Urologic Oncology: Seminars and Original Investigations 39 (2021) 642–663

UROLOGIC ONCOLOGY

Review Article

Non-muscle-invasive bladder cancer: An overview of potential new treatment options

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Received 22 February 2021; received in revised form 29 April 2021; accepted 9 May 2021

Abstract

Aim: This review article summarizes the current clinical practice guidelines around disease definitions and risk stratifications, and the treatment of non-muscle-invasive bladder cancer (NMIBC). Recently completed and ongoing clinical trials of novel and investigational therapies in Bacillus Calmette-Guérin (BCG)-naïve, BCG-recurrent, and BCG-unresponsive patient populations are also described, e.g., those involving immune checkpoint inhibitors, targeted therapies, other chemotherapy regimens, vaccines, and viral- or bacterial-based treatments. Finally, a brief overview of enhanced cystoscopy and drug delivery systems for the diagnosis and treatment of NMIBC is provided.

Background: A global shortage of access to BCG is affecting the management of BCG-naïve and BCG-recurrent/unresponsive NMIBC; hence, there is an urgent need to assist patients and urologists to enhance the treatment of this disease.

Methods: Searches of ClinicalTrials.gov, PubMed, and Google Scholar were conducted. Published guidance and conference proceedings from major congresses were reviewed.

Conclusion: Treatment strategies for NMIBC are generally consistent across guidelines. Several novel therapies have demonstrated promising antitumor activity in clinical trials, including in high-risk or BCG-unresponsive disease. The detection, diagnosis, surveillance, and treatment of NMIBC have also been improved through enhanced disease detection.

Keywords: BCG; Bladder cancer; Immune checkpoint inhibitors; Non-muscle-invasive; Targeted therapy

1. Introduction

Bladder cancer is the eleventh most common cancer worldwide, and the fifth and sixth most prevalent cancer in the European Union and United States, respectively, with urothelial carcinoma the most common histology [1,2]. Bladder cancer stratification can be binary, based upon

Funding: Medical writing support was provided by Anne Marie McGonigal, PhD, and Vardit Dror, PhD, of Engage Scientific Solutions, and was funded by Pfizer. Pfizer provided a formal review of the publication, including for medical accuracy. The authors were not paid for the development of this manuscript. The authors had final authority, including on the choice of journal, on all aspects of the manuscript content and development.

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https://doi.org/10.1016/j.urolonc.2021.05.015

depth of penetration, i.e., muscle-invasive (MIBC) and non-muscle-invasive (NMIBC) bladder cancer. NMIBC accounts for ~75% of newly diagnosed urothelial cell carcinoma of the bladder [3-5].

NMIBC is a heterogeneous disease, with a wide range of progression and recurrence rates that depend on several clinical and pathologic factors [6-9]. Intravesical Bacillus Calmette-Guérin (BCG) is an efficacious treatment for NMIBC, and was the first therapy to reduce the risk of recurrence and progression in high-risk NMIBC [6-9]. Depending on risk, ~70% of patients may achieve a complete response (CR); however, up to 60% of patients may experience recurrence after 1 year [10]. In high-risk patients, ~20% may progress to MIBC within 48 months, despite BCG treatment [11]. The current worldwide shortage of BCG has resulted in rationing/prioritizing schema in clinics, which may lead to increased rates of both disease recurrence and progression in patients with NMIBC [12-14]. Due to BCG shortages, patients are receiving fewer courses of BCG, potentially increasing the proportion of patients undergoing cystectomy [13]. The BCG shortage has also impacted clinical trial access and eligibility [13].

Only 2 treatments for NMIBC have been approved by the US Food and Drug Administration (FDA) or European Medicines Agency for NMIBC in the past 30 years – valrubicin (anthracycline) in September 1998, followed by pembrolizumab (anti-programmed cell death protein-1 [PD-1]) in January 2020 [15,16]. A lack of consensus on clinical trial endpoints and appropriate control arms has slowed research advancements, along with the challenges of enrolling patients in early-stage clinical trials [17]. Following BCG failure in high-risk NMIBC, the standard of care (SOC) is radical cystectomy [6-9]. Given the BCG shortage and the morbidities of radical cystectomy, there is an urgent need for new therapies for high-risk NMIBC.

This review summarizes the current landscape of translational research and clinical trials in BCG-naïve, BCG-recurrent, and BCG-unresponsive NMIBC populations, and discusses possible alternative treatments to BCG for NMIBC. ClinicalTrials.gov and PubMed (MEDLINE) literature searches were conducted to identify relevant ongoing and planned clinical trials and publications in "non-muscle-invasive bladder cancer" for the 3 categories of "BCG-naïve," "BCG-recurrent," and "BCG-non-responsive/unresponsive." Supplementary searches were also performed in Google Scholar. Published guidance and conference proceedings from major urology and oncology congresses (European Association of Urology [EAU], American Urological Association [AUA], Society of Urological Oncology [SUO], National Comprehensive Cancer Network [NCCN], National Institute for Health and Care Excellence, and Society for Immunotherapy of Cancer) on NMIBC were also reviewed, as well as the International Bladder Cancer Group definitions on BCG-recurrent or BCG-unresponsive disease.

1.1. Treatment guidelines

There is a large overlap in AUA/SUO and EAU treatment guidelines (Fig. 1 and 2). A comparison of all major guidelines is reported in Table 1 [6-9,18]. There is a general consensus on patient risk stratification into low-, intermediate-, or high-risk subgroups, with low-grade solitary tumors categorized as low-risk, and high-grade/T1/carcinoma in situ (CIS) categorized as high-risk, although the AUA categorizes high-grade Ta ≤3-cm tumors as intermediate-risk. Tumors in between these 2 definitions are usually assigned as intermediate-risk [6-9,18].

The SOC initial treatment of a bladder lesion involves transurethral resection of bladder tumor (TURBT) followed by intravesical chemotherapy or BCG, depending on patient risk group [6-9,18]. A single instillation of chemotherapy is generally recommended post-TURBT in patients who are presumed to be low- or intermediate-risk. Once risk stratification is confirmed, observation and/or intravesical chemotherapy is the suggested first-line therapy for low-risk patients. Intravesical BCG is typically reserved for high-risk patients in the first-line setting, or as an option for intermediate-risk patients [6-9,18]. In response to BCG shortages, AUA/SUO, EAU, and NCCN guidelines have advised that BCG should be reserved for high-risk patients only, and intermediate-risk patients can be treated with intravesical chemotherapy as an alternative to BCG in the first-line setting [6,19,20]. Induction BCG instillations are given once weekly for 6 weeks. Intermediate-/high-risk patients may also receive an extended period of maintenance therapy, although there is currently no consensus on the duration of maintenance therapy [6-9,18].

Different options exist upon failure of first-line treatment, i.e., following failure of intravesical chemotherapy or BCG, and are largely dependent on the response to prior therapy [6-9,18]. Radical cystectomy is generally recommended following BCG treatment failure.

1.2. Histological variants in NMIBC

An increasingly important consideration in the treatment of NMIBC is the impact of histological variants on treatment outcomes. Despite evidence that the presence of these histological variants is often linked to poorer prognoses, including an increased risk of disease recurrence and progression, the identification and diagnosis of variants during TURBT remains challenging in clinical practice [21-25]. Currently, radical cystectomy is the main option for patients with NMIBC presenting with histological variants, with intravesical BCG an option for select variants [21,23,24].

Studies in urothelial cancer have shown that certain histological variants are associated with molecular subtypes. These molecular subtypes could provide new or alternative targeted therapy options and/or be more susceptible to treatment with chemotherapy, existing targeted agents, or ICIs [26-30]. Therefore, further investigation is needed to

identify which histological variants of NMIBC may be more susceptible to certain treatments, particularly investigational agents directed against specific molecular targets and/or immunophenotypes.

1.3. BCG strains

The mechanism of action of BCG is complex and is thought to involve both urothelial cells and cells of the immune system [31]. Urothelial cells internalize BCG, secrete chemokines and cytokines, and present BCG and/or antigens to the immune system. Cells of the immune system (including but not limited to CD4+ and CD8+ lymphocytes, natural killer (NK) cells, and macrophages) eliminate bladder cancer cells via the direct action of BCG, direct cytotoxicity, and secretion of soluble factors such as tumor necrosis factor–related apoptosis-inducing ligand) [31]. It is likely that BCG strains act via similar mechanisms, but minor differences may exist. Evidence for differences in clinical characteristics among BCG strains in the treatment of NMIBC is limited, predominantly due to a paucity of head-to-head clinical trials [32]. A retrospective review (*N*=2,099) reported that BCG-Connaught reduced the recurrence rate vs. BCG-Tice without maintenance, but the converse was true when maintenance therapy was administered [33]. Additionally, 5-year recurrence-free survival (RFS) was significantly greater with BCG-Connaught vs. BCG-Tice [34]. A network meta-analysis of 65 randomized clinical trials found that, although there were differences in efficacy among BCG strains vs. chemotherapy, no BCG strain showed clear superiority over another [35]. A retrospective review of clinical data (*N*=321) reported no difference in progression-free survival or RFS between BCG-Tice and BCG-Moreau strains [36]. The assessment (*N*=844) of toxicity caused by BCG-Tice, BCG-Moreau, and BCG-RIVM showed patients who received BCG-Tice had mostly mild adverse events vs. those who received the other 2 strains, and BCG-RIVM caused more severe complications [37]. A phase 3 study (NCT03091660) comparing Tokyo-172 strain with the BCG-Tice solution is ongoing (estimated completion: February 2025). Patients with high-grade, BCG-naïve NMIBC are randomized 1:1:1 to intravesical BCG-Tice, intravesical BCG-Tokyo-172, or intradermal BCG-Tokyo-172 followed by intravesical BCG-Tokyo-172 [38].

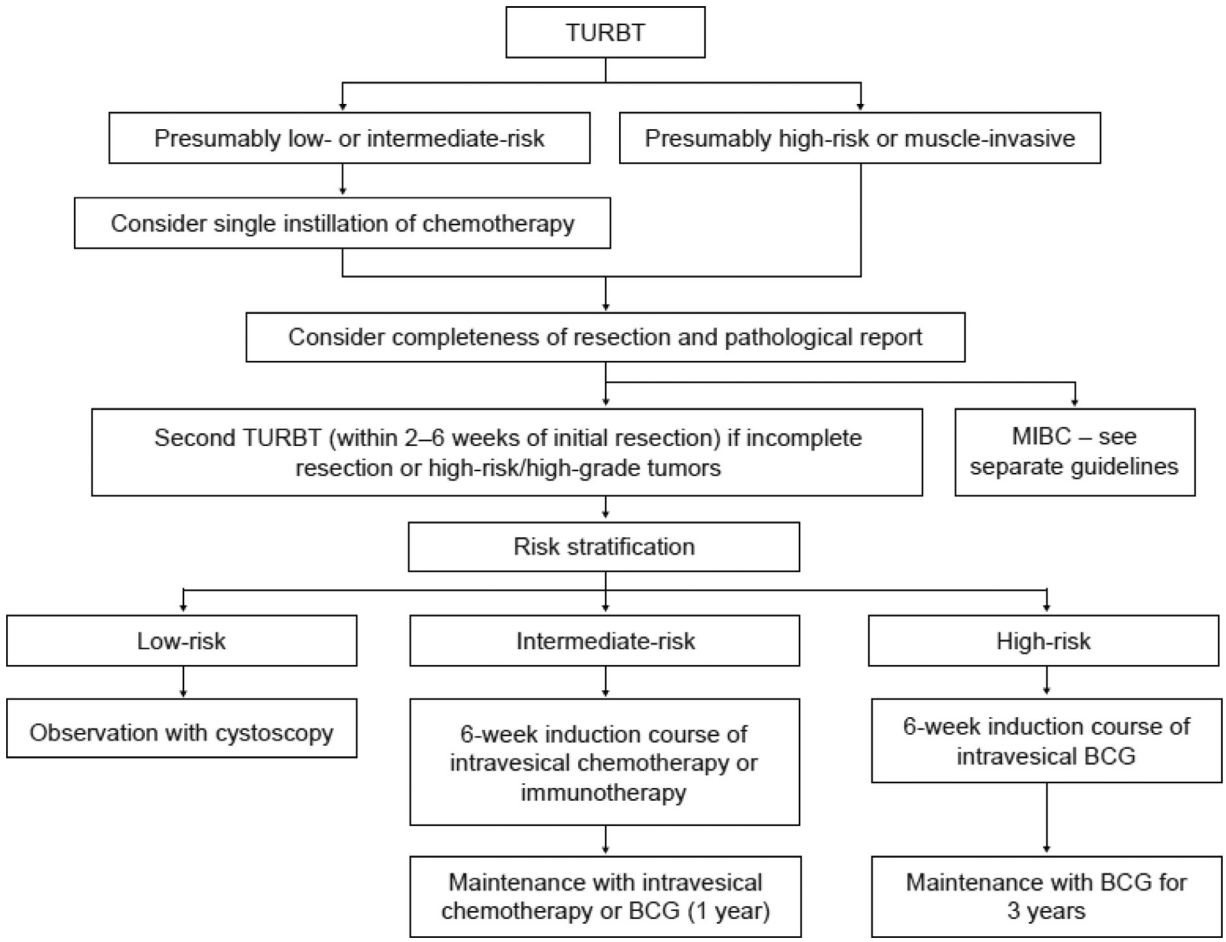

Fig. 1. Overview of AUA/SUO treatment guidelines for NMIBC. AUA = American Urological Association; BCG = Bacillus Calmette-Guérin; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer; SUO = Society of Urologic Oncology; TURBT = transurethral resection of bladder tumor

2. Completed and ongoing clinical trials

BCG-naïve patients are those who have never been treated with BCG. Definitions for BCG-recurrent or BCG-unresponsive disease are outlined in Table 2. A number of active and ongoing clinical trials are exploring the efficacy of new treatments for NMIBC in these disease settings (Table 3).

2.1. BCG-naïve

2.1.1. Immune checkpoint inhibitors (ICIs)/ immunomodulators

Increased expression of programmed cell death ligand-1 (PD-L1) is a mechanism used by tumors to evade the immune response [40-44]. In bladder cancer cells, PD-L1 expression increased in response to BCG [45]. In high-risk NMIBC, PD-L1 expression in tumor cells and the T-cell population in the tumor microenvironment were both predictive factors of BCG response [46]. PD-1 and PD-L1 expression appeared to be induced following BCG in patients with NMIBC [47,48]. Furthermore, high PD-L1 expression in BCG-relapsing tumors was associated with disease progression and reduced 5-year survival rates [47]. The anti-PD-1/PD-L1 antibodies sasanlimab (subcutaneous administration), durvalumab, and atezolizumab are being investigated in combination with BCG in phase 3 trials in high-risk, BCG-naïve NMIBC (Table 3). Subcutaneous sasanlimab +BCG is being evaluated in the 3-arm CREST trial (no prior BCG ≤2 years), including a BCG maintenance-sparing approach. Primary endpoint is event-free survival (EFS), with estimated study completion in December 2026. Durvalumab+BCG is being evaluated in the POTOMAC trial (no prior BCG ≤3 years). Primary endpoint is disease-free survival (DFS), with estimated study completion in November 2024. The ALBAN trial is investigating atezolizumab+BCG vs. BCG in addition to 1-year BCG bladder instillation. Primary endpoint is RFS, with estimated study completion in February 2028. Two single-center trials evaluating atezolizumab+BCG and pembrolizumab are ongoing (Table 3).

Interleukin (IL)-15 stimulates the activation, development, and proliferation of CD8+ T cells and NK cells, but not regulatory T cells [49-51]. ALT-803 (N-803) is an IL-15 receptor superagonist that has antineoplastic activity by promoting innate and adaptive immune responses [49-51]. A synergistic effect of ALT-803+BCG was observed in a rat bladder

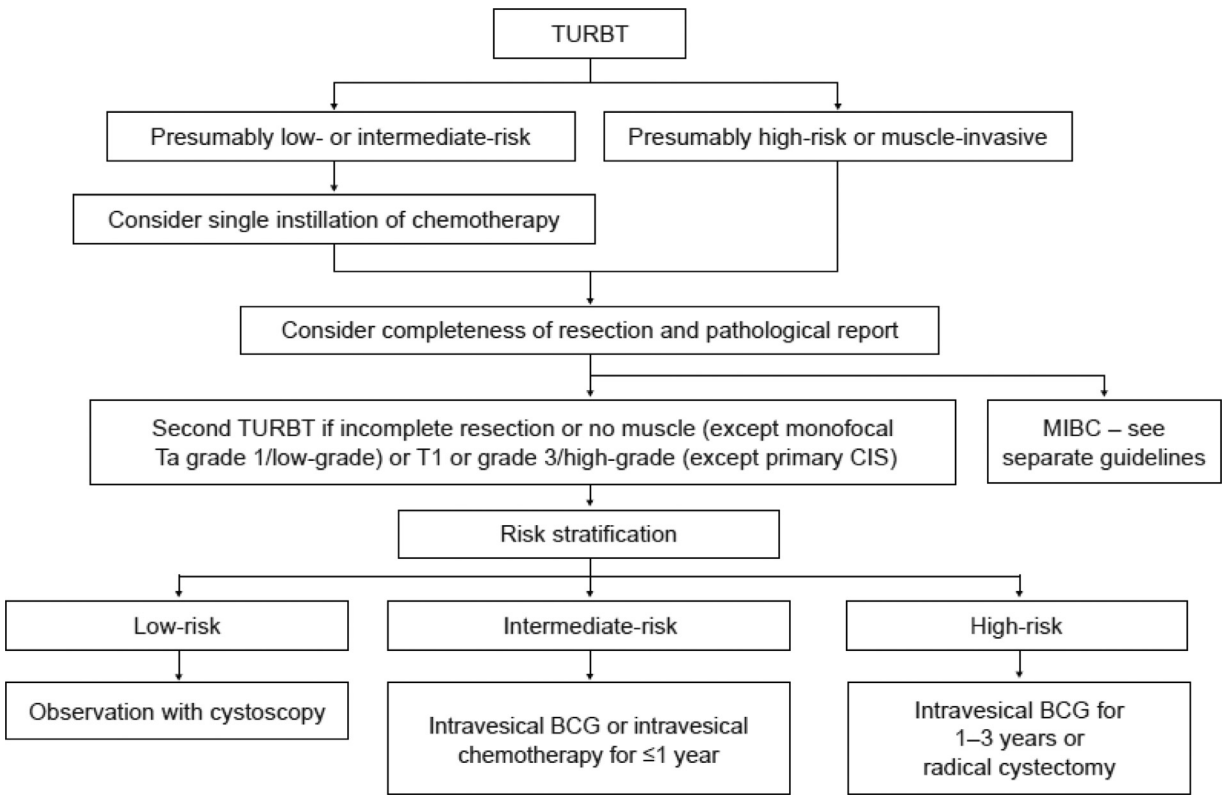

Fig. 2. Overview of EAU treatment guidelines for NMIBC. BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; EAU = European Association of Urology; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer; TURBT = transurethral resection of bladder tumor

Table 1
Summary of treatment strategies across major guidelines

	AUA/SUO	EAU	NCCN	NICE	SITC
Smoking	None explicitly stated	Counsel patients to stop smoking	Recommended to stop smoking	None explicitly stated	None explicitly stated
Risk stratification − Low	• Low-grade solitary Ta ≤3 cm • Papillary urothelial neoplasm of low malignant potential	• Low-grade, primary, solitary, TaG1 (papillary urothelial neoplasm of low malignant potential) • <3 cm • No CIS	Same as AUA/SUO guidelines	• Solitary, low-grade Ta ≤3 cm • Papillary urothelial neoplasm of low malignant potential	• Solitary, primary low-grade Ta
Risk stratification − Intermediate	• Recurrence within 1 y, low-grade Ta • Low-grade solitary Ta >3 cm • Low-grade Ta, multifocal • High-grade Ta, ≤3 cm • Low-grade T1	All tumors not defined in the low- and high-risk categories	Same as AUA/SUO guidelines	• Solitary, low-grade Ta >3 cm • Low-grade Ta, multifocal • High-grade pTaG2 • Any pTaG2, grade not further specified • Any low-risk NMIBC recurring within <12 mo of last tumor occurrence	Up to 2 of the following: • Histologically confirmed multiple and/or recurrent low-grade Ta tumors
Risk stratification − High	• High-grade T1 • Any recurrent, high-grade Ta • High-grade Ta, >3 cm (or multifocal) • Any CIS • Any BCG failure in high-grade disease • Any variant histology • Any lymphovascular invasion • Any high-grade prostatic urethral involvement	• T1 tumor • High-grade tumor • CIS • Multiple, recurrent, and large (>3 cm) TaG1G2/ low-grade tumors (all features must be present)	Same as AUA/SUO guidelines	• High-grade T1 or Ta • CIS • Any aggressive variants	• Any T1, high-grade, and/ or CIS
TURBT	Recommended	Recommended, followed by pathology investigation	Recommended, and consider intravesical chemotherapy within 24 h of TURBT	Recommended	Recommended, and consider intravesical immunotherapy ≥2 wk after TURBT
Second TURBT	• After incomplete initial resection • In high-risk, high-grade Ta tumors • If indicated, perform within 2−6 wk after initial resection	• After incomplete or doubt regarding completeness of initial TURBT • If there is no muscle in the initial specimen, except in Ta low-grade/ G1 tumors and primary CIS • In T1 tumors • If indicated, perform within 2−6 wk after initial resection	• After incomplete initial resection • No muscle in the setting of high-grade tumor • Large or multifocal lesions • Any T1 tumor	• Within 6 wk in low-risk patients if initial resection does not include detrusor muscle • In high-risk tumors within 6 wk of initial resection	• 4−6 wk in all high-grade T1 • 4−6 wk in selected high-grade Ta (per EAU guidelines)
Treatment of primary or BCG-naïve tumors	• Low-risk tumor: should not administer induction intravesical therapy • Low- or intermediate-risk tumor: consider a single postoperative instillation of intravesical chemotherapy within 24 h of TURBT, except in the case of suspected perforation or extensive resection • Intermediate-risk tumor: consider 6-wk course of induction intravesical chemotherapy or immunotherapy • High-risk tumor with newly diagnosed CIS,	• Low- or intermediate-risk tumor with low previous recurrence rate and EORTC recurrence score <5: consider single instillation of chemotherapy • Intermediate-risk tumor with/without immediate instillation chemotherapy: intravesical BCG or intravesical chemotherapy for ≤1 y • High-risk tumor: intravesical BCG for 1−3 y or radical cystectomy in patients at highest risk of tumor progression	• cTa low-grade tumor: observation or 6-wk course of intravesical therapy • cTa high-grade tumor: BCG (preferred), observation, or intravesical chemotherapy • cT1 tumor with residual disease: BCG or cystectomy • CT1 tumor without residual disease: BCG (preferred), observation, or intravesical chemotherapy • Any Tis tumor: BCG	• Low-risk tumor: consider intravesical chemotherapy concurrent with initial TURBT • Intermediate-risk tumor: consider ≥6 courses of intravesical chemotherapy • High-risk tumor: intravesical BCG or radical cystectomy	• Low-risk tumor and low-grade Ta: observation • Intermediate-risk tumor and 1−2 additional criteria: intravesical therapy, preferably BCG induction and ≥1-y maintenance. Other options are observation or chemotherapy • Intermediate-risk tumor and ≥3 additional criteria or high-risk tumor: intravesical therapy, preferably BCG induction and ≥3 y maintenance. Other options are chemotherapy or clinical trial

(*continued*)

Table 1 (***Continued***)

	AUA/SUO	EAU	NCCN	NICE	SITC
	high-grade T1, or high-risk Ta urothelial carcinoma: consider 6-wk induction course of BCG • Intermediate-risk tumor with CR to induction intravesical chemotherapy or induction BCG: consider maintenance therapy (BCG maintenance for 1 y) • High-risk tumor with CR to induction BCG: consider BCG maintenance for 3 y				
Treatment following failure of prior intravesical chemotherapy	Intermediate- or high-risk tumor: consider biopsy and an upper tract evaluation prior to additional intravesical therapy	Consider BCG instillations	Cystoscopy-positive: adjuvant intravesical therapy, cystectomy, or pembrolizumab Persistent cTa, cT1, or Tis tumors: second induction course of induction therapy, followed by TURBT • If no residual disease: maintenance BCG for those who received prior BCG • If residual disease: cystectomy, concurrent chemoradiation, change intravesical agent, or clinical trial enrollment Cytology-positive: intravesical BCG followed by maintenance BCG • BCG-unresponsive: cystectomy, change intravesical agent, or clinical trial enrollment Pembrolizumab can be considered in select patients	None explicitly stated	None explicitly stated
• Intermediate- or high-risk tumor with persistent or recurrent Ta or CIS disease: consider second course of BCG • Patient fit for surgery with high-grade T1 disease: consider radical cystectomy • Intolerance or documented recurrence on TURBT within 6 mo: should not prescribe additional BCG • Persistent or recurrent intermediate- or high-risk NMIBC, unwilling or unfit for cystectomy: consider clinical trial enrollment or intravesical chemotherapy	• BCG-unresponsive: radical cystectomy, clinical trial enrollment or bladder-preserving strategies • Late BCG-relapsing: radical cystectomy or repeat BCG, or bladder-preserving strategies • Low-grade recurrence after BCG for primary intermediate-risk tumor: repeat BCG or intravesical chemotherapy, or radical cystectomy	See previous	Radical cystectomy or further intravesical therapy	BCG failure pattern (resistant, refractory, or relapsing) should be considered in decisions about further therapy	

(*continued*)

Table 1 (***Continued***)

	AUA/SUO	EAU	NCCN	NICE	SITC
Radical cystectomy	Recommended in low- or intermediate-risk tumors following failure of other options or in high-risk tumors	Recommended in high-risk tumors or following BCG failure	Recommended in high-grade tumors or following treatment failure	Recommended in high-grade tumors or following treatment failure	None explicitly stated

AUA = American Urological Association; BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; CR = complete response; EAU = European Association of Urology; EORTC = European Organisation for Research and Treatment of Cancer; NCCN = National Comprehensive Cancer Network; NICE = National Institute for Health and Care Excellence; NMIBC = non-muscle-invasive bladder cancer; SITC = Society for Immunotherapy of Cancer; SUO = Society of Urologic Oncology; Tis = tumor in situ; TURB = transurethral resection of bladder; TURBT = transurethral resection of bladder tumor.

Table 2
Definitions of BCG-recurrent and BCG-unresponsive disease

	BCG-recurrent or -relapsing Disease	BCG-unresponsive or -refractory Disease
International Bladder Cancer Group [17]	BCG-relapsing: recurrence of high-grade disease after achieving a disease-free state at 6 mo following adequate BCG treatment	BCG-unresponsive: includes BCG-refractory and BCG-relapsing (<6 mo since last BCG exposure) disease. Subgroup of patients at highest risk of recurrence and progression and for whom additional BCG treatment is not feasible option BCG-refractory: persistent high-grade disease at 6 mo despite adequate BCG treatment. Includes any stage or grade progression by 3 mo after first BCG cycle
FDA [39]	See BCG-unresponsive	BCG-unresponsive: ≥1 of the following: • Persistent or recurrent CIS alone or with recurrent Ta/T1 (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease <12 mo following adequate BCG treatment • Recurrent high-grade Ta/T1 disease <6 mo following adequate BCG treatment • T1 high-grade disease at the first evaluation after BCG induction
EAU [9]	BCG-relapsing: recurrence of G3/high-grade (WHO guidelines) tumor after completion of BCG maintenance, despite initial response	BCG-refractory: • T1G3/high-grade tumor at 3 mo • TaG3/high-grade tumor after 3 mo and at 6 mo, after either re-induction or first course of maintenance • CIS (without concomitant papillary tumor) at 3 mo and persists at 6 mo after re-induction • High-grade tumor during BCG maintenance BCG-unresponsive: • BCG-refractory • T1Ta/high-grade relapse <6 mo following adequate BCG treatment • Development of CIS <12 mo following adequate BCG treatment
SITC [18]	BCG-relapsing: recurrence of high-grade disease after achieving a disease-free state at 6 mo following adequate BCG treatment BCG-resistant (not currently used but included for clarification purposes): recurrent or persistent disease 3 mo after induction. In these cases, BCG resistance has resolved 6 mo after BCG re-treatment, with or without transurethral resection	BCG refractory: persistent high-grade disease at 6 mo despite adequate BCG treatment. Also includes any stage/grade progression by 3 mo after first BCG cycle BCG unresponsive: includes BCG-refractory and BCG-relapsing (within 6–9 mo of last BCG treatment). Patients for whom further BCG is not indicated and radical cystectomy is a true option

Adequate BCG: received at least 5 out of 6 doses of induction therapy plus at least 2 out of 6 doses of a second induction course or 2 out of 3 doses of maintenance therapy.

BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; EAU = European Association of Urology; FDA = US Food and Drug Administration; SITC = Society for Immunotherapy of Cancer; WHO = World Health Organization.

cancer model [51]. In a phase 1/2 trial of ALT-803+BCG, 9 patients with intermediate-/high-risk NMIBC were disease-free at 24 months [52] (Table 3).

2.1.2. Targeted therapies

Several targeted therapies have demonstrated preclinical efficacy and are in early clinical investigation for BCG-naïve NMIBC, including alpha1H, sirolimus (rapamycin), APL-1202, and sunitinib (Table 3). Alpha1H is a synthetic peptide, consisting of the alpha1 domain of α-lactalbumin in complex with oleic acid, with tumoricidal activity. The mammalian target of rapamycin (mTOR) inhibitor sirolimus (rapamycin) has shown antitumor effects in preclinical bladder cancer studies [53,54]. Furthermore, mTOR pathway activation could be a predictive biomarker for recurrence in high-risk NMIBC [55]. APL-1202 is an inhibitor of methionine aminopeptidase II type (MetAP2) that has shown antiangiogenic and antineoplastic activities in preclinical studies [56]. In a phase 2 trial of sequential BCG-sunitinib (pan tyrosine kinase inhibitor), 72% of patients with high-grade NMIBC (no BCG ≤12 months) achieved CR at 3 months, with low rates of recurrence and progression [57].

2.1.3. Gene therapy, vaccines, viral-, and bacterial-based therapies

BC-819 (inodiftagene vixteplasmid) is a recombinant DNA plasmid carrying the gene for diphtheria toxin-A chain under the regulation of the promoter of *H19* gene, which is upregulated and expressed at high levels only in tumor cells [58]. In a phase 2 trial, intravesical BCG+BC-819 exhibited clinical activity and was well tolerated [59]. Intercellular adhesion molecule 1 (ICAM-1) is upregulated in NMIBC [60,61]. In preclinical studies, the bio-selected ICAM-1-targeted immunotherapeutic coxsackievirus A21 (CVA21; CAVATAK) displayed oncolytic activity in NMIBC cells [62]. In the phase 1 CANON trial, clinical activity of first-line CVA21 was observed [60,61]. In the phase 1b KEYNOTE-200 trial, an objective response rate (ORR) of 31% and median overall survival of 11.2 months were reported following CVA21+pembrolizumab in patients with advanced/metastatic bladder cancer [63].

Ty21a, a commercial vaccine for typhoid fever, improved survival in MB49 bladder tumor–bearing mice and induced infiltration of NK T cells with 1 dose, whereas BCG required multiple doses to elicit the same response [64,65]. A single-center study of intravesical Ty21a is underway (Table 3).

VAX014 is a recombinant bacterial minicell-based immunotherapy that targets 2 NMIBC-associated integrin heterodimers to destabilize tumor cell membranes. Preclinical studies demonstrated a dose-dependent ability of VAX014 to prevent tumor implantation and development in a bladder cancer model [66].

2.1.4. Chemotherapy

Per guidelines, intravesical chemotherapy is recommended for first-line use in patients with low-risk NMIBC, or in intermediate-risk patients as an alternative to BCG in the case of BCG shortages [6-9]. Chemotherapy options include the DNA synthesis inhibitors mitomycin C (MMC) and gemcitabine, and the anthracycline epirubicin, an inhibitor of nucleic acid and protein synthesis [6-9].

Patients with low-/intermediate-risk NMIBC treated with intravesical pirarubicin reported 3-year RFS rates of 63.7–85.3% [67]. Intravesical gemcitabine improved DFS vs. BCG in a retrospective analysis in a largely BCG-naïve NMIBC population (29% and 21% had prior BCG, respectively) [68]. Patients treated with sequential gemcitabine-docetaxel reported treatment success rates of 96%, 89%, and 89% at 3 months, and 1 and 2 years, respectively [69]. Reports of gemcitabine+docetaxel in NMIBC suggest that BCG-naïve patients respond better vs. patients with recurrent/relapsed disease [70,71]. In a phase 3 trial in intermediate- and high-risk superficial papillary bladder cancer, there was no difference in efficacy for patients treated with intravesical MMC-BCG vs. MMC alone [72]. Various trials with other chemotherapy regimens are ongoing (Table 3), including the ANZUP 1301 [73] and GEMDOCE trials.

2.2. BCG-recurrent

2.2.1. ICIs/immunomodulators

Pembrolizumab+BCG is being assessed in a single-center phase 1 trial in high-risk, BCG-recurrent/persistent NMIBC [74]. In the phase 3 KEYNOTE-676 trial, patients with high-risk, recurrent/persistent NMIBC after 1 BCG induction course will receive pembrolizumab+BCG or BCG alone [75]. Primary endpoint is CR rate in patients with CIS, with estimated study completion in November 2024 [75]. The KEYNOTE-676 trial has recently been updated to include a BCG-naïve population (NCT03711032). Nivolumab+BCG vs. BCG is being evaluated in the phase 3 CheckMate 7G8 trial (NCT04149574) in high-risk, BCG-recurrent/persistent NMIBC ≤24 months after last BCG dose. Primary endpoint is EFS, with estimated study completion in August 2030 (Table 3).

TMX-101 is a new formulation of imiquimod, a toll-like receptor agonist with immuno-stimulatory properties, optimized for intravesical delivery. TMX-101 demonstrated promising antitumor activity in a phase 2 trial in recurrent CIS NMIBC (50% had received ≥2 prior courses of BCG) [76].

2.2.2. Targeted therapies

Mutations in fibroblast growth factor receptor (FGFR) genes and dysregulation of FGFR signaling have been implicated in urothelial carcinoma. Additionally, several

Table 3
Active[a] clinical trials in patients with NMIBC

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
BCG-naïve					
Immune checkpoint inhibitors/immunomodulators					
• IV pembrolizumab+intravesical BCG (induction and maintenance) • Intravesical BCG (induction and maintenance)	• High-risk NMIBC • BCG-naïve	NCT03711032 / KEYNOTE-676	3	1525 (all study cohorts)	• EFS up to 5 y
• SC sasanlimab+intravesical BCG (induction and maintenance) • SC sasanlimab+intravesical BCG (induction only) • Intravesical BCG (induction and maintenance)	• High-risk NMIBC • No intravesical BCG within 2 y	NCT04165317 / CREST	3	999	• EFS from randomization up to 55 mo
• IV atezolizumab+intravesical BCG (induction and maintenance) • Intravesical BCG (induction and maintenance)	• High-risk NMIBC • No prior BCG	NCT03799835 / ALBAN	3	614	• RFS after 2 y
• IV durvalumab+intravesical BCG (induction and maintenance) • IV durvalumab+intravesical BCG (induction only) • Intravesical BCG (induction and maintenance)	• High-risk NMIBC • BCG-naïve or no BCG within 3 y	NCT03528694 / POTOMAC	3	973	• DFS up to 4 y
• First-line IV pembrolizumab monotherapy	• BCG-naïve, high-risk T1 NMIBC • Refused cystectomy	NCT03504163	2	37	• DFS at 6 mo
• Intravesical N-803+BCG • Intravesical BCG	• Intermediate or high-risk Ta, T1 or Tis stage NMIBC • No prior BCG	NCT02138734	1/2	596	• CR rate at 12 mo • DFS at 24 mo
• IV atezolizumab+intravesical BCG (induction and maintenance)	• High-risk NMIBC • BCG-naïve or no BCG ≤3 y	NCT04134000 / BladderGATE	1	40	• DLT up to 24 mo • RFS up to 24 mo
Targeted therapies					
• Epirubicin+APL-120 • Epirubicin	• Intermediate- or high-risk chemotherapy-refractory NMIBC • No prior BCG or immunotherapy	NCT04490993	3	359	• EFS up to 30 mo
• Encapsulated rapamycin • Placebo	• Ta, Tis, or T1 NMIBC • No prior BCG	NCT04375813	2	166	• RFS at 1 y • Change in urinary quality of life • Change in cognitive function • Time to recurrence
• Intravesical alpha1H • Intravesical placebo	• NMIBC awaiting TURBT • No intravesical BCG or chemotherapy ≤12 mo	NCT03560479	1/2	52	• AE profile • Cell shedding • Change from baseline in characteristics of papillary tumors
• Sirolimus+intravesical BCG	• Ta, Tis, or T1 NMIBC • Good candidate for BCG (prior BCG not specified)	NCT02753309	1	33	• % change in systemic gamma-delta T-cell frequency at 4 wk and 3 mo • % change in systemic gamma-delta T-cell proliferation in response to BCG-specific antigens at 4 wk and 3 mo

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
					• % change in systemic Ag85 peptide-specific CD4 and CD8 T lymphocytes measured using human IFN-γ release at 4 wk and 3 mo
Gene therapy, vaccines, viral- and bacterial-based					
• Intravesical Ty21a	• Low- or intermediate-risk NMIBC not requiring BCG therapy	NCT03421236	1	25	• AEs after 6 wk
Chemotherapy					
• Intravesical MMC+BCG • Intravesical BCG	• High-grade pTa or stage pT1 (any grade) NMIBC • No prior BCG	NCT02948543 / ANZUP 1301	3	500	• DFS up to 5 y
• Oral lenalidomide+intravesical BCG • Intravesical BCG	• High-grade NMIBC • BCG ≤2 y (response not specified)	NCT01373294	2	17	• PFS at 1 y
• Intravesical gemcitabine+docetaxel	• Intermediate- or high-risk, BCG-naïve NMIBC	NCT04386746 / GEMDOCE	2	26	• CR rate at 3 mo
• Intravesical MMC	• NMIBC • Prior BCG not specified	NCT03058757	2	78	• RFS at 1 y
• Intravesical paclitaxel	• Low-grade, Ta NMIBC • Previous intravesical therapy ≥6 mo	NCT03081858	1/2	15	• MTD at 12 wk • Marker lesion response rate at 12 wk
• Cisplatin-gemcitabine	• T1b NMIBC • Prior BCG not specified	NCT04245618	NA	50	• Evaluation of benefit of neoadjuvant chemotherapy
• Cisplatin-gemcitabine	• Recurrent moderate-/high-risk NMIBC • Prior BCG not specified	NCT02716961	NA	208	• Tumor progression up to 5 y • Drug intervention complications up to 2 y
BCG-recurrent *Immune checkpoint inhibitors/immunomodulators*					
• IV pembrolizumab+intravesical BCG (induction and maintenance) • Intravesical BCG (induction and maintenance)	• High-risk NMIBC • Persistent or recurring after induction BCG therapy	NCT03711032 / KEYNOTE-676	3	1525 (all study cohorts)	• CR rate in patients with CIS by BICR at ∼3.5 y
• IV nivolumab+intravesical BCG • Intravesical BCG	• High-risk NMIBC • Persistent or recurring ≤24 mo following last BCG dose, but not BCG-unresponsive disease	NCT04149574 / CheckMate 7G8	3	700	• EFS at ∼3 y
• IV pembrolizumab+intravesical BCG	• High-risk NMIBC • Persistent or recurring after induction BCG therapy	NCT02324582 / MARC	1	13	• AEs up to 23 wk

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
Targeted therapies					
• Pemigatinib	• Low- or intermediate-risk NMIBC • Documented recurrence	NCT03914794	2	43	• CR rate at 6 wk
Chemotherapy					
• Metformin	• Low-grade primary or recurrent NMIBC	NCT03379909 / TROJAN	2	49	• Overall response at 3 mo
• Intravesical gemcitabine+BCG	• Relapsing but BCG-responsive high-grade, NMIBC ≤24 mo following last BCG dose	NCT04179162	1/2	68	• MTD up to 1 y • Proportion of patients disease-free at 6 mo
BCG-unresponsive					
Immune checkpoint inhibitors/immunomodulators					
• Intravesical ALT-803+BCG	• CIS (with/without Ta or T1 disease) or high-grade Ta or T1 disease • BCG-unresponsive disease: persistent or recurrent CIS with/without recurrent Ta/T1 disease ≤12 mo of BCG; or recurrent high-grade Ta/T1 disease ≤6 mo of BCG; or T1 high-grade disease at first evaluation following BCG induction	NCT03022825 / QUILT-3.032	2	183	• CR at 24 mo • Disease-free rate at 12 mo
• IV pembrolizumab monotherapy	• High-risk, BCG-unresponsive NMIBC • Ineligible for/refusal of radical cystectomy	NCT02625961 / KEYNOTE-057	2	260	• CR rate up to 3 y • DFS rate up to 3 y
• IV pembrolizumab+intravesical gemcitabine	• Persistent high-risk (high-grade Ta, T1, or CIS) NMIBC ≤9 mo of BCG • Ineligible for/refusal of radical cystectomy	NCT04164082	2	163	• CR rate in CIS subpopulation at 6 mo • EFS at 18 mo
• IV nivolumab monotherapy • IV nivolumab+oral BMS-986205 • IV nivolumab+intravesical BCG • IV nivolumab+oral BMS-986205+intravesical BCG	• High-risk, BCG-unresponsive NMIBC	NCT03519256 / CheckMate 9UT	2	358	• Proportion of CIS patients with CR, per PRC, up to 5 y • Duration of CR, per PRC, in CIS patients with CR up to 5 y
• IV atezolizumab	• High-grade Ta, T1, or CIS NMIBC • BCG-unresponsive: persistent or recurrent high-grade Ta/CIS ≤12 mo of BCG (at least	NCT02844816 / SWOG S1605	2	202	• CR rate in subset of patients with CIS at 25 wk • EFS up to 18 mo

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
	induction and first maintenance or second induction; high-grade Ta tumors did not achieve disease-free state for ≥6 mo following last dose of BCG, or had CIS and did not achieve CR); or patient has persistent or recurrent high-grade T1 ≤9 mo of BCG (at least induction); or, disease-free state achieved at 6 mo after induction and maintenance/second induction BCG, but later experiences high-grade Ta/T1 recurrence (with or without concomitant CIS) ≤6 mo after BCG or recurrent CIS ≤12 mo after BCG • Ineligible for/refusal of radical cystectomy				
• Intravesical durvalumab	• High-risk NMIBC • BCG-refractory: high-grade tumor appears during BCG therapy; or, high-grade, non-muscle-invasive papillary tumor is present at 3 mo; or, if CIS (with/without papillary tumor) is present at 3 and 6 mo • Ineligible for/refusal of radical cystectomy	NCT03759496	2	39	• MTD of durvalumab (6 mo after trial initiation) • Possibility of rate of HGRF (6 mo after trial initiation) • 1-y HGRF rate
• IV avelumab+radiotherapy	• High-risk (high-grade, T1, or CIS) NMIBC • BCG-unresponsive: persistent high-grade disease at 6 mo despite BCG or recurrence of high-grade disease ≤6 mo of BCG • Ineligible for/refusal of radical cystectomy	NCT03950362 / PREVERT	2	67	• High-risk RFS at 1 y
• BCG-refractory NMIBC: persistence of high-grade CIS at 6 mo after BCG; or, stage/grade progression at 3 mo after induction BCG; or, recurrence of high-grade CIS after achieving disease-free state following BCG induction <9 mo after last BCG; or, persistent CIS noted on the bladder biopsies ≤3 mo after completing ≥2 BCG induction and 1 maintenance in a 6-mo period, except for any patient with grade/stage progression after induction BCG		NCT02901548	2	34	• CR rate at Month 6

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
• IV ALT-801+gemcitabine	• High-risk (high grade Ta, T1, or CIS, tumor >4 cm or multifocal) NMIBC • Refractory/relapsing of ≥1 prior BCG treatment	NCT01625260	1/2	52	• Safety profile at 12 wk • Tolerability at 12 wk • Clinical benefit up to 13 wk
• IV atezolizumab • IV atezolizumab+BCG	• High-risk, BCG-unresponsive NMIBC: persistence of high-grade CIS at 6 mo after BCG; or, stage/grade progression at 3 mo after induction BCG; or, recurrence of high-grade CIS after achieving disease-free state after BCG induction <6 mo after last BCG • Includes BCG-recurrent and BCG-naïve populations	NCT02792192	1/2	24	• % patients with AEs from baseline up to end of study (∼3.5 y) • % patients with DLT BCG (up to 21 days) • MTD of BCG (up to 21 days) • % patients with CR as assessed by investigator at 6 mo
• IV durvalumab monotherapy • IV durvalumab+intravesical BCG • IV durvalumab+external beam radiotherapy	• Phase 1: BCG-unresponsive NMIBC: persistent or recurrent CIS with/without concurrent Ta or T1 tumors ≤12 mo of BCG; or, recurrent high-grade Ta or T1 tumors ≤6 mo of BCG • Phase 2: intermediate- or high-risk BCG-relapsing or persistent NMIBC	NCT03317158 / ADAPT-BLADDER	1/2	186	• Phase 1: RP2D at 6 mo • Phase 2: 6-mo RFS rates
• IV avelumab+intravesical BCG (induction and maintenance)	• BCG-unresponsive NMIBC: tumor lesion present after prior response	NCT03892642 / ABC	1/2	27	• Proportion of patients receiving complete induction course (8 wk)
• IV durvalumab+SC S-488210/S-488211	• High-risk, BCG-unresponsive NMIBC • Ineligible for/refusal of radical cystectomy	NCT04106115 / DURANCE	1b/2	64	• DLT at end of cycle 1 (29 days) • Pathological DFS rate 1 y after start of treatment
• Intravesical E7766	• Intermediate-risk NMIBC • BCG-unresponsive: persistent or recurrent CIS alone or with recurrent Ta/T1 disease ≤12 mo of BCG; or, recurrent high-grade Ta/T1 disease ≤6 mo of BCG; or, T1 high-grade disease at first evaluation after BCG induction • Refusal of radical cystectomy	NCT04109092 / INPUT-102	1	110	• DLTs up to 6 wk • AEs • CR rate at 3, 6, 12, 18, and 24 mo

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
• IV pembrolizumab+BCG solution	• High-risk NMIBC • Persistent high-grade disease or BCG-refractory: recurrence ≤6 mo of ≥2 courses of BCG; or, T1 high-grade disease at first evaluation after BCG induction	NCT02808143	1	9	• MTD up to 9 wk
• IV durvalumab+vicinium	• High-grade NMIBC • BCG-unresponsive: per SUO and FDA	NCT03258593	1	40	• AEs in a 1-y period
Targeted therapies					
• Intravesical vicinium	• CIS (with or without papillary disease), T1, or high-grade Ta NMIBC • BCG-refractory: persistent disease after BCG; or, recurrence after CR	NCT02449239 / VISTA	3	134	• CR rate up to 24 mo
• Oral erdafitinib • Investigator's choice (intravesical gemcitabine or MMC)	• High-risk, BCG-unresponsive NMIBC • FGFR mutations or fusions • Ineligible for/refusal of radical cystectomy	NCT04172675	2	280	• RFS up to 4 y
• APL-1202	• High-risk NMIBC • Failed/relapsed on prior intravesical BCG or chemotherapy	NCT04498702	2	41	• RFS rate at 12 mo
Gene therapy, vaccines, viral- and bacterial-based					
• Intravesical nadofaragene firadenovec (Adstiladrin®)	• CIS or Ta/T1 high-grade disease with/without CIS NMIBC • BCG-unresponsive: high-grade NMIBC unlikely to benefit from or receive further BCG. Includes: nonresponders; persistent high-grade recurrence ≤12 mo after BCG; relapse following CR after BCG; relapse with high-grade CIS ≤12 mo of BCG; relapse with high-grade Ta/T1 NMIBC ≤6 mo of BCG	NCT02773849	3	157	• CR rate at 12 mo in patients with CIS

(*continued*)

Table 3 (***Continued***)

Intervention	Population	NCT Number/Name	Phase	Estimated Enrollment, *n*	Primary Outcome Measures
• Intravesical BC-819	• Intermediate-risk NMIBC, including BCG failure • BCG failure: intolerance, such that treatment was discontinued or after ≥6 BCG instillations there is recurrent/persistent disease ≥3 mo after BCG initiation	NCT00595088	2	47	• CR rate at 9 wk
• Intravesical CG0070+IV pembrolizumab	• NMIBC with CIS (with/without Ta/T1 disease) • BCG-unresponsive: persistent or recurrent CIS alone or with recurrent Ta/T1 disease ≤12 months of BCG • Ineligible for/refusal of radical cystectomy	NCT04387461 / Core-001	2	37	• CR rate at 12 mo
Chemotherapy					
• Intravesical cabazitaxel, gemcitabine, cisplatin	• BCG-unresponsive/recurrent NMIBC • BCG-refractory: persistent high-risk Ta, T1, and/or CIS after BCG induction • BCG-recurrent: recurrence after achieving a tumor-free status by 6 mo after at least BCG induction ≤18 mo after last BCG dose	NCT02202772	1	19	• Serious AEs up to 6 wk

[a] Excludes completed trials, except those not yet published.AE = adverse event; BCG = Bacillus Calmette-Guérin; BICR = blinded independent central review; CIS = carcinoma in situ; CR = complete response; DFS = disease-free survival; DLT = dose-limiting toxicity; EFS = event-free survival; FDA = US Food and Drug Administration; FGFR = fibroblast growth factor receptor; HGRF = high-grade relapse-free; IFN = interferon; IV = intravenous; MMC = mitomycin C; MTD = maximum tolerated dose; NCT = National Clinical Trial; NMIBC = non-muscle-invasive bladder cancer; PFS = progression-free survival; PRC = Pathology Review Committee; RFS = relapse/recurrence-free survival; RP2D = recommended phase 2 dose; SC = subcutaneous; SUO = Society of Urologic Oncology; Tis = tumor in situ; TURBT = transurethral resection of bladder tumor.

FGFR inhibitors have shown clinical efficacy in advanced bladder cancer [77]. BGJ398, an oral FGFR inhibitor, demonstrated antitumor activity in intermediate-risk NMIBC [78]. The FGFR1-3 inhibitor pemigatinib is under investigation in a phase 2 trial (Table 3).

2.2.3. Chemotherapy

BCG+intravesical gemcitabine is being investigated in a phase 1/2 trial (Table 3). Metformin is being investigated in the phase 2 TROJAN trial in low-grade primary/recurrent NMIBC [79]. Following sequential MMC-BCG, 91.7% of patients with primary/recurrent NMIBC were disease-free after 21.4 months' follow-up in a phase 1 trial [80].

2.3. BCG-unresponsive

2.3.1. ICIs/immunomodulators

Pembrolizumab was recently approved by the FDA for patients with high-risk, BCG-unresponsive NMIBC with CIS with or without papillary tumors and ineligible for/elected not to undergo cystectomy [15]. This approval was based on the ongoing phase 2 KEYNOTE-057 trial evaluating pembrolizumab monotherapy in high-risk, BCG-unresponsive NMIBC [81]. After >2 years' follow-up (N=96), the CR rate at 3 months was 40.6% and median duration of response (DOR) was 16.2 months [81]. Of 39 patients with CR, 18 (46.2%) patients had a DOR ≥12 months. Of the 57 nonresponders, 9 had stage progression at 3 months, and 3 of 36 patients who underwent cystectomy had progression to ≥T2 disease [81].

In the phase 2 SWOG S1605 trial of atezolizumab (anti-PD-L1) monotherapy in 74 patients with CIS, CR rates were 41.1% and 26.0% at 3 and 6 months, respectively; the trial has now closed as it failed to meet the primary endpoint [82]. A number of other ICI trials are underway in BCG-unresponsive NMIBC (Table 3), including the durvalumab+vicinium (fusion protein) trial and DURANCE, evaluating durvalumab+S-488210/S-488211, a 5-peptide cancer vaccine that stimulates a cytotoxic T-lymphocyte response against tumor cells and leads to tumor cell lysis.

Indoleamine 2,3-dioxygenases catalyze the conversion of tryptophan into kynurenine. This leads to the activation of regulatory T cells and myeloid-derived suppressor cells, and the suppression of NK cells and effector T cells [83]. BMS-986205 (linrodostat) is an indoleamine 2,3-dioxygenase-1 inhibitor that restores and promotes the proliferation and activation of various immune cells [83]. Preliminary efficacy was observed in patients with advanced bladder cancer treated with BMS-986205+nivolumab (anti-PD-1 therapy) [84]; the phase 2 CheckMate 9UT trial is now underway (Table 3).

Based on preliminary results from the ongoing phase 2 QUILT-3.032 trial, the FDA granted breakthrough therapy designation to the IL-15 receptor superagonist ALT-803+BCG for BCG-unresponsive NMIBC CIS [49]. Of 20 patients with CIS, 90% achieved CR [49]. In 16 patients with high-grade Ta/T1 papillary disease, DFS was 75% at 6 months and 54% at 9 months [49].

ALT-801 is a first-in-class fusion protein between IL-2 and a T-cell receptor directed toward a p53 epitope displayed on tumor cells. ALT-801 promotes the expression of IL-2 receptors on immune cells and subsequent trafficking of immune cells to tumors, leading to an enhanced antitumor immune response [50,85]. Preliminary clinical activity and immune responses were observed with ALT-801+gemcitabine in a phase 1/2 trial [85].

The stimulator of interferon (IFN) genes (STING) pathway is a cytosolic DNA-sensing pathway that plays a crucial role in the activation of the innate and adaptive immune responses [86-89]. STING activates the innate immune system via the production of cytokines, such as Type 1 IFN, resulting in the generation of cytotoxic T-cell responses and T-cell infiltration, as well as the activation of dendritic cells and antigen cross-presentation [86-89]. E7766 is a novel STING agonist that has demonstrated potent antitumor immune responses in preclinical models of NMIBC insensitive to BCG and anti-PD-1 [90], and is being investigated in the INPUT-102 trial (Table 3).

2.3.2. Targeted therapies

Erdafitinib is an FGFR 1-4 inhibitor being assessed vs. intravesical chemotherapy in a phase 2 trial in patients with high-risk, BCG-unresponsive NMIBC who harbor FGFR mutations (Table 3). In a phase 1b study in patients with intermediate-/high-risk NMIBC, BCG+APL-1202 (MetAP2 inhibitor) was well tolerated [56]. A phase 2 trial of APL-1202 is ongoing.

Vicinium (oportuzumab monatox) is a fusion protein consisting of an epithelial cell adhesion molecule–specific antibody fragment fused to *Pseudomonas* exotoxin that exerts antitumor effects by inhibiting protein synthesis [91]. In phase 1 and 2 studies of intravesical vicinium, a CR rate of 29–40% at 3 months was reported in patients with CIS NMIBC [91]. The phase 3 VISTA trial was recently completed and vicinium was granted fast-track designation by the FDA. Initial phase results reported a 40% CR rate at 3 months in evaluable CIS patients [92]. Of patients with CR at 3 months, 52% had CR for ≥12 months [92,93].

2.3.3. Gene therapy

In a phase 2b trial of intravesical BC-819 in patients with intermediate-risk NMIBC, 33% had tumor ablation and 64% had no new tumor growth at 3 months [58]. Another phase 2 trial is ongoing (Table 3).

Nadofaragene firadenovec (Adstiladrin®) is an intravesical human IFN-α2b gene-mediated therapy that delivers the *IFN-α2b* gene to increase IFN-α2b expression [94]. In a phase 3 study, a CR of 53.4% at 3 months was reported in patients with CIS, with 24.3% remaining free of high-grade recurrence at 1 year [94]. In patients with high-grade Ta/T1

alone, 72.9% and 43.8% were free from recurrence at 3 and 12 months, respectively. Overall, responses were durable to 1 year [94].

CG0070 is an oncolytic serotype 5 adenovirus with an *E2F-1* promoter gene and granulocyte macrophage colony–stimulating factor gene that is replication-selective for retinoblastoma pathway-defective tumors [95]. CG0070 demonstrated antitumor activity in preclinical bladder cancer models [95]. In a phase 1 study of intravesical CG0070 in NMIBC, CR was 48.6% [96]. In an interim analysis of a phase 2 study of intravesical CG0070, the overall 6-month CR rate was 47% [97]. The overall 18-month CR rate was 23%: 35% in BCG-refractory and 17% in BCG-relapsed disease [98]. CG0070+pembrolizumab is under investigation in the Core-001 trial (Table 3).

2.3.4. Chemotherapy

A meta-analysis of patients with NMIBC (all therapy lines) reported that intravesical chemotherapy+BCG improved clinical outcomes vs. BCG [99]. In a phase 1 trial of patients treated with intravesical cabazitaxel, cisplatin, and gemcitabine, partial and CR rates were 94% and 89%, respectively. RFS was 83% and 64% at 1- and 2-years, respectively [100]. A CR rate of 36% (median 41 months' follow-up) was reported in patients with BCG-recurrent NMIBC treated with intravesical nab-paclitaxel in a phase 2 trial [101]. Gemcitabine+docetaxel (an antimitotic agent) was evaluated in subgroups of BCG-unresponsive/recurrent NMIBC with promising clinical efficacy observed [70,71]. Of 59 patients with NMIBC, 63% had failed ≥2 induction BCG. DFS was 49% and 29% at 1 and 2 years, respectively [71].

2.4. Future and potential targets in NMIBC

The therapies reviewed in earlier sections represent those that are currently in clinical trials for the treatment of NMIBC. Some recent studies have performed next-generation sequencing and multi-omics analyses on NMIBC tissue samples to identify potential new therapeutic targets for the treatment of NMIBC [102-106]. Different molecular and genetic features were observed between cohorts of samples, stratified according to NMIBC grading/risk or transcriptomic/proteomic subtypes, that could translate into future molecular targets. These targets include those involved in DNA damage repair, p53 pathways, cell cycle, chromatin remodeling, and hormone receptor signaling [102-106].

3. Intravesical drug delivery systems

Intravesical device-assisted therapies use increased temperatures to improve drug tissue penetration vs. passive-diffusion intravesical therapy. The most common include electromotive drug administration (EMDA), conductive hyperthermic chemotherapy, and radiofrequency-induced thermochemotherapeutic effect [50,107-109].

EMDA uses an electrical current to promote intravesical drug uptake through electroporation, electro-osmosis, and iontophoresis [107,108,110,111]. A systematic review suggested EMDA-MMC may delay time to recurrence in select populations [112]. Retrospective studies have shown that EMDA-MMC and sequential BCG-EMDA-MMC are effective in NMIBC, including BCG-failure NMIBC [109,113]. The effectiveness of BCG vs. sequential BCG-EMDA-MMC in preventing recurrence and progression of high-risk NMIBC is under investigation in a phase 3 trial (NCT03664869).

Hyperthermic intravesical chemotherapy (HIVEC) has demonstrated reduced recurrence and improved bladder preservation rates vs. intravesical chemotherapy [114]. More recent studies reported clinical efficacy in patients with intermediate-/high-risk NMIBC treated with HIVEC (MMC and pirarubicin) [115-119]. Immediate Combat-HIVEC following TURBT is being investigated in a phase 1 trial (NCT03689478).

Various trials have also evaluated the Synergo system of microwave-induced chemohyperthermia, including in high-risk or recurrent NMIBC, with varying results [120-124]. Unfortunately, several phase 3 trials (NCT02471495; NCT02254915; NCT00384891; NCT03335059) in NMIBC with the Synergo system have been terminated/withdrawn in recent years.

Following treatment with reverse thermal hydrogel formulated with MMC (UGN-102), 65% of patients achieved CR at 3 months in a phase 2 trial in intermediate-risk NMIBC (no BCG ≤2 years) [125].

TAR-200 (GemRIS device; TARIS Biomedical, Lexington, MA) is a device that delivers a continuous and prolonged dose of gemcitabine over a period of weeks [126]. The device slowly releases gemcitabine tablets via a semi-permeable silicone tube that functions as an osmotic pump, resulting in 60–70% of gemcitabine delivered over 2 weeks (vs. 2 hours for intravesical drugs) [126]. TAR-200 is under investigation in several clinical trials, including in low-/intermediate-risk NMIBC (NCT02720367).

Photodynamic therapy involves the administration of an appropriate wavelength of light and a photosensitizing agent to destroy malignant tissue [50,108,127]. Studies have reported clinical benefit in patients with recurrent/refractory NMIBC who received photodynamic therapy with 5-aminolevulinic acid or photoporphyrin [127-131]. The photodynamic therapy cis-Urocanic acid has shown antitumor effects in rat bladder cancer cells [132]. An ongoing phase 1 trial (NCT01458847) in primary/recurrent NMIBC is evaluating cis-Urocanic acid. A phase 1 trial (NCT03053635) of TLD-1433 and photodynamic therapy was recently completed in high-risk, BCG-refractory NMIBC, and a phase 2 trial (NCT03945162) is underway.

4. Lesion detection

The current SOC surveillance for NMIBC is cystoscopic evaluation using white light cystoscopy (WLC); however, it is limited in CIS detection, and thus can lead to disease recurrence or progression [6,8,133]. Blue light cystoscopy (BLC) uses an intravesical instillation of hexaminolevulinate and blue light to enhance tumor detection. In a meta-analysis, BLC significantly improved tumor detection, with a subsequent reduction in tumor recurrence vs. WLC [134]. Experience in Europe has shown advantages of BLC in terms of locating additional lesions, and confirming tumor ablation and no tumor recurrence [133]. Accessibility to BLC in the United States is different from Europe due to restrictions on reimbursement. More recently, in a phase 3 trial, BLC was found to significantly improve the detection of recurrent bladder cancer, including CIS, when compared with WLC; 20.6% of recurrence cases and 34.6% of CIS cases were seen only with BLC [135].

Improving TURBT using en-bloc is an emerging alternative to standard TURBT, and could potentially improve staging assessment, perioperative morbidity, and report on clinical outcomes [9,136-139]. En-bloc uses a monopolar or bipolar current Thulium:YAG or Holmium:YAG laser to provide high-quality resected specimens, with high rates of detrusor muscle [9,136-139].

5. Conclusion

Across clinical practice guidelines, the initial SOC treatment for NMIBC often involves TURBT followed by intravesical chemotherapy or BCG, depending on patient risk group. Pembrolizumab is the therapy most recently approved by the FDA for the treatment of patients with BCG-unresponsive CIS. Several clinical trials with investigational agents are ongoing or have completed, including ICIs or other immunomodulators, targeted therapies, other chemotherapy regimens, and vaccines or viral- and bacterial-based therapies. Evidence of clinical activity for the treatment of NMIBC, including patients with high-risk or BCG-unresponsive disease, have been observed. Advances in lesion detection and intravesical drug delivery systems are also improving the detection, diagnosis, surveillance, and treatment of patients with NMIBC. Urologists have witnessed the development of new, and potentially more beneficial therapies for the optimal management of patients with bladder cancer.

Author contribution

All authors participated in discussions regarding this review. All authors contributed to developing and correcting the draft manuscript, and provided additional recommendations. All authors read and approved the final manuscript.

Disclosure

- Neal D. Shore: consultant/advisor for AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi Genzyme, Sesen Bio, Tolmar; research funding from AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Ferring, Janssen, Merck, Myovant, Novartis, Pfizer, Sanofi Genzyme, Sesen Bio, Tolmar.
- Joan Palou Redorta: consultant/advisor for Astellas, Janssen, Merck, Ferring, AstraZeneca, Sandoz, Novartis.
- Gregoire Robert: nothing to disclose.
- Thomas E. Hutson: speaker/consultant for, and research funding from Pfizer, Astellas, Exelixis, Bristol-Myers Squibb, AstraZeneca, Janssen, Eisai, Aveo.
- Rossano Cesari and Subramanian Hariharan: employees and stockholders of Pfizer.
- Óscar Rodríguez Faba: nothing to disclose.
- Alberto Briganti: consultant/advisor for Astellas, Janssen, Merck, Ferring, AstraZeneca, Sandoz, Novartis.
- Gary D. Steinberg: stock/other ownership in EpiVax Oncology, UroGen; consultant/advisor for Heat Biologics, Cold Genesys, Photocure, Merck, Roche/Genentech, Ciclomed, TARIS Biomedical, MDxHealth, Fidia Farmaceuticals, UroGen, Ferring, Aduro, Boston Scientific, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen, EpiVax Oncology, Natera, FKD, Ferring, enGene Bio, Sesen Bio, BioCanCell, Nucleix, Ipsen, Combat Medical, Astellas, FerGene; clinical trial protocol committee member for Merck, Bristol-Myers Squibb, Janssen, Cold Genesys, Pfizer, Photocure, Fidia Farmaceuticals.

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