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COMMENTARY

On the Horizon: A Global Multidisciplinary Perspective on Delivering Emerging Therapies for Patients with BCG-Naïve High-Risk NMIBC

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ABSTRACT

Patients with high-risk non-muscle invasive bladder cancer (NMIBC) are generally treated with transurethral resection of the bladder tumor followed by intravesical bacillus Calmette-Guérin (BCG), the current standard of care. However, recurrence or progression is common and may result in patients requiring radical cystectomy. Additionally, BCG continues to be in short supply worldwide. Therefore, there is an unmet need for new therapies that provide durable disease control and maintain quality of life. In the BCG-naïve high-risk NMIBC setting,

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potential new treatment options are emerging, with several regimens combining intravesical therapy with systemic PD-1 or PD-L1–directed immune checkpoint inhibitors (ICIs) currently under investigation in several Phase 3 trials. In routine clinical practice, NMIBC has traditionally been managed almost entirely by urologists. However, the introduction of systemic ICIs would likely require medical oncology expertise to help assess patients' fitness for these therapies and potentially for treatment administration and immune-related adverse event management. While multidisciplinary workflows are common practice for advanced bladder cancer, they would represent a paradigm shift in NMIBC. Based on current experience of managing patients with NMIBC across different countries and healthcare systems from our perspective as urologists, medical oncologists, and nurses, we discuss best practices for the potential integration of emerging therapies such as ICIs into the treatment of BCG-naïve high-risk NMIBC. We emphasize the need for multidisciplinary care, either through formalized multidisciplinary teams or cross-discipline collaborative workflows adapted to local needs, to ensure efficient coordination and sharing of responsibilities. Specialized nurses have the potential to play key roles across multiple aspects of patient care. We also highlight the crucial importance of effective communication across teams, increases in resourcing, and education for healthcare professionals, patients, and caregivers to enable eligible patients with high-risk NMIBC to benefit optimally from the introduction of these potential new treatment options.

Keywords: BCG-naïve; Immune checkpoint inhibitor; Medical oncologist; Multidisciplinary; Non-muscle invasive bladder cancer; Nurse; Patient experience; PD-1 inhibitor; PD-L1 inhibitor; Urologist

Key Summary Points

For patients with high-risk non-muscle invasive bladder cancer (NMIBC), bacillus Calmette-Guérin (BCG) is generally an effective treatment option. Nonetheless, many patients ultimately experience recurrence or progression, and a substantial unmet need remains for new therapeutic options that can improve disease control and maintain quality of life.

New potential treatments are on the horizon for BCG-naïve NMIBC, notably systemic PD-(L)1 inhibitors in combination with intravesical BCG; however, their utilization would require a shift from the traditional model of NMIBC treatment as almost entirely the responsibility of urologists to a new paradigm of multidisciplinary care to harness the expertise of medical oncologists in the administration of these agents and overall patient management.

To integrate PD-(L)1 inhibitors into the treatment algorithm for NMIBC, urologists and medical oncologists, supported by nurses, pharmacists, and other disciplines, would need to work together closely, through either formalized multidisciplinary teams or cross-discipline collaborative workflows adapted to local needs.

Effective communication across teams, increased levels of resources, and education for healthcare professionals, patients, and caregivers would all be of utmost importance to ensure eligible patients with high-risk NMIBC could derive optimal benefit from the availability of such treatment options.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.28633256.

INTRODUCTION

Bladder cancer is the ninth most common cancer globally and sixth most common in the US, with non-muscle invasive bladder cancer (NMIBC) accounting for approximately 75% of cases [1–3]. Initial treatment for NMIBC is generally the attempted complete removal of the tumor through transurethral resection of bladder tumor (TURBT) surgery. Risk stratification based on clinical and pathological features, including stage, grade, and other prognostic risk factors, is pivotal for subsequent treatment recommendations [3–7]. For high-risk NMIBC, intravesical bacillus Calmette-Guérin (BCG) is the standard of care post TURBT and typically consists of induction followed by maintenance therapy. Another option is radical cystectomy, especially if very high-risk features are present [3, 5–7].

The unmet need for high-risk NMIBC remains substantial. This is only partly due to the current global shortage of BCG. BCG is generally efficacious, with most patients achieving an initial response that is durable [8]. Nonetheless, many patients experience BCG failure, resulting in recurrence or progression of their disease. This includes patients who are BCG-refractory, characterized by persistent or rapidly recurring disease during treatment, patients who relapse after having achieved a response to BCG, and patients whose disease recurs or persists as a result of inadequate treatment due to BCG intolerance [9, 10]. In such cases, radical cystectomy with urinary diversion is considered standard of care. However, many patients with bladder cancer are elderly and may not be candidates for cystectomy or may decline such life-altering surgery. As an alternative, intravesical chemotherapy may be offered. For BCG-unresponsive high-risk NMIBC, including BCG-refractory and early BCG-relapsing tumors, several additional treatment options have gained US FDA approval, including the PD-1 inhibitor pembrolizumab, the gene-based therapy nadofaragene firadenovec, and the immunomodulating drug nogapendekin alfa inbakicept plus BCG, but are not available in many other countries [3, 5, 6, 9, 11–13]. This highlights the ongoing need for new safe and effective treatment options in the BCG-naïve setting to increase durability of disease control while optimally maintaining quality of life.

A paradigm shift may be on the horizon for BCG-naïve high-risk NMIBC. New treatment options, including systemic immune checkpoint inhibitors (ICIs) targeting PD-1 or PD-L1 (PD-[L]1) are being evaluated in combination with intravesical therapy in a number of pivotal Phase 3 trials in this setting [13–19]. PD-(L)1 inhibitors are widely used in advanced and metastatic bladder cancer [6, 20–22], and their introduction for treatment of NMIBC holds great promise. However, for patients to benefit fully, adjustments to how treatment is delivered may be required. NMIBC is predominantly managed by urologists. In contrast, treatment for muscle-invasive and metastatic bladder cancer is typically delivered through multidisciplinary care, with medical oncologists responsible for administering systemic therapies, including ICIs. To successfully deliver PD-(L)1 inhibitors for NMIBC, efficient integration of urology and medical oncology expertise into the treatment framework is essential [14, 23].

In this commentary, we examine the current management of NMIBC across different countries and healthcare systems, including in Canada, Germany, Spain, the UK, and the US, from the perspective of urologists, medical oncologists, and nurses. Based on this, we recommend best practices for integrating potentially emerging therapies such as ICIs to improve clinical outcomes in BCG-naïve high-risk NMIBC.

CURRENT MANAGEMENT OF PATIENTS WITH BLADDER CANCER

Patients with suspected bladder cancer typically present to their primary care provider or emergency care team, usually with hematuria. Patients are referred to urologists for assessment, risk stratification, and diagnosis, which are performed with support from nurses, radiologists, and pathologists. For NMIBC, treatment is led by urologists. For high-risk NMIBC, initial TURBT, intravesical BCG or intravesical chemotherapy,

and radical cystectomy are standard options managed by the urology team [5–7, 9, 11, 12]. If localized muscle-invasive bladder cancer (MIBC) is diagnosed, standard treatment is either radical cystectomy, with neoadjuvant chemotherapy for eligible patients, or bladder preservation with maximum TURBT followed by concurrent chemotherapy and radiation (trimodal therapy) [6, 7, 20]. These modalities involve close collaboration among urologists, radiation oncologists, and medical oncologists, with shared decision-making by multidisciplinary teams (MDTs) [24–26]. Advanced or metastatic bladder cancer is typically treated with systemic chemotherapy, including antibody-drug conjugates, and/or ICIs, or sometimes chemoradiotherapy or palliative radiotherapy [6, 7, 20], mostly managed by medical oncologists and clinical/radiation oncologists.

MULTIDISCIPLINARY CARE IN BLADDER CANCER

High-risk NMIBC is largely regarded as the responsibility of urologists. For a limited number of complex cases, radiation or medical oncologists may be involved, via either MDTs or less formal collaborative arrangements between disciplines. Such input may be sought for patients with very high-risk features or with BCG-unresponsive NMIBC and limited intravesical or surgical options, who may require alternative approaches such as radiation therapy or systemic treatment. While multidisciplinary care for NMIBC is currently not routine in most settings, approaches can vary considerably by country and practice type. In countries with centralized cancer treatment pathways that mandate MDTs, such as the UK, patients with high-risk NMIBC are included in MDT discussions. Individual uro-oncology practices that offer a full range of approved treatments, relatively common in the US, may also use multidisciplinary approaches for NMIBC. However, given the number of patients with high-risk NMIBC, MDT discussion of all cases is currently not seen as practical in many locations, including clinics in Canada, Germany, Spain, and the US.

In contrast, multidisciplinary care is well established in MIBC and metastatic bladder cancer, where systemic treatments and radiation therapy require additional expertise. Bladder cancer MDTs typically include urologists, medical oncologists, radiation oncologists, radiologists, pathologists, and specialized nurses. Pharmacists or genetic counselors may also be involved. MDT coordinators supporting planning and administrative tasks may be included, too. However, variations on a full MDT approach are also commonly adopted. These include joint clinics between urologists and radiation oncologists, potentially with concurrent medical oncology clinics for prompt referral, and additional discussion of difficult cases. Alternatively, established relationships and close communication between urologists and other disciplines can enable effective collaboration without formal MDT structures.

Successful bladder cancer MDT meetings can take a range of formats. They may be dedicated bladder cancer forums, specialize in pelvic malignancies, or cover a broader range of genitourinary cancers, such as kidney, testicular, and retroperitoneal tumors. Typically, MDTs meet on a weekly basis for between 1 h and half a day; however, some centers may hold meetings at varying intervals as needed. Meetings can be conducted either in-person or virtually. They may include healthcare professionals (HCPs) from a single institution or participants from several hospitals or clinics across a region.

Nurses and advanced practice providers are integral members of urology, medical oncology, and multidisciplinary teams, with essential roles in treatment and follow-up for all stages of bladder cancer. Depending on country or practice type, specialized nurses may schedule and administer intravesical and intravenous (IV) therapies, including BCG, chemotherapy, and ICIs, request laboratory analyses and imaging, and monitor adverse events (AEs). In addition, nurses may conduct tasks such as diagnostic and surveillance cystoscopies; however, there are notable differences in workflow between countries, with this being common practice in the UK but not in Canada, Germany, or Spain, and varying by clinic in the US. Nurses are also key for liaising between patients and doctors,

providing patient education, and supporting patients through their cancer treatment journey. In addition, patient advocates may sometimes be included for patient-to-patient support.

CURRENT EXPERIENCE WITH PD-(L)1 INHIBITORS IN NMIBC

There is currently limited experience with PD-(L)1 inhibitors in NMIBC outside clinical trials. Pembrolizumab monotherapy is FDA approved for some patients with BCG-unresponsive high-risk NMIBC, although use in clinical practice appears relatively low. In many other countries, including Canada, Germany, Spain, and the UK, regulatory and/or funding constraints mean that standard PD-(L)1 inhibitor therapy is not currently available for patients with NMIBC.

PD-(L)1 inhibitors are, however, emerging as potential combination partners for BCG in the BCG-naïve setting [14–18]. BCG is a live, attenuated strain of *Mycobacterium* that infects bladder epithelial cells, resulting in immune cell recruitment and immune-mediated killing of tumor cells [12]. PD-L1 is frequently overexpressed in cancer and can mediate immune escape by binding PD-1 on T cells, suppressing antitumor immunity [27]. Preclinical and clinical studies have suggested that BCG may upregulate PD-L1 expression in bladder cancer cells, which may in turn reduce the antitumor response to BCG [28, 29]. Combining BCG with PD-(L)1 inhibitors could therefore be an effective strategy for inhibiting tumor growth and addressing the unmet need for improved and more durable responses in BCG-naïve high-risk NMIBC [12, 14, 23, 28, 29]. Early safety data support the feasibility of combining PD-(L)1 inhibitor with BCG [30, 31]. Preliminary efficacy results in the BCG-naïve setting for atezolizumab plus BCG from the Phase 1b/2 BladderGATE trial appear promising, with a 2-year local recurrence rate of 14% [31], and Phase 3 data for several PD-(L)1 inhibitor combinations with BCG are awaited [15–18].

Clinical trials have provided the first opportunity for many urologists to gain experience with PD-(L)1 inhibitors in BCG-naïve high-risk NMIBC. While some urologists or uro-oncologists can administer systemic treatments, medical oncology expertise is typically required. PD-(L)1 inhibitors are usually administered IV, a procedure not offered by most urology practices. There is increasing interest in evaluating subcutaneous (SC) formulations of PD-(L)1 inhibitors [32–34]. One of these, sasanlimab, is being studied in BCG-naïve high-risk NMIBC [16], where multidisciplinary collaboration has allowed urologists to acquire familiarity with PD-(L)1 inhibitors and their characteristic safety profile. While ICIs are relatively well tolerated compared with chemotherapy, immune-related AEs (irAEs) are potentially serious, and early identification and prompt management are imperative [35, 36]. To date, medical oncologists have largely been responsible for administering PD-(L)1 inhibitors and managing irAEs or have supported urologists in the context of clinical trials in NMIBC. Efficient communication coupled with a clear allocation of responsibilities underpins optimal care when multiple disciplines are involved in treatment. Agreement on how to share monitoring and management of AEs is particularly important.

A MULTIDISCIPLINARY APPROACH TO DELIVERING PD-(L)1 INHIBITOR THERAPY IN HIGH-RISK NMIBC

Clinical data establishing the potential for a combination of PD-(L)1 inhibitors with BCG to improve outcomes in BCG-naïve high-risk NMIBC are on the horizon. Ongoing Phase 3 studies include ALBAN (atezolizumab, IV), CREST (sasanlimab, SC), KEYNOTE-676 (pembrolizumab, IV), and POTOMAC (durvalumab, IV) [15–18, 23]. Additionally, an IV ICI combined with intravesical chemotherapy is being investigated in BCG-naïve high-risk NMIBC in the Phase 3 SunRISe-3 trial, which is evaluating TAR-200, a novel gemcitabine delivery system with and without the PD-1 inhibitor cetrelimab (Table 1) [19, 37].

For patients to fully benefit from such therapies in clinical practice, current workflows in high-risk NMIBC would require modification,

Table 1 Overview of ongoing Phase 3 trials including PD-(L)1 inhibitor combinations for BCG-naïve high-risk NMIBC

Trial	Key eligibility criteria	Treatment regimen	Endpoints
ALBAN [15, 44] (NCT03799835) Target size: $n = 614$	BCG-naïve high-risk NMIBC T1, high grade, or CIS TURBT No prior BCG No prior ICIs or immunostimulatory agents	**Atezolizumab + BCG** **Atezolizumab** (IV): q3w for up to 18 cycles (1 year) **BCG** (intravesical): Induction, 6 × qw. Maintenance, 3 × qw at 3, 6, and 12 months **BCG alone** **BCG** (intravesical): Induction, 6 × qw. Maintenance, 3 × qw at 3, 6, and 12 months	**Primary:** EFS[a] **Key secondary:** OS PFS CR HRQOL Safety
CREST [16, 45] (NCT04165317) Target size: $n \approx 1000$	BCG-naïve high-risk NMIBC T1, high-grade Ta, or CIS TURBT ≤ 12 weeks prior No BCG in previous 2 years No prior PD-1, PL-L1, PD-L2, or CTLA-4 inhibitor, or immune-stimulatory agents	**Sasanlimab + BCG** **Sasanlimab** (SC): For up to 25 cycles **BCG** (intravesical): Induction, 6 × qw. Maintenance, up to cycle 25 **Sasanlimab + BCG** **Sasanlimab** (SC): For up to 25 cycles **BCG** (intravesical): Induction only, 6 × qw **BCG alone** **BCG** (intravesical): Induction, 6 × qw. Maintenance, up to cycle 25	**Primary:** EFS[a] **Key secondary:** OS CR (CIS only) DOCR (CIS only) Safety HRQOL

Table 1 continued

Trial	Key eligibility criteria	Treatment regimen	Endpoints
KEYNOTE-676 Cohort B [17, 46] (NCT03711032) Target size: *n* = 975	BCG-naïve high-risk NMIBC T1, high-grade Ta, or CIS TURBT ≤ 12 weeks prior No BCG in previous 2 years No prior inhibitor of PD-1, PL-L1, PD-L2, or another stimulatory or co-inhibitory T-cell receptor	**Pembrolizumab + BCG** **Pembrolizumab** (IV): q6w for 9 cycles (≈1 year) **BCG** (intravesical): Induction Full maintenance, up to 18 months **Pembrolizumab + BCG** **Pembrolizumab** (IV): q6w for 9 cycles (≈1 year) **BCG** (intravesical): Induction Reduced maintenance, up to 6 months **BCG alone** **BCG** (intravesical): Induction Full maintenance, up to 18 months	**Primary:** EFS[a] **Key secondary:** CR DOR 12-month DOR (CIS only) 24-month EFS OS Safety
POTOMAC [18, 23, 47] (NCT03528694) Target size: *n* = 975	BCG-naïve high-risk NMIBC T1, high grade, CIS, or multiple, recurrent and large TURBT ≤ 4 months prior No BCG in previous 3 years No prior immune-mediated cancer therapy	**Durvalumab + BCG** **Durvalumab** (IV): q4w for 13 cycles **BCG** (intravesical): Induction, 6 × qw. Maintenance, 3 × qw at 3, 6, 12, 18, and 24 months **Durvalumab + BCG** **Durvalumab** (IV): q4w for 13 cycles **BCG** (intravesical): Induction only, 6 × qw **BCG alone** **BCG** (intravesical): Induction, 6 × qw. Maintenance, 3 × qw at 3, 6, 12, 18, and 24 months	**Primary:** DFS **Key secondary:** DFS at 24 months OS OS at 5 years Pharmacokinetics Safety HRQOL

Table 1 continued

Trial	Key eligibility criteria	Treatment regimen	Endpoints
SunRISe-3 [19, 37, 48] (NCT05714202) Target size: $n = 1050$	BCG-naïve high-risk NMIBC T1, high-grade Ta, or CIS TURBT No BCG in previous 3 years	**TAR-200 + cetrelimab** **TAR-200** (intravesical): Induction, q3w. Maintenance, q12w **Cetrelimab** (IV) **TAR-200 alone** **TAR-200** (intravesical): Induction, q3w. Maintenance, q12w **BCG** **BCG** (intravesical): Induction, 6 × qw. Maintenance, 3 × qw at 12, 24, 48, 72, and 96 weeks	**Primary:** EFS[a] **Key secondary:** CR DOCR RFS OS Safety HRQOL

BCG bacillus Calmette-Guérin, *CIS* carcinoma in situ, *CR* complete response, *DFS* disease-free survival, *DOCR* duration of CR, *DOR* duration of response, *EFS* event-free survival, *HRQOL* health-related quality of life, *ICI* immune checkpoint inhibitor, *IV* intravenous, *NMIBC* non-muscle invasive bladder cancer, *OS* overall survival, *PFS* progression-free survival, *qw* once weekly, *q3w* once every 3 weeks, *q4w* once every 4 weeks, *q6w* once every 6 weeks, *q12w* once every 12 weeks, *RFS* recurrence-free survival, *SC* subcutaneous, *TURBT* transurethral resection of bladder tumor

[a]EFS is defined as the time from randomization to the time of first EFS event, with the details of what constitutes an EFS event specific to each trial

with a focus on multidisciplinary collaboration and shared responsibility. Urologists would need to consider patients for PD-(L)1 inhibitor treatment and potentially involve medical oncologists for assessment, therapy administration, and subsequent monitoring. Some urology practices may be able to offer systemic PD-(L)1 inhibitor therapy in-house. However, most may have to partner with medical oncologists and harness their existing expertise and infrastructure, including pharmacy and nursing support, and space for infusions for IV (but not SC) agents.

Parallel treatment with intravesical BCG and systemic PD-(L)1 inhibitors requires coordination [23]. Flexible cooperation would allow adapting to either IV or SC administration. SC agents may provide greater ease of use and reduce infusion chair requirements. In addition, many patients prefer SC over IV administration because of shorter treatment times and decreased discomfort [32–34, 38]. Depending on efficacy in the ongoing Phase 3 trials, there may be a potential for a PD-(L)1 inhibitor–only maintenance schedule. This could relieve pressures resulting from the ongoing BCG supply shortage [3, 23]. Monitoring patients throughout their treatment journey would probably require input from both urology and medical oncology, at least initially. Urologists conduct surveillance cystoscopies, biopsies, and follow-up monitoring to assess treatment response, recurrence, and cancer progression. Depending on country or institute, laboratory parameter analyses, irAE management, and patient education may remain the primary responsibility of medical oncology, unless or until urology teams receive full training and adequate resource for these aspects of PD-(L)1 inhibitor therapy. Developing robust collaborative workflows would be essential to ensure patient safety and continuity of care, especially regarding irAEs. As healthcare systems continue to evolve, delivery models may need to adapt. On a practical level, with appropriate training, nurses and advanced practice providers could perform many of the tasks required, as the experience from countries such as the UK demonstrates, where specialized nurses can deliver most of the care in NMIBC.

MDTs form a cornerstone of cancer care in many countries and settings [24, 39, 40], and well-structured and appropriately resourced MDTs would probably bring significant value to the delivery of PD-(L)1 inhibitors in BCG-naïve high-risk NMIBC. In MIBC, multidisciplinary care models were shown to impact treatment recommendations, encourage increased utilization of new therapies such as ICIs, and improve outcomes [26, 41, 42]. Such benefits may translate to earlier disease stages. However, to be effective, MDTs need efficient organization and sufficient levels of resourcing [39, 40]. Capacity challenges may result in recommendations to streamline MDT approaches to focus discussion on selected more complex cases [39, 43].

While formalized MDTs that include all relevant disciplines provide several advantages, multidisciplinary care can also be promoted through more flexible arrangements adapted to local needs and specific disease settings. If PD-(L)1 inhibitors gained approval for BCG-naïve high-risk NMIBC, not all eligible patients would necessarily require wider MDT discussion. This could be reserved for complex cases, while for standard scenarios, close working relationships allowing direct referrals from urologists to medical oncologists might be most appropriate. Other disciplines, such as radiation oncology and pathology, could be involved as required. In settings with limited experience of multidisciplinary care in NMIBC, the creation of new structures would be important. Regardless of the format chosen, increased focus on collaborative workflows among disciplines, underpinned by effective communication, would be crucial. This can be facilitated by clearly defined roles and responsibilities and optimal utilization of support from nurses, other care providers, and coordinators.

The collaborative treatment pathways already mapped out in the context of PD-(L)1 inhibitor trials in NMIBC could potentially provide a foundation for expanding established patterns to a

Table 2 Examples of organizations with roles in supporting changes to patient management and providing peer-to-peer education in NMIBC

Urology and oncology associations
American Urological Association
Large Urology Group Practice Association
Canadian Urological Association
Society of Urologic Oncology
Genitourinary Medical Oncologists of Canada
European Association of Urology
European Society for Medical Oncology
British Association of Urological Surgeons
Educational initiatives
International Bladder Cancer Network
International Bladder Cancer Group
International Bladder Cancer Update
GU CONNECT
GU NURSES CONNECT
Nursing organizations
Society of Urologic Nurses and Associates
European Association of Urology Nurses
British Association of Urological Nurses
Patient advocacy groups
World Bladder Cancer Patient Coalition
Bladder Cancer Advocacy Network

wider patient population in routine clinical practice. However, given the substantial increase in the number of patients eligible for multidisciplinary care in case of regulatory approval, a shift in the treatment paradigm would need to be accompanied by an expansion in staffing, resources, and space. Important limiting factors include the availability of urologists, medical oncologists, pharmacists, and nurses or other care providers to coordinate and administer systemic treatment and manage AEs and the provision of locations for IV infusion.

Education and training for participating HCPs is a further key priority. For urologists especially, integrating systemic ICIs into their practice would involve several new responsibilities. Familiarity with the new treatment options is necessary to assess patients for potential benefits and risks. Regardless of medical oncology input, urology teams would require training on the safety profile of PD-(L)1 inhibitors to support irAE identification and management throughout the treatment journey. Medical oncology teams should gain knowledge of AEs related to BCG.

From a patient perspective, additional education and support would also be essential. This would probably rely primarily on nurses. Patients need sufficient information to participate in shared decision-making. For PD-(L)1 inhibitor treatment, they must be able to recognize and report symptoms in a timely manner, and a close connection between patient and healthcare team needs to be in place in case of emergencies. Patients and caregivers would likely need increased support to navigate a more complex treatment pathway, with more clinic visits and interactions with a broader range of clinicians and nurses. This would be facilitated by closely integrated multidisciplinary care.

We would also like to emphasize the role of urology and bladder cancer organizations in helping to shape the evolving management framework for patients with NMIBC. National and international urology and oncology associations, scientific societies, educational initiatives, and patient advocacy groups can promote structural changes and provide peer-to-peer education for clinicians, nurses, and patients (Table 2). To reach as wide an audience as possible, this should be complemented by the involvement of experts in education and training at a local level.

ENSURING BEST PRACTICE FOR HIGH-RISK NMIBC IN A CHANGING TREATMENT LANDSCAPE

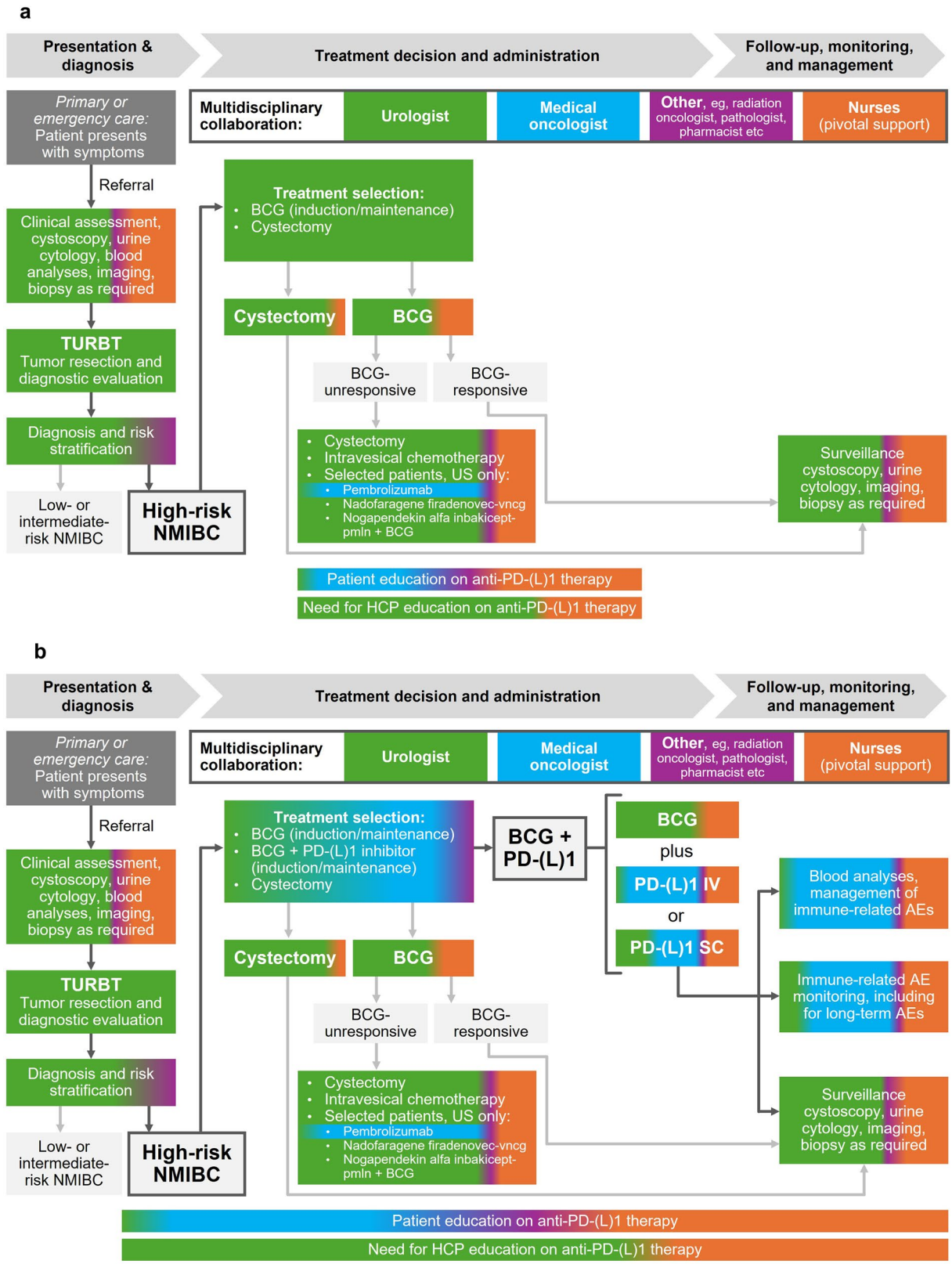
High-risk NMIBC remains an area of substantial unmet need. Many patients experience

recurrence and progression post BCG but wish to avoid, or may not be fit for, radical cystectomy [3, 5, 9]. PD-(L)1 inhibitors in combination with BCG are emerging as potentially promising options for improving response rates and durability of response in BCG-naïve high-risk NMIBC. They may delay recurrence and progression and could provide a bladder-sparing alternative to help maintain quality of life [14, 23]. If approved, a shift from traditionally urology-based treatment to multidisciplinary care underpinning their introduction in BCG-naïve high-risk NMIBC would be a key step toward ensuring that PD-(L)1 inhibitors are used optimally for patient care (Fig. 1).

Based on upcoming clinical data and current workflows for bladder cancer, we would like to make the following recommendations to support the potential integration of PD-(L)1 inhibitor therapy into the treatment of high-risk NMIBC:

- *Treatment of high-risk NMIBC should be based on either formalized MDTs conducting regular meetings or adapted pathways focused on collaborative workflows involving urologists, medical oncologists, pathologists, radiation oncologists, nurses, and advanced practice providers, with an emphasis on effective coordination and shared patient care.*
- *Countries and treatment centers currently practicing multidisciplinary approaches for NMIBC, including in the context of clinical trials, should be encouraged to share their insights and best practices to help drive wider adoption of collaborative strategies.*
- *Guidance and training should be developed to support best practices for integrating effective, timely, high-quality multidisciplinary care for high-risk NMIBC into existing local treatment frameworks (*Figure S1).
- *SC options for PD-(L)1 inhibitor therapy should be considered in high-risk NMIBC, depending on upcoming clinical trial data, as they may facilitate treatment delivery by allowing urology-led administration. SC formulations may also reduce infusion chair requirements and cost burden for healthcare systems compared with IV agents. In addition, patients frequently favor SC over IV administration as it is less invasive and less time-consuming.*
- *Peer-to-peer education for HCPs, especially for urology teams, is a key priority. Educational activities via scientific societies, congresses, and continuing medical education, alongside training and workshops delivered at the local or regional level, can all play a vital role. Virtual events and online training materials can further facilitate participation.*
- *Urology and oncology organizations should be encouraged to support education and training and promote the implementation of new efficient multidisciplinary pathways for high-risk NMIBC to foster best practice.*

In summary, the potential emergence of PD-(L)1 inhibitors for BCG-naïve high-risk NMIBC may transform the treatment landscape in early-stage bladder cancer, necessitating a paradigm shift to more multidisciplinary care. Developing collaborative treatment pathways, sharing best practices across disciplines and healthcare systems, and providing educational and training opportunities for HCPs are all crucial to ensure that eligible patients with high-risk NMIBC benefit optimally from such new treatment options.


a
Presentation & diagnosis
Treatment decision and administration
Follow-up, monitoring, and management
Primary or emergency care: Patient presents with symptoms
Multidisciplinary collaboration:
Urologist
Medical oncologist
Other, eg, radiation oncologist, pathologist, pharmacist etc
Nurses (pivotal support)
Referral
Clinical assessment, cystoscopy, urine cytology, blood analyses, imaging, biopsy as required
TURBT
Tumor resection and diagnostic evaluation
Diagnosis and risk stratification
Low- or intermediate-risk NMIBC
High-risk NMIBC
Treatment selection:
BCG (induction/maintenance)
Cystectomy
Cystectomy
BCG
BCG-unresponsive
BCG-responsive
Cystectomy
Intravesical chemotherapy
Selected patients, US only:
Pembrolizumab
Nadofaragene firadenovec-vncg
Nogapendekin alfa inbakicept-pmln + BCG
Surveillance cystoscopy, urine cytology, imaging, biopsy as required
Patient education on anti-PD-(L)1 therapy
Need for HCP education on anti-PD-(L)1 therapy
b
Presentation & diagnosis
Treatment decision and administration
Follow-up, monitoring, and management
Primary or emergency care: Patient presents with symptoms
Multidisciplinary collaboration:
Urologist
Medical oncologist
Other, eg, radiation oncologist, pathologist, pharmacist etc
Nurses (pivotal support)
Referral
Clinical assessment, cystoscopy, urine cytology, blood analyses, imaging, biopsy as required
TURBT
Tumor resection and diagnostic evaluation
Diagnosis and risk stratification
Low- or intermediate-risk NMIBC
High-risk NMIBC
Treatment selection:
BCG (induction/maintenance)
BCG + PD-(L)1 inhibitor (induction/maintenance)
Cystectomy
BCG + PD-(L)1
BCG
plus
PD-(L)1 IV
or
PD-(L)1 SC
Cystectomy
BCG
BCG-unresponsive
BCG-responsive
Cystectomy
Intravesical chemotherapy
Selected patients, US only:
Pembrolizumab
Nadofaragene firadenovec-vncg
Nogapendekin alfa inbakicept-pmln + BCG
Blood analyses, management of immune-related AEs
Immune-related AE monitoring, including for long-term AEs
Surveillance cystoscopy, urine cytology, imaging, biopsy as required
Patient education on anti-PD-(L)1 therapy
Need for HCP education on anti-PD-(L)1 therapy

◂**Fig. 1** Treatment pathways for high-risk NMIBC with currently approved options (**a**) and multidisciplinary management of BCG-naïve high-risk NMIBC following the potential introduction of PD-(L)1 inhibitors (**b**). **a** Treatment pathways for high-risk NMIBC: Currently approved options. **b** Introduction of PD-(L)1 inhibitors in BCG-naïve high-risk NMIBC: Multidisciplinary management. *AE* adverse event, *BCG* bacillus Calmette-Guérin, *HCP* healthcare professional, *IV* intravenous, *NMIBC* non-muscle invasive bladder cancer, *SC* subcutaneous, *TURBT* transurethral resection of bladder tumor

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