitinib in BCG-unresponsive CIS Cohort 3: erdafitinib in intermediate-risk NMIBC without CIS	II	RFS/ time to progression, time to disease worsening, DFS, OS, TRAE, quality of life	June 10, 2026
NCT04109092 [93]	E7766 (intravesical)	110	Multi-arm, dose escalation & expansion trial Arm 1 (dose escalation): MNIBC and BCG-unresponsive NMIBC Arm 2 (dose expansion): CIS with/without Ta or T1 Arm 3 (dose expansion) high-grade Ta or T1 without CIS	I	DLTs, TRAE, CRR	September 29, 2022
NCT02371447 [94]	VPM1002BC (intravesical)	39	Single-arm trial <Phase I> Induction (6 instillations) <Phase 2> Induction (6 instillations)+maintenance (3 instillation at 3, 6, and 12 months)	I/II	DLTs, recurrence-free rate/ time to recurrence, time to progression, OS, TRAE, quality of life	December 31, 2022
NCT02773849 [74,75]	Instiladrin (intravesical)	157	Single arm, open label study	III	CRR/DoR, EFS, durability of EFS, incidence of cystectomy, OS	August 31, 2022

Table 4. Continued

Clinical trial number	Interventions	Population enrollment	Study design	Phase	Measured endpoints (primary/secondary)	Study completion
NCT02449239 (VISTA) [78]	Vicinium (intravesical)	134	Open-label, multicenter, single arm trial	III	CRR/recurrence rate, EFS, PFS, OS	November 2021
NCT04452591 (BOND3) [95]	CG0070 (intravesical)	110	Global, single arm, open label study	III	CRR/DoR, PFS, cystectomy free OS, safety	December 2024
NCT03711032 (KEYNOTE-676) [96]	Pembrolizumab (intravenous)+BCG	550	Randomized, comparator-controlled clinical trial Arm 1: BCG+pembrolizumab Arm 2: BCG alone	III	CRR/EFS, RFS, OS, DSS, time to cystectomy, DoR, TRAE	November 25, 2024
NCT04149574 [97]	Nivolumab (intravenous)+BCG	700	Randomized, double-blind trial Arm A (experimental): nivolumab+BCG Arm B (comparator): placebo+BCG	III	EFS/WFS, OS, CRR, DoR, TRAE	August 16, 2030

BCG, bacillus Calmette–Guérin; NMIBC, non-muscle-invasive bladder cancer; CRR, complete response rate; DFS, disease-free survival; DoR, duration of response; MTD, maximum tolerated dose; DLTs, dose-limiting toxicities; TRAE, treatment-related adverse events; OS, overall survival; PFS, progression-free survival; EpCAM, epithelial cell adhesion molecule; PD-L1, programmed cell death 1 protein ligand; PD-1, programmed cell death 1 protein; EBRT, external beam radiotherapy; RFS, recurrence-free survival; VEGF, vascular endothelial growth factor; EFS, event-free survival; CIS, carcinoma *in situ*; MMC, mitomycin C; WFS, worsening-free survival; DSS, disease-specific survival.

intravesical CG0070 yielded the CR rate of 50% in patients with CIS containing tumors (58% in pure CIS) at 6 months, with an acceptable level of toxicity [71]. The ongoing phase III BOND3 trial (NCT04452591) aims to evaluate the efficacy and safety of intravesical CG0070 monotherapy in BCG-unresponsive settings (Table 4).

Another promising viral gene therapy is instiladrin (rAd-IFNα/Syn3, nadofaragene firadenovec), which is a replication-deficient recombinant adenovirus vector encoding *IFNα-2b* with anti-tumor activity. Instiladrin was investigated in a phase I trial of 17 patients with BCG-unresponsive disease, and a CR rate of 36% was observed at 12 months after intravesical instiladrin treatment [72]. A multi-center phase II trial (NCT01687244) including 40 BCG-unresponsive patients reported a CR rate at 3 months of approximately 57%, and 35% of patients maintained disease-free status up to 12 months [73]. An interim analysis of the results of a single arm phase III trial (NCT02773849) presented at the Society of Urologic Oncology (SUO) Meeting in December 2019 were recently published [74,75]. A total of 151 patients, consisting of 103 patients with CIS and 48 with papillary disease, were enrolled in this study. The efficacy results demonstrated that 53.4% of patients with CIS demonstrated a CR at 3 months, and 24.3% of patients maintained disease-free at 12 months after intravesical instiladrin treatment (Table 3) [74,75]. Even more favorable results were observed in patients with papillary-only disease (12-month CR rate of 43.8%).

3. Antibody-drug conjugates (vicinium/oportuzumab monatox)

ADCs are a novel therapeutic approach combining the high specificity of monoclonal antibodies with highly active cytotoxic agents. UC may be an optimal candidate for these drugs, because it expresses unique cell surface antigens that permit specific targeting of these cells. Enfortumab vedotin, an ADC consisting of a Nectin-4-directed antibody and microtubule inhibitor, recently became the first FDA-approved ADC for the treatment of mUC based on the results of the single-arm phase II EV-201 trial [76]. This ADC is also being studied in BCG-unresponsive NMIBC. Vicinium (oportuzumab monatox) is a recombinant fusion protein comprising a humanized anti-EpCAM (epithelial cell adhesion molecule) single-chain antibody linked to *Pseudomonas* exotoxin A. Vicinium was investigated in a phase II trial (NCT00462488) of 45 BCG-unresponsive CIS patients. The results demonstrated that 40% (18/45) of the enrolled patients exhibited a CR at 3 months after intravesical vicinium instillation, and the 12-month CR rate was 15.6%, with minimal treatment-related

AEs [77]. Currently, a phase III VISTA trial (NCT02449239) is underway to confirm the efficacy and tolerability of intravesical vicinium in a larger number of similar BCG-unresponsive NMIBC patients (Table 4). An interim analysis results were presented at the 2020 AUA annual meeting [78]. In CIS patients (n=89) who recurred within 12 months after the last BCG treatment, intravesical vicinium resulted in CR rates of 40%, 28%, 17%, and 11% at 3, 6, 12, and 24 months, respectively [78]. More favorable results were observed for papillary-only tumors (n=38), with recurrence-free rates of 71%, 58%, 50%, and 37% at 3, 6, 12, and 24 months, respectively [78]. Further, vicinium was well-tolerated with only 52% of patients experiencing treatment-related AEs, the majority being grade 1–2 [78]. The favorable toxicity profile of ADC has led to several combination strategies, especially with checkpoint inhibitors. For instance, a phase I single-arm trial (NCT03258593) evaluating the combination of durvalumab, PD-L1 inhibitor, and vicinium in high-grade BCG-unresponsive NMIBC is currently ongoing (Table 4).

Table 3 summarizes the results of five representative novel therapeutic agents (pembrolizumab, atezolizumab, CG0070, instiladrin, and vicinium) recently investigated in BCG-unresponsive NMIBC patients. Although promising results have been reported, the small sample sizes of the studies are a limitation. Confirmation of these promising results in well-designed clinical trials with long follow-up periods and larger sample sizes will support the use of these drugs as salvage bladder-sparing treatments in BCG-unresponsive NMIBC patients in clinical practice.

4. Fibroblast growth factor receptor inhibitor (erdafitinib)

Erdafitinib is the pan-fibroblast growth factor receptor (FGFR) kinase inhibitor approved by the FDA for second-line and beyond treatment in patients with mUC with susceptible FGFR3/2 alterations based on phase II BLC2001 trial results [79]. In that trial, the confirmed response rate to erdafitinib among all enrolled patients (n=99) was 40%. In patients who received previous ICI (n=22), the confirmed response rate was 59% [79]. Generally, patients with FGFR3 alterations exhibit lower responses to ICI, although FGFR3 alterations are correlated with a lower grade and stage of NMIBC and a favorable prognosis [80]. For these reasons, FGFR3 alterations are presumed to predict BCG responses. Results of a relevant trial were recently presented at the SUO meeting in December 2019. In 119 patients with high-grade NMIBC treated with intravesical BCG, FGFR3 alterations were identified in 51 of them (43%). Significant differences in high-grade recurrence free rates were observed

between the FGFR3 alteration group and FGFR3 wild-type group (39% vs. 65%, p<0.05) over a median follow-up duration of 60 months. These results suggested that FGFR3-altered NMIBC portends high recurrence following BCG. As such, patients with NMIBC with these alterations may benefit from an alternative therapy with FGFR3 kinase inhibitors. Based on this hypothesis, a phase II clinical trial (NCT04172675) investigating the use of erdafitinib in BCG-unresponsive NMIBC is currently underway [81].

5. Ongoing clinical trials

Table 4 presents an overview of ongoing clinical trials for BCG-unresponsive NMIBC [82-97]. Current clinical studies in BCG-unresponsive NMIBC patients have mainly focused on the efficacy of the combination of various treatment modalities. Based on the efficacy observed in the KEYNOTE-057 trial [65], pembrolizumab is being investigated using combination approaches with intravesical use of BCG (NCT02808143) [82] and intravesical CG0070 [83] in phase I or II settings. Other ICIs including durvalumab, avelumab, atezolizumab, and nivolumab are being actively examined as monotherapies (intravenous or intravesical use) or as a part of combination approaches with various treatment modalities, such as radiotherapy, BCG, and intravesical ADC (vicinium) [84-89]. In particular, the results of clinical studies on the combination of intravenous ICI with intravesical viral gene therapy (pembrolizumab+CG0070) (NCT04387461, CORE1 trial) [83] or ADC (durvalumab+vicinium) (NCT03258593) [84] will reveal whether these combinations exert synergistic effects that increase the effectiveness of each treatment. In addition, several phase I and II trials testing intravesical multiple chemotherapy combinations (cabazitaxel, gemcitabine, and cisplatin) (NCT02202772) [90], PDT with TLD-1443 as a photosensitizer (NCT03945162) [91], and intravesical BCG and gemcitabine combination (NCT04179162) [92], are underway. The efficacy and safety of several other novel agents are being assessed in a phase I or II setting. These agents include oral erdafitinib (NCT04172675) [81], intravesical E7766 (NCT04109092) [93], which is an agonist of macrocycle-bridged stimulator of interferon genes (STING) protein, and VPM1002BC (modified mycobacterium BCG) (NCT02371447) [94]. Finally, five phase III clinical trials are in progress. These include the aforementioned studies on instiladrin (NCT02773849) [74,75], vicinium (VISTA trial, NCT02449239) [78], and CG0070 (BOND3 trial, NCT04452591) [95], and trials of intravesical BCG with intravenous pembrolizumab (NCT03711032) [96] or nivolumab (NCT04149574) [97]. The results of these phase III clinical studies will provide clearer evidence of the effectiveness of each treatment in BCG-unresponsive NMIBC patients.

CONCLUSIONS

BCG-unresponsive NMIBC, which is defined as BCG refractory or BCG relapse with high-risk NMIBC within 6 months or CIS development within 12 months from last BCG exposure, results in an increased risk of cancer progression and even death. Although RC is currently the recommended salvage option in BCG-unresponsive NMIBC, nonsurgical bladder-preserving strategies are required, given the high morbidity and mortality rates associated with RC. To date, many studies on various intravesical and systemic therapies have been conducted. In particular, systemic ICIs (pembrolizumab and atezolizumab), intravesical viral gene therapy (CG0070 and instiladrin), and intravesical vicinium may be considered novel standard non-surgical treatment options in patients with BCG-unresponsive high-risk NIMBC with CIS who are ineligible for or RC.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Ho Kyung Seo and Hyung Suk Kim. Data acquisition: Ho Kyung Seo and Hyung Suk Kim. Statistical analysis: Hyung Suk Kim. Data analysis and interpretation: Ho Kyung Seo and Hyung Suk Kim. Drafting of the manuscript: Hyung Suk Kim. Critical revision of the manuscript: Ho Kyung Seo. Obtaining funding: Ho Kyung Seo. Administrative, technical, or material support: Ho Kyung Seo and Hyung Suk Kim. Supervision: Ho Kyung Seo. Approval of the final manuscript: Ho Kyung Seo and Hyung Suk Kim.

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