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Review article

# Optimizing outcomes for high-risk, non-muscle-invasive bladder cancer: The evolving role of PD-(L)1 inhibition

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**Abstract**

Transurethral resection of bladder tumor followed by intravesical Bacillus Calmette-Guérin (BCG) is the standard of care in high-risk, non-muscle-invasive bladder cancer (NMIBC). Although many patients respond, recurrence and progression are common. In addition, patients may be unable to receive induction + maintenance due to intolerance or supply issues. Therefore, alternative treatment options are urgently required. Programmed cell death (ligand) 1 (PD-[L]1) inhibitors show clinical benefit in phase 1/2 trials in BCG-unresponsive NMIBC patients. This review presents the status of PD-(L)1 inhibition in high-risk NMIBC and discusses future directions. PubMed and Google scholar were searched for articles relating to NMIBC immunotherapy and ClinicalTrials.gov for planned and ongoing clinical trials. Preclinical and early clinical studies show that BCG upregulates PD-L1 expression in bladder cancer cells and, when combined with a PD-(L)1 inhibitor, a potent antitumor response is activated. Based on this mechanism, several PD-(L)1 inhibitors are in phase 3 trials in BCG-naïve, high-risk NMIBC in combination with BCG. Whereas PD-(L)1 inhibitors are well characterized in patients with advanced malignancies, the impact of immune-related adverse events (irAE) on the benefit/risk ratio in NMIBC should be determined. Alternative routes to intravenous administration, like subcutaneous and intravesical administration, may facilitate adherence and access. The outcomes of combination of PD-(L)1 inhibitors and BCG in NMIBC are highly anticipated. There will be a need to address treatment resources, optimal management of irAEs and education and training related to use of this therapy in clinical practice. 

*Keywords:* BCG; High risk; Immune checkpoint inhibitors; non-muscle-invasive bladder cancer; PD-(L)1 inhibition

*Abbreviations:* AE, Adverse event; AUA, American Urologic Association; BCG, Bacillus Calmette-Guérin; CI, Confidence interval; CIITA, Class II transactivator; CIS, Carcinoma *in situ*; CR, Complete response; CUETO, Club Urológico Español de Tratamiento Oncológico; DFS, Disease-free survival; EAU, European Association of Urology; EBR, External beam radiotherapy; EFS, Event-free survival; EORTC, European Organisation for Research and Treatment of Cancer; FDA, Food and Drug Administration; HIVEC, Hyperthermic intravesical chemotherapy; irAE, Immune-related adverse event; mAb, Monoclonal antibody; MIBC, Muscle-invasive bladder cancer; NCCN, National Comprehensive Cancer Network; NMIBC, Non-muscle-invasive bladder

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cancer; OS, Overall survival; PD-1, Programmed cell death protein 1; PD-(L)1, Programmed cell death-(ligand) 1; PFS, Progression-free survival; PUNLMP, Papillary urothelial neoplasm of low malignant potential; RFS, Recurrence-free survival; SUO, Society of Urologic Oncology; TMB, Tumor mutational burden; TURBT, Transurethral resection of bladder tumor; UC, Urothelial carcinoma

## 1. Introduction

Each year across the globe more than half a million individuals are diagnosed with bladder cancer, around 75% of whom present with non-muscle-invasive bladder cancer (NMIBC) [1,2]. NMIBC tumors are classified as papillary tumors either confined to the urothelium (stage Ta) or invading the lamina propria (stage T1) or nonpapillary—flat, high-grade tumors, confined to the mucosa (carcinoma *in situ* [CIS]) [1,3]. Approximately 25% of all newly diagnosed patients with NMIBC have high-risk disease, as defined by different risk classification approaches, outlined below [4]. Patients with early stage NMIBC can be treated effectively using intravesical Bacillus Calmette-Guérin (BCG), with around 70% of such patients achieving a complete response (CR), depending on risk group and adherence to guidelines [5]; however, despite this, T1 tumors are associated with significant rates of recurrence and progression [6].

Real-world evidence from 160 studies assessing BCG-naïve patients with high-risk NMIBC, who received intravesical BCG, if suitable, revealed marked variation in response rates, depending on how well treatment guidelines were followed by providers, and if patients were able to tolerate side effects [7]. Five-year recurrence-free survival (RFS; 17%−89%), progression-free survival (PFS; 58%−89%) and overall survival (OS; 28%−90%), were lowest when BCG induction/maintenance schedules were not adhered to or when patients did not receive BCG [7]. Although there is no formal statement on the optimal duration of BCG maintenance treatment, guidelines suggest it should be 1 to 3 years [8−10].

Despite the benefits of treatment with BCG, there are significant challenges detracting from its optimal use, one of which is the ongoing supply difficulty due to limited manufacturing capabilities [5]. There are also a variety of physician- and patient-related issues which contribute to the observed nonadherence to treatment schedules and guidelines. A study in the US found that just 1 in 4,545 patients with high-grade NMIBC, who retained their bladder for 2 years after diagnosis, without radiation or chemotherapy, received all the recommended surveillance and treatment measures [11]. Patient comorbidities/contraindications to BCG treatment often account for why physicians may have to deviate from treatment schedules. These include gross hematuria, traumatic catheterization, bladder or prostate surgery within 7 to 14 days of planned BCG treatment, total bladder incontinence, previous adverse reactions to BCG, significant immunosuppression (e.g., HIV infection, pregnancy, organ transplant recipients), febrile illness, symptomatic urinary tract infection, muscle-invasive bladder cancer, large tumor volume, active infection requiring concurrent antibiotic use and tumor recurrence. Until recently, patients with a history of tuberculosis were also precluded from BCG treatment, however, recent evidence suggests that prior tuberculosis infection does not affect BCG efficacy or safety [3,12,13].

Mild adverse events (AEs) are common in patients receiving intra-vesical BCG and do not normally require treatment interruption or cessation. These include bladder irritation (urinary frequency, dysuria, and mild hematuria), general malaise, and fever. For patients experiencing systemic complications [10,14,15], however, these events may significantly impact quality of life and disrupt BCG treatment schedules [4,11,16,17]. Furthermore, healthcare systems bound by financial constraints may have difficulty meeting the high economic burden of NMIBC, which is particularly high in patients with progressive disease [4].

Therefore, although transurethral resection of bladder tumor (TURBT) followed by BCG therapy is a highly effective therapeutic strategy for patients with high-risk NMIBC, there remains an urgent need for additional treatment options with higher response rates, more durable efficacy, and better tolerability, as well as agents that overcome BCG unresponsiveness. Research into novel therapies for NMIBC has gained momentum over the past few years, with many new developments. It is beyond the scope of this paper to describe all these advances; instead, the current review focuses on the use of immune checkpoint inhibitors, specifically programmed cell death (ligand) 1 (PD-[L]1) inhibitors, to enhance treatment and optimize patient outcomes. Information for the review was derived using PubMed and Google Scholar, using various combinations of the following keywords: "adherence, adverse events, atezolizumab, BCG, BCG-naïve, BCG-unresponsive, bladder cancer, cetrelimab, clinical trials, cost burden, durvalumab, high-risk, immune checkpoint inhibitors, immune-related adverse events, immunotherapy, intravesical chemotherapy, management guidelines, NMIBC, original report, overall survival, PD-(L)1 inhibition, prognosis, pembrolizumab, progression, radical cystectomy, recurrence, review article, risk stratification, sasanlimab, side-effects, transurethral resection, treatment, treatment guidelines, and tumor staging."

## 2. Risk stratification: The key to patient management

Two reviews compared established risk scales (including the EORTC risk tables and the CUETO risk factors), taking into consideration the different treatments that patients

received [18,19]. More recently, updated guidelines on the management of NMIBC stratify it into risk groups according to the EORTC risk tables' probabilities of recurrence and progression after TURBT and using both the EORTC and CUETO risk scales in patients treated with BCG [3,8]. Jobczyk et al. [20] evaluated the concordance and accuracy of using EAU-recommended tools (EAU risk groups, EORTC and CUETO) in predicting recurrence and progression in NMIBC and attempted to validate these scales using 1- and 5-year probabilities of recurrence, progression, and mortality in a mixed population of patients. The authors concluded that the scales poorly predicted both recurrence and progression [20]. This might result from the BCG therapy in the studies not conforming to current standard induction and maintenance guidelines. Furthermore, a restaging TURBT was not performed routinely in studies used to establish risk scales [21]. Consequently, these scales overestimate rates of recurrence and progression in patients treated according to current guidelines [22]. Some refinements have been achieved in more recent stratification tools [8] (Table 1) but the above-mentioned limitations are the same—absence of BCG treatment and re-TURBT. Recent updates of the AUA/SUO and EAU risk stratification tools broadly agree and align in defining the NMIBC risk groups, though differences remain.

Guerrero-Ramos et al. [23] reported the first systematic review of NMIBC risk stratification scales, used to predict recurrence and/or progression in NMIBC. A total of 25 studies (22,737 patients) reporting at least one discrimination measure (area under the curve or concordance-Index) were included. Six classifications were identified, three of them predictive models (EORTC, CUETO, EAU 2021) and three based on expert opinion (EAU 2020, AUA, NCCN). A high risk of bias in most of the studies was reported, with nonstandardized definitions of oncologic outcomes. The most validated scoring systems were CUETO and EORTC; however, the validations had a poor discriminative ability to predict recurrence that was only slightly better for progression. They showed furthermore that the EAU 2021 model overestimated the risk of progression in patients treated with BCG and that CIS was under-represented in all studies. The authors highlighted an unmet need for accurate risk models for patients with NMIBC, and proposed that future models should include a

Table 1
NMIBC risk stratification according to EAU and AUA/SUO guidelines [3,9].

| Risk group | EAU 2019 | EAU 2021 | AUA/SUO 2021 |
|---|---|---|---|
| Low risk | Primary, solitary, LG (including PUNLMP), stage Ta, <3 cm, no CIS | • Primary, single Ta/T1 LG/G1 tumor <3 cm, no CIS, pts aged ≤70 years<br>• Primary Ta LG/G1, no CIS, with ≤1 additional clinical risk factor[a] | LG solitary Ta ≤3 cm PUNLMP |
| Intermediate | Tumors not defined as low or high risk | Tumors without CIS and not classified as low, high, or very high risk | • LG Ta: recurrence <1 year<br>• LG Ta: solitary >3 cm<br>• LG Ta Multifocal<br>• HG Ta ≤3 cm<br>• LG T1 |
| High risk | Any of:<br>• T1 tumor<br>• G3 (HG) tumor<br>• CIS<br>• Multiple, recurrent, large (>3 cm) TaG1G2/LG tumors | • All T1 HG/G3, no CIS, except those in very high-risk group<br>• All CIS, except those in very high-risk group Stage, grade with additional clinical risk factors:[a]<br>• Ta LG/G2 or T1 G1 with CIS and all 3 risk factors<br>• Ta HG/G3 or T1 LG, no CIS, ≥2 risk factors<br>• T1 G2, no CIS, ≥1 risk factor | • HG T1<br>• Any recurrent HG Ta<br>• HG Ta >3 cm (or multifocal)<br>• Any CIS<br>• Any BCG failure in HG cases<br>• Any variant histology<br>• Any lymphovascular invasion<br>• Any HG prostatic urethral involvement |
| Very high risk (subgroup of "high risk") | • T1 G3/HG associated with concurrent bladder CIS<br>• Multiple and/or large T1G3/HG and/or recurrent T1G3/HG<br>• T1 G3/HG with CIS in the prostatic urethra<br>• Some histologic subtypes of urothelial carcinoma<br>• Lymphovascular invasion | Stage, grade with additional risk factors:[a]<br>• Ta HG/G3, CIS, with all 3 risk factors<br>• T1 G2, CIS, ≥2 risk factors<br>• T1 HG/G3, CIS, ≥1 risk factor<br>• T1 HG/G3, no CIS, with all 3 risk factors | Not applicable |

AUA = American Urologic Association; BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; EAU = European Association of Urology; HG = high grade (mixture of some G2 and all G3); LG = low grade (mixture of G1 and G2); NMIBC = nonmuscle-invasive bladder cancer; PUNLMP = papillary urothelial neoplasm of low malignant potential; SUO = Society of Urologic Oncology.

[a] Additional risk factors: age >70 years, multiple papillary tumors, and tumor diameter ≥3 cm.

combination of clinicopathologic and possibly molecular data [23].

## 3. Molecular stratification of NMIBC

NMIBC shows molecular heterogeneity; to improve outcomes for high-risk patients, there needs to be a clearer understanding of the links between BCG resistance and molecular alterations in the tumor [24]. The largest integrative multiomics analysis of NMIBC to date was performed by the UROMOL group, which profiled a mix of tumors from 834 patients. Based on RNA expression in the tumors, they identified four classes (1, 2a, 2b, and 3) that reflected tumor biology and disease aggressiveness [25]. The key limitations of the UROMOL study were the absence of BCG therapy in most patients and the heterogeneity of tumors analyzed. Despite the large number of tumor samples involved in RNA sequencing, more than half comprised low grade Ta tumors ($n$ = 397) with an almost complete absence of pure CIS tumors without a papillary component ($n$ = 3) [25].

Hurst et al. [26,27] were among the first groups to stratify NMIBC into molecular subtypes after separation into different subgroups based on stage (noninvasive Ta vs. superficially invasive T1). Robertson et al. [28] focused specifically on T1 tumors treated with BCG. They identified and characterized five transcriptome subtypes, two of which were associated with Myc-target genes and appeared to be associated with a worse prognosis than the other three. Bellmunt et al.[29] similarly focused on a cohort of T1 patients treated with BCG. They analyzed genomic mutations in these tumors relative to patient outcome. Tumor mutational burden (TMB), which was associated with mutations in DNA damage response genes, was highest in patients with favorable outcomes. *TP53*, *ATM*, *ARID1A*, *AHR*, and *SMARCB1* mutations were identified more frequently in tumors that subsequently progressed, as was copy-number gain in *CCNE1* and deletion of *CDKN2A* [29]. Bacon et al. [24] also performed genomic analysis of patients with high-risk NMIBC undergoing BCG therapy; they focused on comparisons of genomic alterations before and after BCG in those patients with recurrent or progressive disease. They independently identified a key role for some of the same alterations as Bellmunt et al., including enrichment of *ARID1A* mutations, *CCNE1* gain, and low TMB in tumors with adverse outcomes. *ARID1A* mutations had also been described as a prognostic alteration in an earlier series of high-risk NMIBC treated with BCG [30], making ARID1A the target of ongoing investigation to understand its relationship to BCG response.

Overall, it would appear that stage-stratified subclassification identifies clinically relevant tumor features and insights, suggesting the feasibility of more precise prognosis. These findings should be considered in future trial designs to ensure stratified treatment approaches where applicable.

## 4. Evolving treatments in NMIBC

The treatment landscape for patients with NMIBC has advanced rapidly over the last few years, with several immunotherapies poised to offer an alternative to existing treatments. Bladder-sparing strategies are particularly important for very high-risk treatment-naïve tumors and in recurrent/progressive disease, despite adequate BCG treatment. Radical cystectomy is the standard treatment in patients with BCG-unresponsive disease, but it represents a life-changing intervention, with a high risk of morbidity and non-negligible rate of mortality. Maibom et al. [31] conducted a systematic review of 66 studies involving patients undergoing radical cystectomy for bladder cancer. Short-term (<90 days) mortality and morbidity were high; at 90 days, mortality rate was 4.7% and morbidity rate for major complications was 58.5% [31]. Many patients are not fit for or decline radical cystectomy, highlighting the need for alternative treatments. Novel treatment options include intravesical combination chemotherapy [32,33], immunotoxin therapy [34], device-assisted therapies [35], and a variety of intravesical [36–38] and systemic immunotherapies [39].

## 5. Immunotherapy

Targeted immune modalities in development include anticancer vaccines, chimeric antigen receptors, PD-(L)1 inhibitors, and adoptive T-cell transfer. The PD-(L)1 inhibitors are the most extensively evaluated to date.

### *5.1. Rationale for combination BCG + PD-(L)1 inhibitor*

There is recent evidence that “trained immunity” underpins the nonspecific molecular mechanism by which BCG exerts its immunotherapeutic effects in bladder cancer, and that this therapeutic response may be enhanced by a second, unrelated stimulus [40,41]. Chamie et al. [42] postulate that, in their study of patients with NMIBC, a combination of the IL-15 superagonist N-803 plus BCG acts synergistically to bring about a durable CR. Furthermore, initial data from clinical trials in NMIBC, investigating combinations of BCG and anti-PD-(L)1 agents show potent antitumor immune responses, leading to inhibition of tumor growth and prolonged patient survival [43,44]. Response to the combination is greater than would be expected from additive effects of each drug administered as monotherapy, suggesting that these agents could potentially be acting synergistically. While synergy for BCG plus anti-PD-(L)1 combinations for the treatment of NMIBC has not yet been equivocally proven, studies on drug combinations in oncology using mathematical models are underway [45,46].

PD-L1 is expressed on tumor cells and tumor immune cell infiltrates. Tumor PD-L1 binds to PD-1 expressed on T cells and, by so doing, transmits an inhibitory signal to the T cells limiting function of the immune system, essentially

"switching it off" and preventing tumor destruction [47,48]. Several studies report that PD-L1 expression in bladder cancer carries an unfavorable prognosis [49-51] and may contribute to reduced susceptibility to BCG, with resultant treatment failure [51,52]. However, other research finds inconsistent or no association between tumor PD-L1 positivity and clinical outcomes [53,54].

A recent preclinical study reported that although tumor expression of class II transactivator (CIITA) is required for activation of tumor-specific CD4 T-cell response and immunity to BCG, CIITA expression is not required for a response to PD-1 immunotherapy, hinting at a potential benefit for different types of immunotherapy for bladder cancer [55]. Vandeever et al. used a murine model of NMIBC (MB49 tumor cells) to evaluate the antitumor effects of avelumab, a PD-L1 inhibitor [56]. In this model, murine tumor cells form multifocal tumors on the mucosal wall of the bladder and test highly positive for PD-L1 expression. Avelumab was found to induce significant ($P < 0.05$) antitumor effects that suggested this model could be used to identify host antitumor immune mechanisms. Furthermore, the authors suggest that it would enable researchers to evaluate combinations of immune-based therapies for CIS and NMIBC leading the way into future clinical studies [56]. In a rat bladder cancer model, the combination of BCG with a PD-(L)1 inhibitor activated a potent antitumor response, including increased number and activity of tumor-infiltrating CD8+ T cells and reduced myeloid-derived suppressor cells, and prolonged survival to a greater extent than either alone [57].

In a small cohort of patients with BCG-resistant tumors, PD-L1 expression was increased in bladder cancer cells and tumor-infiltrating immune cells after BCG treatment [51]. Woldu et al. [58] found most patients with high-risk NMIBC did not express PD-L1 (5.9% of Ta, 30.0% of T1, and 3.6% of CIS); those who did were more likely to respond to BCG. Kates et al. [59] examined PDL-1 expression in two independent cohorts of patients with treatment-naïve, histologically confirmed NMIBC. Patients underwent treatment with TURBT and intravesical BCG, and the investigators compared immune cell populations among BCG responders ($n$ = 31) and BCG nonresponders ($n$ = 32). PD-L1 expression was present at baseline in 25% to 28% of nonresponders but in just 0% to 4% of responders ($P < 0.01$). The authors comment that baseline tumor PD-L1 expression may predict an unfavorable response to BCG, related to PDL-1-mediated resistance. If these data are validated, this particular group of patients may benefit from simultaneous checkpoint inhibition and BCG therapy [59].

This general tenet is the foundation for further clinical investigation of these agents in NMIBC, and is supported by different lines of clinical data (summarized below). Treatment options and rationale for combining BCG with anti-PD-(L)1 inhibitors to boost antitumor immune responses are shown in Fig. 1. The following section focuses on current clinical trials evaluating PD-(L)1 inhibitors. Phase 3 trials conducted in BCG-naïve, high-risk NMIBC patients are summarized in Table 2. Clinical trials in the second-line setting, for BCG-unresponsive or BCG-exposed, high-risk NMIBC are shown in Table 3.

### 5.2. Atezolizumab

Intravenous administration of the PD-L1 inhibitor atezolizumab has been assessed in a single-arm phase 2 trial (SWOG S1605; NCT02844816) in 166 patients with BCG-unresponsive NMIBC [60,61]. In the subset of patients with CIS ($n$ = 74, with or without concomitant Ta/T1a), a CR was observed in 20/74 patients at 6 months (27.0%; 95% CI 17, 38), based on mandatory re-biopsy [61,62], and CR rate was 13.5% at 18 months. The median duration of response was 16.5 months and 56% of the responses were durable to at least 12 months [60,61]. The 18-month event-free survival (EFS) in patients with Ta/T1 disease ($n$ = 55) was 49% (90% CI 38, 60) [61]. A subsequent Phase 1b/2 study evaluated the clinical efficacy of azetolizumab in 24 patients with high-risk BCG-unresponsive NMIBC (NCT02792192) [44]. Patients were assigned to two cohorts; cohort 1A received intravenous atezolizumab, 1200 mg every 3 weeks, for up to 96 weeks, while cohort 1B additionally received standard BCG induction and maintenance treatment. The 6-month CR rate was 33% in cohort 1 (median duration of CR, 6.8 months) and 42% in cohort 1B (median duration of CR, not yet reached, but ≥12 months) [44]. These data suggest clinically relevant activity for atezolimumab, with a combination approach favoring a longer duration of response. The open-label, randomized, phase 3 trial ALBAN (NCT03799835) is evaluating intravenous atezolizumab with intravesical BCG therapy, or BCG alone, in patients with BCG-naïve, high-risk NMIBC ($n$ = 516 estimated). The primary endpoint is recurrence-free survival [63].

### 5.3. Cetrelimab

Cetrelimab is a humanized IgG4 monoclonal antibody (mAb) that binds PD-1 [64]. It is being evaluated in combination with intravesical gemcitabine (225 mg) using the TAR200 delivery system, compared with each drug as monotherapy in patients with BCG-unresponsive NMIBC (CIS ± concurrent Ta/T1 tumor) who are ineligible for or who have elected not to undergo radical cystectomy. The primary endpoint is overall CR at any time point (SunRISe-1; NCT04640623) [65]. Assessment of CR was based on cystoscopy, centrally assessed urine cytology and mandated biopsy at weeks 24 and 48. Initial data from the monotherapy arms presented at AUA 2023, (TAR-200, $n$ = 23 and cetrelimab, $n$ = 24), indicated that 73% of patients in the TAR-200 arm achieved a CR, compared with 38% in the cetrelimab arm. These efficacy data (as well as preliminary safety data) support the ongoing study of TAR-200

with or without cetrelimab in patients with BCG-unresponsive high-risk NMIBC. Cetrelimab is also being evaluated in combination with intravesical gemcitabine using the TAR200 delivery system in patients with BCG-naïve high-risk NMIBC (EudraCT 2020-004506-64) [66].

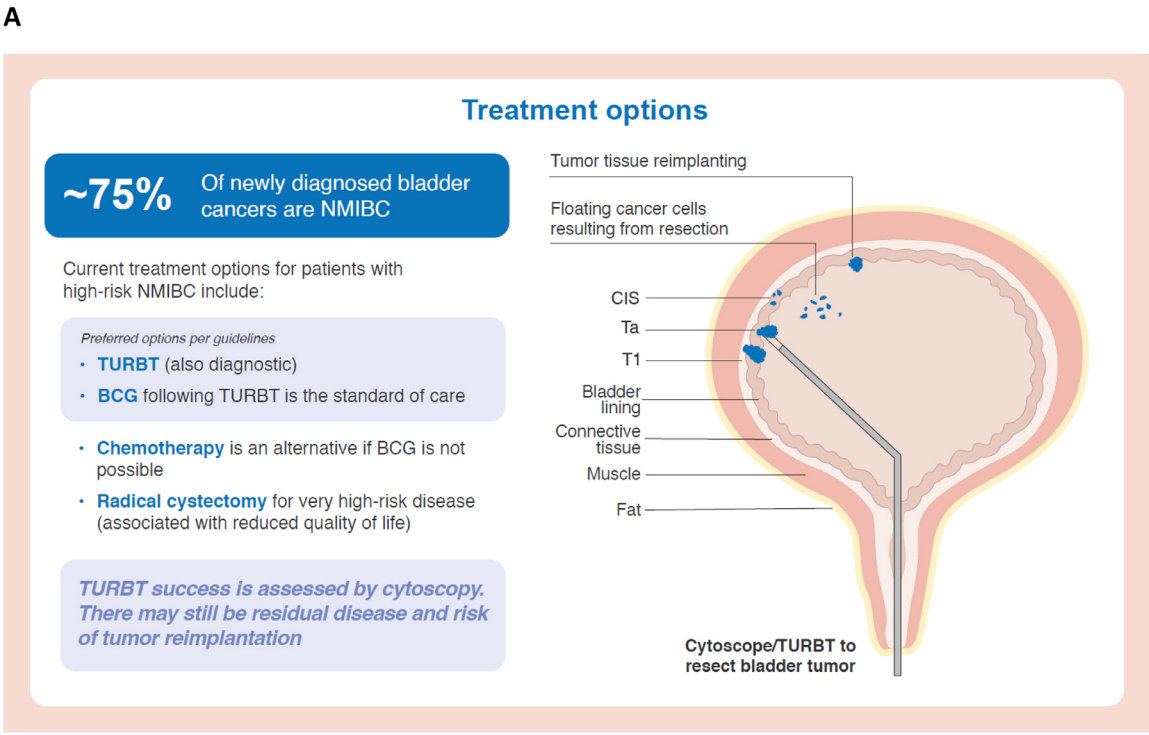
### 5.4. Durvalumab

The PD-(L)1 inhibitor durvalumab was evaluated in a phase 1 multiarm, multistage trial involving 28 BCG-unresponsive, high-risk NMIBC patients with CIS ($n$ = 15), high-grade Ta/T1 ($n$ = 9), or high-grade Ta/T1 + CIS ($n$ = 4) [43]. Patients were assigned to receive durvalumab alone, durvalumab and BCG, or durvalumab and external-beam radiotherapy. The intravenous durvalumab dose was 1120 mg on day 1 of each 3-week cycle up to a maximum of eight cycles. The primary endpoint was to establish the recommended phase 2 dose of each combination regimen. CR rates (95% CI) at 3 and 6 months, respectively, were reported in 33% (0.8%, 90.6%) and 0% for durvalumab alone, 83% (51.6%, 97.9%) and 71% (29.0%, 96.3%) for durvalumab + BCG, and 55% (23.4%, 83.3%) and 33% (4.3%, 77.7%) for durvalumab + EBR. No unexpected adverse events were observed (NCT03317158) [43]. The phase 2 portion enrolled patients into a number of high-risk NMIBC populations with variable BCG exposure histories (BCG-exposed or BCG-unresponsive NMIBC (NCT03759496). Data are currently available for the patients with BCG-unresponsive CIS ($n$ = 17) who received durvalumab IV, 1500 mg every 4 weeks for up to 12 months. The primary endpoint was CR at 6 months, defined by negative cystoscopy, urine cytology, and absence of high-grade recurrence on biopsy. Of the 17 patients, 2 (12%) achieved a CR at 6 months, with a duration of response of 10 months and 18 months [67].

Durvalumab is also being investigated in a phase 3, randomized, open-label study for treatment of high-risk, BCG-naïve patients with NMIBC (the POTOMAC trial; NCT03528694). The primary endpoint is to determine disease-free survival for patients with NMIBC treated with combination intravenous durvalumab + BCG (induction + 2-year maintenance), durvalumab + BCG (induction only), or BCG monotherapy (induction + 2-year maintenance).

### 5.5. Pembrolizumab

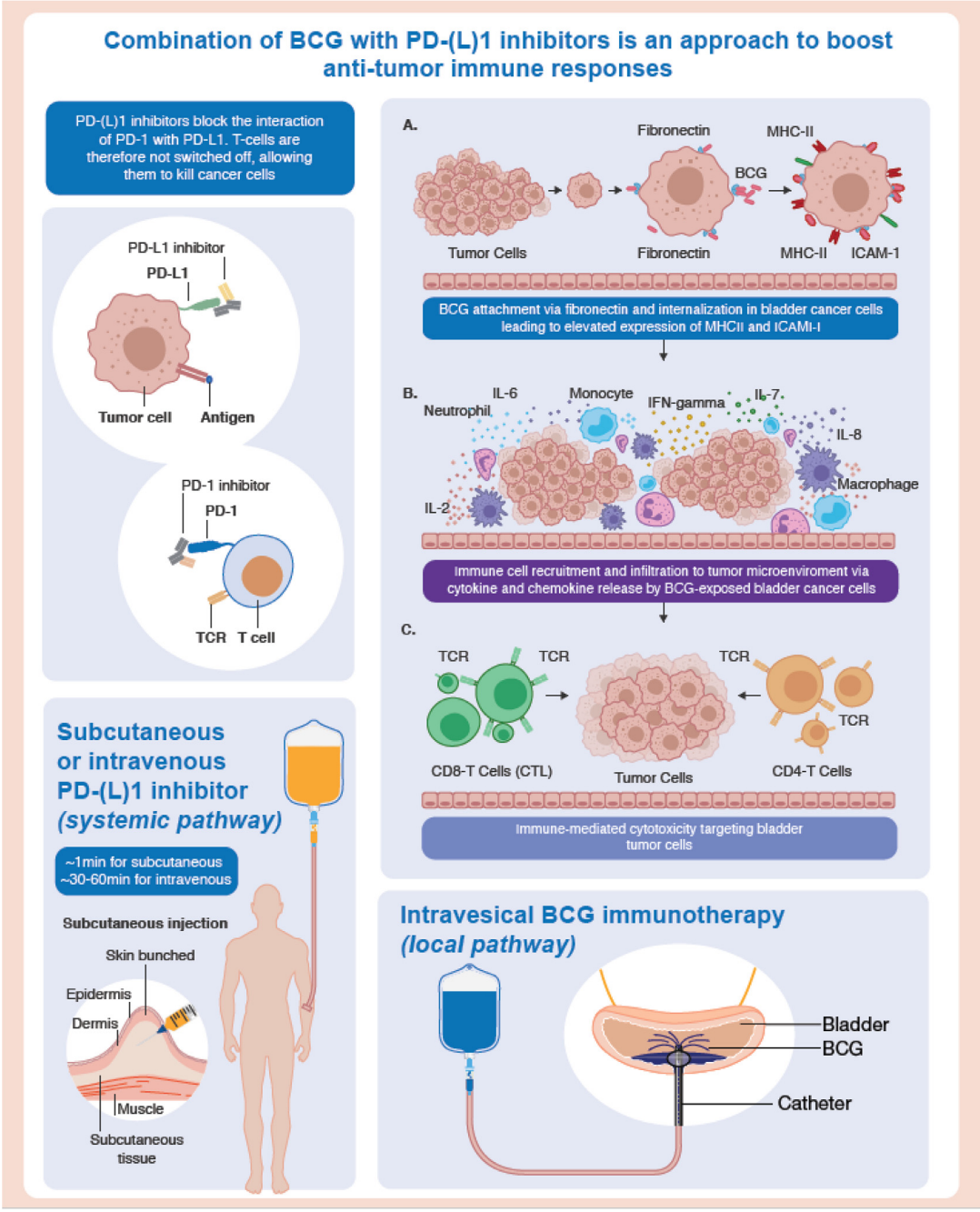
The PD-1 inhibitor, pembrolizumab, was approved by the US Food and Drug Administration (FDA) in 2020 for intravenous treatment (200 mg every 3 weeks) of patients with BCG-unresponsive, high-risk NMIBC with CIS, with or without papillary tumors, who were ineligible for radical cystectomy or chose not to undergo the surgery. In the sin-




BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer; PD-(L)1, programmed cell death-(ligand) 1; TURBT, transurethral resection of bladder tumor.

Fig. 1. Treatment options and rationale for combining BCG with anti-PD-(L)1 inhibitors to boost antitumor immune responses. (A) Treatment options. (B) Combination of BCG with PD-(L)1 is an approach to boost antitumor immune responses.

**B**




BCG pathway image adapted from Li J, et al. NPJ Vaccines. 2021 Jan 25;6(1):14. doi: 10.1038/s41541-020-00278-0. https://creativecommons.org/licenses/by/4.0/

BCG, Bacillus Calmette-Guérin; CTL, cytotoxic T-lymphocyte; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; PD-(L)1, programmed cell death-(ligand) 1; TCR, T-cell receptor

Fig. 1. Continued

Table 2
PD-(L)1 inhibitors in phase 3 trials—first-line therapy for BCG-naïve, high-risk NMIBC.

| | Durvalumab | Atezolizumab | Sasanlimab | Pembrolizumab |
|---|---|---|---|---|
| NCT number (familiar name) | NCT03528694 (POTOMAC) | NCT03799835 (ALBAN) | NCT04165317 (CREST) | NCT03711032 (KEYNOTE-676)[a] |
| Start/estimated primary completion dates | May 2018/Oct 2024 | Jan 2019/Apr 2024 | Dec 2019/Jun 2024 | Dec 2018/Dec 2025 |
| Trial design | Randomized, open-label, parallel-group, multicenter | Randomized, open-label, parallel-group, multicenter | Randomized, open-label, parallel-group, multicenter | Randomized, open-label, parallel-group, multicenter |
| Enrolled pts | $n$ = 1018 (actual) | $n$ = 516 (estimated) | $n$ = 1160 (estimated) | $n$ = 1405 (estimated) |
| Treatment arms | Durvalumab + BCG (IND + MAIN) or + BCG (IND) vs. BCG control | Atezolizumab + BCG (IND + MAIN) vs. BCG control | Sasanlimab + BCG (IND + MAIN) or + BCG (IND) vs. BCG control | Pembrolizumab + BCG (IND + MAIN) or + BCG (IND + reduced MAIN) vs. BCG (IND + MAIN) |
| PD-(L)1 regimen | Intravenous | Intravenous | Subcutaneous | Intravenous |
| Primary endpoint | DFS | RFS | EFS | EFS |
| Secondary endpoints[b] | DFS at 24 months; OS at 5 years | PFS, OS, DSS, CR, DW | OS, CR (pts with CIS), DSS, time to cystectomy | CR, DOR, 12-month DOR (CIS pts), RFS, OS, DSS |

NCT details available at www.clinicaltrials.gov, accessed December 2022.
BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; CR = complete response rate; DFS = disease-free survival; DOR = duration of response; DSS = disease-specific survival; DW = disease worsening; EFS = event-free survival; IND = induction; MAIN = maintenance; NMIBC = non-muscle-invasive bladder cancer; OS = overall survival; PD-(L)1 = programmed cell death-(ligand) 1; PFS = progression-free survival; RFS = recurrence-free survival.
[a] The KEYNOTE-676 trial is also evaluating pembrolizumab in BCG-exposed, high-risk NMIBC.
[b] Represents a selection of secondary endpoints. Additional information is disclosed at www.clinicaltrials.gov.

gle-arm phase 2 KEYNOTE-057 trial (NCT02625961), CR was achieved after 3 months in 39/96 patients (41%) and the median duration of response was 16.2 months [68], resulting in an ongoing CR of 19% (18/96) at 15 months.

A phase 3 study evaluating the efficacy and safety of BCG and intravenous pembrolizumab for persistent/recurrent, high-risk NMIBC (Cohort A) or BCG-naïve NMIBC (Cohort B; KEYNOTE-676, NCT03711032) is ongoing. Cohort A will receive BCG induction and maintenance only or pembrolizumab and BCG induction and maintenance. Patients with BCG-naïve, high-risk NMIBC (Cohort B) will receive pembrolizumab and BCG (induction + reduced/full maintenance) or BCG induction and maintenance alone. The primary endpoint is CR for Cohort A patients [69] and EFS for patients in Cohort B [70].

Pembrolizumab is being investigated for intravesical delivery in combination with BCG for patients with BCG-unresponsive NMIBC. A 3+3 phase 1 trial (NCT02808143) assessed safety and antitumor activity in nine patients receiving intravesical pembrolizumab (1−5 mg/kg for 2 hours) prior to BCG induction, up to disease recurrence or end of trial at 52 weeks [71]. Patients received a preinduction dose of pembrolizumab 2 weeks before BCG induction, followed by BCG at weeks 0 to 5 along with intravesical pembrolizumab at weeks 0, 2, and 4. Participants then received pembrolizumab every 2 weeks up to 17 weeks and then every 4 weeks for the remainder of the trial. Median follow-up was 35 months for the five patients still living at the end of the trial. The 6-month and 1-year recurrence-free rates (95% CI) were 67% (42%, 100%) and 22% (7%, 75%), respectively. A total of 21 grade 1 to 2 AEs were recorded, related to BCG and/or pembrolizumab; one grade 5 event (autoimmune disorder) related to pembrolizumab was reported. Transcriptomic analysis revealed evidence of decreased expression of T-cell exhaustion markers in patients with longer RFS [71].

### 5.6. Sasanlimab

Sasanlimab is a humanized IgG4 mAb with high affinity for human PD-1, evaluated in a phase 1 trial (multiple parts; NCT02573259) in patients with advanced or metastatic solid tumors. The safety and tolerability of both administration methods (intravenous and subcutaneous) was comparable. Exposure following subcutaneous administration was within the expected efficacious dose range and objective responses were seen, meaning subcutaneous administration of a PD-1 inhibitor in patients with advanced solid tumors is feasible [72]. In a phase 1b/II dose expansion study, patients with NSCLC ($n$ = 68) or urothelial carcinoma (UC) ($n$ = 38) received subcutaneous sasanlimab. Overall, sasanlimab was well tolerated; 13.2% of patients experienced grade 3 treatment-related AEs. The confirmed objective response rate was 16.4% and 18.4% in the NSCLC and UC cohorts, respectively and median PFS was 3.7 and 2.9 months. Corresponding median OS was 14.7 and 10.9 months, respectively. Overall, longer median PFS and OS correlated with high PD-L1 expression and high tumor mutational burden. Longer median PFS and OS were also associated with T-cell inflamed gene signature in the UC cohort. Subcutaneous sasanlimab may be a potential treatment option for patients with NSCLC or UC [73].

To prove clinical benefit, sasanlimab is under investigation in high-risk NMIBC in the phase 3 CREST trial (NCT04165317). This trial enrolled patients with BCG-

Table 3
Antitumor efficacy of PD-(L)1 inhibitors in ongoing clinical trials (alone or in combination)—second-line therapy for BCG-unresponsive or BCG-exposed, high-risk NMIBC.

| NCT number (acronym) | Phase | Study drug/treatment | Primary endpoint | Patients enrolled | Status/results |
|---|---|---|---|---|---|
| NCT04387461<br>CORE-001 | 2 | Pembrolizumab + CG0070 | CR | *n* = 35 (actual) | • CR 87.5% (14/16) at the 3-month assessment<br>• All pts in CR at 3 months remain in CR at 6 months (9/9), 9 months (6/6), and at 12 months (3/3) |
| NCT02808143 | 1 | Pembrolizumab + BCG | MTD up to 9 weeks | *n* = 9 (estimated) | Active |
| NCT02625961<br>(KEYNOTE-057) | 2 | Pembrolizumab only | CR | • Cohort A (CIS): *n* = 101<br>• Cohort B (non-CIS): *n* = 47 | 41% (39/96 pts; 95% CI 30.7%, 51.1%) |
| NCT03711032<br>(KEYNOTE-676) | 3 | • Pembrolizumab + BCG<br>• BCG | CR in CIS ~3.5 years | • *n* = 1405 (Dec 2022) | Recruiting |
| NCT04164082 | 2 | Pembrolizumab + gemcitabine[a] | CR in CIS (6 months) EFS (18 months) | *n* = 161 | Recruiting |
| NCT02901548 | 2 | Durvalumab | CR | Not applicable | Terminated early due to futility |
| NCT03759496 | 2 | Durvalumab [a] | • MTD at 6 months<br>• RFS at 6 and 12 months | *n* = 39 | Active |
| NCT03317158<br>(ADAPT-BLADDER) | 1/2 | • C 1: Durvalumab<br>• C 2: Durvalumab + BCG<br>• C 3: Durvalumab + EBR<br>• C 4: Durvalumab + GEM/DOC [a] | • Phase 1: RP2D (6 months)<br>• Phase 2: CR (at 6 months) | *n* = 186 (estimated) | Recruiting (ongoing)<br>• CR/3 months: 33% (D), 83% (D+BCG), 55% (D+EBR)<br>• CR/6 months: 0% (D), 71% (D+BCG), 33% (D+EBR) |
| NCT02792192 | 1/2 | P1: Atezolizumab<br>P2: Atezolizumab + BCG | Pts with AEs (%) | *n* = 24 | Terminated |
| NCT02844816<br>(SWOG S1605) | 2 | Atezolizumab only | CR at 6 months in CIS cohort<br>EFS up to 18 months in all pts | *n* = 128<br>CIS cohort: *n* = 74<br>Non-CIS cohort: *n* = 54 | CR (CIS) : 41% (3 months), 27% (6 months)<br>12-month duration of CR 54% (pts with CR 6 months)<br>EFS 18 months (CIS): 17% (90% CI 9%, 25%)<br>EFS 18 months (all pts): 29% (90% CI 22%, 36%)<br>EFS 18 months (Ta, T1): 45% (90% CI 34%, 57%) |
| NCT04640623<br>(SunRISe-1) | 2 | Cetrelimab + TAR200[a]<br>TAR200 [a]<br>Cetrelimab | CR | *n* = 200 (estimated) | Recruiting |

NCT details available at www.clinicaltrials.gov, accessed December 2022.
AE = adverse event; BCG = bacillus Calmette-Guérin; C = cohort; CI = confidence interval; CIS = carcinoma *in situ*; CR = complete response rate; D = durvalumab; DOC = docetaxel; EBR = external beam radiotherapy; EFS = event-free survival; GEM = gemcitabine; MTD = maximum tolerated dose; NMIBC = non-muscle-invasive bladder cancer; PD-(L)1 = programmed cell death-(ligand) 1; RFS = recurrence-free survival; RP2D = recommended phase 2 dose.
[a] Intravesical gemcitabine.

naïve, high-risk NMIBC and was designed to evaluate whether the combination of subcutaneous sasanlimab and BCG (induction + maintenance) or sasanlimab and BCG (induction only) is superior to BCG alone (induction + maintenance) in prolonging EFS (primary endpoint). The subcutaneous route of administration could result in lower drug administration-related healthcare costs and resource use [74].

## 6. Other therapies for NMIBC

Various other intravesical agents have been investigated in the pursuit of enhanced outcomes, including single-agent chemotherapy (e.g., mitomycin, gemcitabine, or docetaxel), sequential gemcitabine/docetaxel, and nanoparticle albumin-bound (nab)-paclitaxel. Responses to single-agent chemotherapy have been moderate and nondurable in first- and

second-line settings [75]. Multicenter retrospective results with gemcitabine/docetaxel are encouraging, leading to development of the phase 3 trial comparing gemcitabine/docetaxel administered intravesically vs. BCG in patients with BCG-naïve high-risk NMIBC (NCT05538663).

Other emerging treatments include intravesical nadofaragene firadenovec (rAd-IFNα/Syn3), a replication-deficient recombinant adenovirus that delivers human interferon alfa-2b cDNA into the urothelium. Nadofaragene demonstrated efficacy in BCG-unresponsive high-risk NMIBC [36] and was recently approved by the FDA for treatment of these patients. N-803, the immune cell–activating interleukin-15 (IL-15) superagonist, nogapendekin alfa inbakicept (NAI), was assessed in an open-label, 3-cohort study (QUILT 3.032) in patients with BCG-unresponsive bladder CIS with or without Ta/T1 papillary disease. Cohort A received intravesical N-803 plus BCG; cohort C received N-803 monotherapy, while Cohort B patients with high-grade Ta/T1 papillary NMIBC, received N-803 plus BCG. Cohort A (combination) achieved a CR rate of 71% (58/82), with a median duration of CR of 26.6 months. Cohort B (combination) had a Kaplan–Meier estimated DFS rate of 55.4% at 12 months with a median DFS of 19.3 months. Patients in cohort C (N-803 monotherapy) had a low response rate of 20% (2/10), with only 1 patient (10%) maintaining a CR at 6 months (cohort C was subsequently discontinued for futility). For cohorts A and B, CR rates were achieved with a persistence of effect, cystectomy avoidance, and 100% bladder cancer-specific survival at 24 months [42].

CG0070 is an oncolytic adenovirus with a granulocyte macrophage colony-stimulating factor transgene that is replication-selective for retinoblastoma pathway-defective tumors. It has demonstrated antitumor activity in NMIBC [37] and is being investigated as monotherapy in a single-arm phase 3 trial (BOND3; NCT04452591) and in combination with pembrolizumab in the phase 2 CORE-001 trial (NCT04387461)—both trials in patients with BCG-unresponsive CIS with or without Ta/T1 tumor [76].

A phase 2 randomized controlled trial involving high-risk NMIBC patients (excluding those with CIS) evaluated intravesical BCG, administered over 1 year, vs. hyperthermic intravesical chemotherapy (HIVEC) with mitomycin C, 40 mg, administered using the combat BRS system. The primary endpoint was RFS. After 24 months, RFS was 95.0% for HIVEC and 75.1% for BCG ($P = 0.064$) in the per-protocol analysis; mean time to recurrence was 21.5 and 16.1 months, respectively, for HIVEC and BCG. PFS for HIVEC vs. BCG was 100% and 75.1% ($P = 0.018$), respectively, in the per-protocol analysis [77].

## 7. Needs and challenges facing the introduction of PD-(L)1 therapies in NMIBC

PD-(L)1 inhibition-based therapies have set new standards in the treatment of patients with many cancer types, including advanced UC, particularly in those who have progressed on previous treatments. In general, immune checkpoint inhibitors targeting the PD1 /PD-L1 axis are well tolerated with a well defined rate of grade 3/4 toxicity, characterized by a well balanced risk-benefit ratio for patients with advanced UC, although the risk-benefit ratio for patients with NMIBC may be different. There is evidence of their efficacy in BCG-unresponsive NMIBC, but their potential benefit for BCG-naïve NMIBC relative to standard of care remains to be determined.

Optimal integration of these inhibitors earlier into clinical practice has several challenges that will need addressing (Box 1). Most critical will be the early recognition and treatment of potentially serious, irreversible and sometimes fatal immune-related adverse events (irAEs), elicited through activation of the immune system [78]. The most common systems/organs affected are the skin, gastrointestinal, endocrine, hepatic, renal, and pulmonary organ systems. Such events differ from non-irAEs seen with other therapies: they can have an unconventional clinical presentation and response to treatment, and can occur in any organ, at any time, during or after discontinuation of treatment [79].

**Box 1** Challenges to address for the introduction and practical implementation of novel PD-(L)1 inhibitors for NMIBC.

- Optimal management of irAEs by a well-trained, vigilant multidisciplinary team.
- Identification of provision barriers after PD-(L)1-based treatments are approved by the appropriate regulatory body.
- Review and adjustment of infrastructure to ensure that clinics in which PD-(L)1 inhibitors will be used are streamlined, thus permitting appropriate patient monitoring and management.
- Creative and up-to-date electronic systems for AE monitoring and management.
- Education for all members of the multidisciplinary team, on an ongoing basis (possibly included in CME programs), to optimize knowledge and management of AEs, particularly irAEs.
- Integrated patient management—especially between medical oncologists and urologists—wherever medical oncologists are administering the PD-(L)1 inhibitors.
- Define the optimal route of administration.
- AE = adverse event; CME = continuing medical education; irAE = immune-related adverse event; NMIBC = non-muscle-invasive bladder cancer; PD-(L)1 = programmed cell death-(ligand) 1.

Experience across cancer types suggests that the occurrence, frequency and severity of irAEs may depend on the specific PD-(L)1 inhibitor used, type of cancer, and individual patient characteristics (e.g., age, ethnicity). Treatment of irAEs often demands input from a multidisciplinary clinical team [80] and close monitoring and early recognition of signs and symptoms will enable prompt intervention, for example, by administering steroids [81].

A number of reviews have estimated the overall frequency of irAEs associated with PD-(L)1 inhibitors to be

around 70% [82]. In patients with pre-existing autoimmune disease, it has been reported that up to 75% experience irAEs, an exacerbation of a pre-existing autoimmune condition, or both [83]. Perhaps not surprisingly, a greater frequency of irAEs has been reported during combination therapy [84].

Fatal irAEs are uncommon (0.3%−1.3%) and generally occur early on during the course of treatment and evolve rapidly, particularly among patients receiving combination therapy with CTLA-4 inhibitors [85,86]. Fatal irAEs include myocarditis (8%), pneumonitis (35%), hepatitis (22%), colitis (17%), and neurologic events (15%) [86]. The most common irAEs associated with PD-(L)1 monotherapy are diarrhea (9.5%), hypothyroidism (6.1%), hyperthyroidism (2.8%), vitiligo (3.3%), pneumonitis (2.8%) and colitis 1.2% [81]. Reviewing the severity of irAEs, Wang et al. [81] commented that pneumonitis, hepatitis, colitis, and other endocrine dysfunctions were more likely to be grade 3 or higher.

A meta-analysis of 15 atezolizumab trials (mono- or combination therapy) in various cancers and involving more than 10,000 patients found that, overall, 44.8% of patients experienced at least 1 irAE of any grade; 9.3% experienced a ≥grade 3 event [87]. The most common irAEs (any grade) were rash (22.8%), hepatitis (12.4%), hypothyroidism (9.0%), pneumonitis (3.0%) and hyperthyroidism (2.4%). Most irAEs were mild (grade 1), while more severe irAEs (grade 3 or 4) tended to be cases of hepatitis and pneumonitis [87].

In KEYNOTE-045 and -052, which evaluated the efficacy of pembrolizumab in the treatment of metastatic UC, the overall frequency of irAEs was 19.5% (KEYNOTE-045) and 26.5% (KEYNOTE-052), mostly grade 1 or 2 [88]. The most common irAEs across the two studies were hypothyroidism, pneumonitis, hyperthyroidism, colitis, and severe skin reactions.

Some specific irAEs have a high mortality rate, namely myositis, myocarditis, and myasthenia gravis which commonly occur together and which can rapidly deteriorate [85,89,90]. For example, in the SWOG S1605 trial of atezolizumab three patients (1.8%) died, one due to immune-related myasthenia gravis followed by respiratory failure, one due to immune-related myositis, and one due to sepsis [61]. Clinicians treating patients with PD-(L)1 inhibitors need to be highly vigilant and must counsel patients and their families in relation to what they might experience and what course of action they should take. PD-(L)1 inhibitors are, however, the current standard of care in many types of advanced cancer (melanoma, colo-rectal cancer, renal cell cancer, Hodgkin's lymphoma, and NSCLC), and pre-existing guidelines and practices are well established in the medical oncology community, permitting successful early management [89,91]. To achieve optimal patient outcomes during PD-(L)1 treatment, urologists, medical oncologists, and other caregivers of patients with NMIBC will need to adopt these established practices for irAE management [79]. Treatment for irAEs includes temporary interruption of PD-(L)1 therapy and initiation of symptomatic and immunosuppressive and/or replacement therapy, as needed (e.g., corticosteroids) [79]. Essentially, for appropriate management, there is a need to fully understand the characteristics of irAEs associated with PD-(L)1 inhibitors. In some cases, complex irAEs dictate the need for a well-trained multidisciplinary team approach, encompassing front-line prescribers, other primary care staff who manage the patient outside of their oncology treatment, pharmacists, nurses, urologists, and organ-specific experts, such as rheumatologists, gastroenterologists, endocrinologists, and dermatologists. Educational programs should include patients and caregivers, who are at the front line of identifying AEs.

When PD-(L)1 inhibitors become a common treatment for patients with NMIBC, multidisciplinary care is likely to be needed to ensure that physicians deliver PD-(L)1 therapies across multiple settings. For example, combination treatment with PD-(L)1 inhibitors and intravesical therapies may be managed solely by urologists in large urologic group practices. Multidisciplinary care models involving patient referrals (and handoffs) from urologists to medical oncologists practicing in separate (or co-located and shared) facilities/locations may also be required. Alternatively, advanced practice providers may have a critical role to play in the multidisciplinary care setting involving urologists and medical oncologists. Whatever the care model, functional communication will be paramount.

At the core of achieving optimal management of NMIBC including complications associated with various treatments, is a need for a robust, creative, and wide-reaching approach to education. This might include sharing of best practice and dissemination of harmonized training at a regional (or wider) level. Ideally, this would be part of continuing medical education schemes. It might also include innovative use of digital therapeutics to support patients through their care and ease the burden on clinical teams, and perhaps "from trial to practice" approaches to help bring forward clinical implementation of new and evolving evidence, as well as leveraging knowledge from other indications.

Potential barriers to patient access must also be considered, such as financial constraints, which may impact staffing levels, both in and out of the clinic; adequate infrastructure and workflow procedures within clinics; and development of training and educational initiatives for patients, carers, and healthcare professionals to ensure optimal patient management. In some countries, the use of PD-(L)1-based therapies requires approval by local tumor boards; thus, uptake of new treatments is likely to be driven by urologists in tertiary care settings. There is a need to understand the impact of anti-PD-(L)1 uptake on provision of care, as well as a duty to ensure that tertiary care urologists receive adequate training and support to provide optimal care for patients.

## 8. Conclusions

Transurethral resection of bladder tumor with or without BCG is the current gold standard for high-risk NMIBC disease and response rates are high in most patients. Nevertheless, disease recurrence and progression are common (particularly in high-grade T1 disease) and new treatments are required to advance durable responses and help avoid the need for radical cystectomy and progression to systemic disease. The supply challenges, treatment compliance, and shortcomings of BCG have stimulated research into alternative therapies and several studies are exploring whether PD-(L)1 inhibitors used in combination with BCG may enhance outcomes. Early evidence suggests that addition of a PD-(L)1 inhibitor to the BCG regimen could extend the durability of response related to greater antitumor immune activation. Ongoing phase 3 trials with a reduced BCG regimen (induction only / PD-(L)1 inhibitor) will further inform the potential option to reduce the number of BCG administrations to reduce patient burden. Further research into the molecular mechanisms of NMIBC via molecular profiling will provide greater insight into the heterogeneity of NMIBC and identify drivers of treatment resistance and new therapeutic targets.

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## Author contributions

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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