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European Association of Urology

Review – Bladder Cancer – Editor's choice

Editorial by Shahrokh F. Shariat on pp. 528–530 of this issue

Bladder-sparing Therapy for Bacillus Calmette-Guérin–unresponsive Non–muscle-invasive Bladder Cancer: International Bladder Cancer Group Recommendations for Optimal Sequencing and Patient Selection

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Article info

Article history:
Accepted August 3, 2024

Abstract

Background and objective: There has been a recent surge in the development of agents for bacillus Calmette-Guérin–unresponsive (BCG-U) non–muscle-invasive bladder cancer (NMIBC). Critical assessment of these agents and practical recommendations for

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https://doi.org/10.1016/j.eururo.2024.08.001

Associate Editor:
Sarah P. Psutka

Keywords:
Bacillus Calmette-Guérin–unresponsive non–muscle-invasive bladder cancer
Bladder-sparing therapy
Intravesical chemotherapy
Immune checkpoint inhibitors
Gene-based therapy
Targeted treatments
Gemcitabine/docetaxel
Pembrolizumab
Nadofaragene firadenovec
Nogapendekin alfa inbakicept-pmln

optimal selection of patients and therapies are urgently needed, especially in the absence of randomized trials on bladder-sparing treatment (BST) options.

Methods: A global committee of bladder cancer experts was assembled to develop recommendations on BST for BCG-U NMIBC. Working groups reviewed the literature and developed draft recommendations, which were then voted on by International Bladder Cancer Group (IBCG) members using a modified Delphi process. During a live meeting in August 2023, voting results and supporting evidence were presented, and recommendations were refined on the basis of meeting discussions. Final recommendations achieved >75% agreement during the meeting, and some were further refined via web conferences and e-mail discussions.

Key findings and limitations: There is currently no single optimal agent for patients with BCG-U disease who seek to avoid radical cystectomy (RC). BST selection should be personalized, taking into account individual patient characteristics and preferences, tumor attributes, and efficacy/toxicity data for the agents available. For patients with BCG-U carcinoma in situ (CIS), gemcitabine/docetaxel (GEM/DOCE), nadofaragene firadenovec (NFF), and nogapendekin alfa inbakicept-pmln (NAI) + BCG are recommended; because of its systemic toxicity, pembrolizumab should only be offered after other options are exhausted. For patients with BCG-U papillary-only tumors, GEM/DOCE, NFF, NAI + BCG, single-agent chemotherapy, hyperthermic mitomycin C, and pembrolizumab are recommended. Given the modest efficacy of available options, clinical trial participation is encouraged. For unapproved agents with reported data, IBCG recommendations await the final results of pivotal trials.

Conclusions and clinical implications: The IBCG consensus recommendations provide practical guidance on BST for BCG-U NMIBC.

ADVANCING PRACTICE

What does this study add?

The International Bladder Cancer Group provides consensus treatment recommendations for bacillus Calmette-Guérin (BCG)-unresponsive non–muscle-invasive bladder cancer, with incorporation of new findings from pivotal clinical trials. For patients aiming to avoid radical cystectomy, bladder-sparing therapy should be personalized according to patient preferences, tumor characteristics, and the efficacy/toxicity profile of the treatment. For those with BCG-unresponsive carcinoma in situ, recommended options include gemcitabine/docetaxel (GEM/DOCE), nadofaragene firadenovec (NFF), and nogapendekin alfa inbakicept-pmln (NAI) + BCG; because of its systemic toxicity, pembrolizumab is reserved for cases in which other treatments have been exhausted. For patients with BCG-unresponsive papillary-alone tumors, GEM/DOCE, NFF, NAI + BCG, single-agent chemotherapy, hyperthermic mitomycin C, and pembrolizumab are recommended.

Clinical Relevance

The field of treatment options for BCG-unresponsive nonmuscle invasive bladder cancer has rapidly expanded in the wake of a surge of single-arm registrational trials. The emergence of these novel options represents tremendous progress for patients seeking bladder sparing treatment options but is accompanied by uncertainty regarding optimal treatment selection and sequencing for individual patients in the absence of comparative efficacy data. Key questions remain regarding the definition of treatment failure to these novel agents, and determination of risk for disease progression with multiple lines of therapy to inform consideration of radical cystectomy. In this manuscript, the authors present consensus recommendations from the International Bladder Cancer Group to guide decisions around treatment options and sequencing for patients with BCG-unresponsive NMIBC derived from a modified Delphi process. This manuscript summarizes practical guidance to inform decision-making that is immediately relevant in current clinical practice. Associate Editor: Sarah Psutka, MD, MS.

Patient Summary

We developed consensus recommendations for bladder-sparing treatment options for people with non–muscle-invasive bladder cancer that is unresponsive to bacillus Calmette-Guérin (BCG) therapy. Various treatments are available, and selection needs to be tailored according to each patient's individual situation, including tumor characteristics, personal preferences, and factors affecting access to care. Participation in clinical trials of bladder-sparing therapies is encouraged.

1. Introduction

Adoption of the bacillus Calmette-Guérin–unresponsive (BCG-U) definition by the US Food and Drug Administration (FDA) [1] (Table 1) has galvanized the clinical development of novel bladder-sparing treatment (BST) options. A joint open meeting between the FDA and American Urological Association (AUA) provided benchmark efficacy rates [2] that were subsequently refined by the International Bladder Cancer Group (IBCG) [3]. Following these advances, single-arm registrational studies of pembrolizumab [4], nadofaragene firadenovec [5], and nogapendekin alfa inbakicept-pmln [6] for BCG-U carcinoma in situ (CIS) led to their approval. Additional therapies are being investigated, and intravesical sequential gemcitabine (GEM) and docetaxel (DOCE) has emerged as an off-label alternative adopted by many [7].

Practical concerns have arisen with the emergence of novel therapies for BCG-U disease. Specifically, how do we define therapeutic failure following BST? Can we identify prognostic clinicopathological indicators or predictive biomarkers to inform BST sequencing? In the context of "once BCG-U, always BCG-U", whereby patients who meet BCG-U criteria are able to participate in multiple lines of BST [8], how many sequential treatments are safe before risking disease progression? The IBCG aimed to address these critical knowledge gaps by providing consensus recommendations based on current data and expert opinion.

2. Methods

An international multidisciplinary steering committee of global bladder cancer experts (urologists, medical oncologists, radiation oncologists, genitourinary pathologists, and research scientists) and patient advocates was assembled to develop consensus recommendations on BST for BCG-U NMIBC. Recommendations were based on literature evidence where possible, and clinical experience where appropriate. Literature searches in relevant databases were performed and publications were screened for inclusion in the evidence base. Working groups used a system whereby synthesis of recommendation statements was based on literature review and expert opinion-based open communication and scientific debate. Specifically, panel members participated in a modified Delphi process [9]. Recommendation statements were initially circulated via an anonymized online voting system for pre-meeting voting by the IBCG membership.

On August 25–26, 2023, during a live, in-person consensus meeting, working groups presented the voting results and the recommendation statements were subsequently discussed along with summarized evidence supporting the draft recommendations. Bladder cancer patient advocates also provided their perspective on the recommendations.

Recommendation statements were revised in accordance with all feedback, and there was a further live vote on the final statements (restricted to bladder cancer experts and patient advocates); consensus was defined as >75% agreement. These recommendations then formed the basis of this manuscript, refined via subsequent web conferences and e-mail discussions. In some cases, when additional practice-changing data or clinical trial results became available in the time between the live meeting and the manuscript submission date, the authors considered and incorporated new evidence into the recommendations. All authors reviewed, edited, and agreed on the final recommendations laid out in this manuscript.

3. Results

The IBCG consensus recommendations for BST in BCG-U NIMBC are presented in Table 2 and supporting evidence for these recommendations is discussed in the text below. All BST recommendations presented here relate to patients with BCG-U disease who have been counseled that radical cystectomy (RC) is the preferred option for durable disease control [10–12] but who have refused or are ineligible for RC, and who have also been offered access to clinical trials.

3.1. Definition and evaluation

For disease to be considered as BCG-U, the criteria outlined in Table 1 must be met. Before offering BST, patients with BCG-U disease must undergo optimal staging, with the use of enhanced cystoscopy and cross-sectional imaging as appropriate, to minimize the risk of unrecognized muscle-invasive bladder cancer (MIBC) or metastatic urothelial carcinoma (mUC) [13]. Pathology reports should also be standardized (and preferably reported/reviewed by a pathologist with bladder cancer expertise) as variation in pathological reading significantly affects both proposed management and patient prognosis [14–16].

3.2. Chemotherapy-based treatments

Various intravesical chemotherapies have been tested in patients after BCG failure [17–19], but few have been studied specifically in patients who meet the strict FDA BCG-U criteria [1]. The IBCG reviewed data from trials that enrolled patients with similar BCG exposure states and risk classifications in CIS-containing versus papillary-only subgroups

Table 1 – Definition of BCG-unresponsive non–muscle-invasive bladder cancer [1]

At least one of the following:
1. Persistent or recurrent carcinoma in situ with or without non–muscle-invasive papillary disease within 12 mo of completion of adequate BCG therapy [a]
2. Recurrent high-grade Ta/T1 tumor within 6 mo of completion of adequate BCG therapy [a]
3. High-grade T1 disease at the first evaluation following BCG induction

BCG = bacillus Calmette-Guérin.
[a] Adequate BCG therapy is defined as at least five of six doses of an initial induction course with at least two additional doses (either as part of maintenance therapy or a second induction course).

Table 2 – International Bladder Cancer Group consensus recommendations for BST in BCG-U NMIBC

Definition
● To be considered BCG-U, patients must meet the criteria outlined in Table 1.
Evaluation
● Optimal staging is required before BST, including enhanced optical imaging of the bladder mucosa and evaluation of sanctuary sites (upper tract, prostatic urethra [in men]) [13]. This includes repeat TURBT for all patients with high-grade T1 and risk-stratified patients with high-grade Ta [10–12].
● Pathology reports should be standardized to include grade, stage, presence of histological subtypes, LVI, concomitant CIS, prostatic urethral involvement, and muscularis propria sampling, and should preferably be reviewed by a pathologist with expertise in bladder cancer.
Chemotherapy-based treatments
● For BCG-U CIS (with or without papillary disease):
● Single-agent chemotherapy is not recommended.
● Induction doublet intravesical GEM/DOCE with extended monthly maintenance for at least 12 mo is recommended.
● For BCG-U high-grade papillary disease, the following may be considered:
● Induction + maintenance doublet intravesical GEM/DOCE.
● Induction + maintenance single-agent chemotherapy (eg, GEM, mitomycin C [preferably optimized mitomycin C] [22]).
● Hyperthermic mitomycin C.
Immune checkpoint inhibitors
● Pembrolizumab is the only ICI approved for patients with BCG-U CIS who refuse/are ineligible for RC. We recommend offering pembrolizumab to these patients after exhaustion of other BST options.
● Patients must be counseled on the balance between modest treatment efficacy and the risk of significant adverse events.
Gene-based therapies
• Nadofaragene firadenovec is indicated and approved for patients with BCG-U CIS, and may also be considered for patients with BCG-U high-grade papillary Ta/T1 tumors without CIS.
Intravesical immunotherapy-based agents
● NAI (N-803) + BCG is indicated and approved for patients with BCG-U CIS, and may also be considered for patients with BCG-U high-grade papillary Ta/T1 tumors without CIS.
Targeted treatments
● Novel targeted agents hold promise; patients should be counseled on available clinical trials.
Miscellaneous therapies
● Radiation-based treatment may be considered for the subset of patients with BCG-U T1 bladder cancer who refuse or are ineligible for RC and who have no access to approved/recommended BST options and/or are unable to participate in a clinical trial.
● TURBT/surveillance alone is not recommended for BCG-U disease. Patients for whom this option is being considered should be referred to clinicians with bladder cancer expertise for approved therapies, consideration for RC, or clinical trial enrollment.
General recommendations for BST
● At the time of BCG-U diagnosis, BST may be offered as a safe alternative to RC in appropriately selected patients.
● Therapeutic failure for BST should be defined as high-grade urothelial carcinoma recurrence (Ta, T1, CIS) or clinical stage progression (≥T2, N+, M+) within 12 mo.
● At each tumor recurrence, patients should be restaged via TURBT, bimanual examination under anesthesia, and cross-sectional imaging.
● Patients with BCG-U disease who experience non–muscle-invasive therapeutic failure of BST (≤T1) and refuse or are ineligible for RC can be considered for additional BCG-U clinical trials and BST on the basis of shared decision making.
● Progression to muscle-invasive disease (cT2+) on BST should prompt evaluation in a multidisciplinary setting.
Optimal agent for each patient subgroup
● Consider each patient individually and personalize BST to the patient's specific tumor characteristics and physiological make-up and real-world considerations.
● Inform patients that RC is the standard treatment for BCG-U disease, but also counsel them on the approved BST options in this setting. For those who refuse or are ineligible for RC, counseling on approved and off-label agents should include discussions about efficacy, toxicity, and QoL parameters for each agent.
● For BCG-U CIS, nadofaragene firadenovec (approved), pembrolizumab (approved), NAI (N-803) + BCG (approved), and GEM/DOCE (off-label) are recommended.
● For BCG-U papillary-only tumors, GEM/DOCE, nadofaragene firadenovec, pembrolizumab, NAI (N-803) + BCG, single-agent chemotherapy, and hyperthermic mitomycin C (all off-label) are recommended.
● Patients with BCG-U NMIBC should be encouraged to participate in a clinical trial given the modest efficacy of currently available BST options.

BCG = bacillus Calmette-Guérin; BCG-U = BCG-unresponsive; BST = bladder-sparing therapy; CIS = carcinoma in situ; DOCE = docetaxel; GEM = gemcitabine; ICI = immune checkpoint inhibitor; LVI = lymphovascular invasion; NAI = nogapendekin alfa inbakicept; NMIBC = non–muscle-invasive bladder cancer; QoL = quality of life; RC = radical cystectomy; TURBT = transurethral resection of bladder tumor.

and reviewed or calculated disease-free rates at 12 and 24 mo (Supplementary material) [20,21]. These calculations were simply to generate discussion among experts and to arrive at consensus, as cross-trial comparisons are not recommended by the IBCG [3].

3.2.1. *Single-agent chemotherapy*

Intravesical agents evaluated include single-agent mitomycin C (MMC), valrubicin, and taxanes, as well as gemcitabine, which is the most well-studied chemotherapeutic agent for recurrent disease after BCG (Supplementary Tables 1 and 2 and Supplementary Fig. 1). Mean 12-mo and 24-mo disease-free survival (DFS) rates with gemcitabine were significantly lower for patients with CIS-predominant tumors (24% and 17%, respectively) than for patients with non-CIS tumours (72% and 61%, respectively; $p < 0.001$; Supplementary Table 1) [20]. Valrubicin is the only chemotherapy agent approved for use after BCG, but it is not specifically indicated for BCG-U disease. The valrubicin studies included predominantly patients with CIS, with mean 12-mo and 24-mo complete response (CR) rates of 13.5% and 8%, respectively (Supplementary Table 2 and Supplementary Fig. 1). Hyperthermic MMC was retrospectively studied in BCG-refractory patients (approaching the FDA definition for BCG-U disease; Supplementary Table 3). The 12-mo and 24-mo recurrence-free survival (RFS) rates were 58% and 36% for patients with CIS, and 71% and 56% for patients with papillary disease, respectively (Supplementary Fig. 2). In a randomized phase 3 trial of optimized MMC versus standard-dose MMC that included patients with papillary disease (including T1 and CIS), the optimized regimen was associated with significantly better RFS at 5 yr

(41% vs 25%) [22]. However, the IBCG noted that owing to a lack of uniform MMC availability in the USA, the solubility of MMC varies and optimal concentrations may not be achieved. If MMC is used, the IBCG recommends confirming its solubility with the local pharmacy [23].

Although the general IBCG consensus is that single-agent chemotherapy has limited efficacy in patients with BCG-U NMIBC, it may be considered for BCG-U papillary-only disease. The investigational TAR-200 drug delivery system is currently being used to deliver gemcitabine into the bladder in a sustained manner. Preliminary results from the phase 2 SunRISe-1 study evaluating TAR-200 gemcitabine and cetrelimab as monotherapies in BCG-U NMIBC found 3-mo CR rates of 73% and 38%, respectively [24]. A more recent analysis of the TAR-200 monotherapy group found an overall CR at any time of 83% [25].

3.2.2. Combination chemotherapy

Before the approval of pembrolizumab and nadofaragene firadenovec by the FDA, intravesical GEM/DOCE emerged as the de facto "standard" therapy for patients refusing or ineligible for RC. Even today, this remains the option preferred by many, especially in countries outside the USA. Cumulative data from various nonprospective and nonrandomized studies using doublet sequential GEM/DOCE in different subgroups of patients with BCG failure (Supplementary Table 4) demonstrate average 12-mo and 24-mo durable RFS rates of 56% and 40% in the "any CIS" population, and 61% and 50%, respectively, in the papillary disease–only population (Supplementary Fig. 3) [21].

Pooled multicenter data sets have allowed analysis of outcomes in patients who fit the FDA BCG-U definition [1]. In one such analysis of long-term outcomes for patients with BCG-U treated with GEM/DOCE (six weekly instillations followed by monthly maintenance for 2 yr), 5-yr survival rates were 28% for high-grade RFS, 89% for progression-free survival, 74% for cystectomy-free survival (CFS), 92% for cancer-specific survival (CSS), and 66% for overall survival (OS) [26]. Mirroring other studies, the results were numerically better for the group with papillary-only disease, with 1-yr, 2-yr, and 5-yr RFS rates of 64%, 49%, and 25%, and 1-yr, 2-yr, and 5-yr CR rates of 48%, 38%, and 22%, respectively, among patients with BCG-U CIS. More intensive intravesical chemotherapy combinations have been tested in small prospective clinical trials. However, despite preliminary demonstration of efficacy, these regimens are unlikely to be moved forward because of logistical constraints [27].

The IBCG agreed that induction doublet intravesical GEM/DOCE with extended monthly maintenance (12–24 mo) should be considered as the intravesical chemotherapy option of choice (including MMC and hyperthermia) for both BCG-U CIS and papillary-only disease. This doublet should be evaluated in single-arm prospective trials based on the 2018 FDA guidance [1], in randomized controlled trials (RCTs) with an FDA-approved comparator, or as an experimental regimen in a randomized phase 2 trial.

3.3. Immune checkpoint inhibitors

Pembrolizumab was the first immune checkpoint inhibitor (ICI) approved by the FDA in 2020 for BCG-U CIS on the basis of results from the KEYNOTE-057 trial, which demonstrated a 3-mo CR rate of 41% and durable responses up to 16.2 mo [4]. At 18 mo, a CR was maintained in only 13.5% of patients, with a cumulative cystectomy rate at 3-yr follow-up of 49%. The toxicity profile was similar to that seen in mUC trials, with grade 3–4 treatment-emergent adverse events (TEAEs) occurring in 13% (13/101) of patients [4]. In the cohort with papillary tumors (n = 132), the 12-mo RFS rate was higher at 43.5%, and median RFS was 7.7 mo [28]. Notably, 10.6% of patients discontinued treatment because of TEAEs. The current National Comprehensive Cancer Network (NCCN) guidelines recommend pembrolizumab as a BST option for both patients with CIS and those with high-grade papillary-only disease [11].

Atezolizumab has also been studied in the phase 2 SWOG S1605 trial, with 3-mo, 12-mo, and 18-mo CR rates of 43%, 25%, and 13.5%, respectively, for patients with BCG-U CIS, and a median duration of response (DOR) of 17 mo [29]. For patients with papillary-only disease the 18-mo RFS rate was 49%. Three treatment-related deaths were reported and although full accrual was achieved for the CIS arm of the trial, SWOG 1605 was closed prematurely because of results from a prespecified futility analysis. Similarly, another phase 2 study of durvalumab in BCG-U CIS found minimal efficacy and high rates of immune-related AEs; the trial was also stopped because of futility [30].

Building on the approval of pembrolizumab, regimens combining ICIs with other agents have been launched with the goal of improving on the modest efficacy seen with single-agent pembrolizumab. Early results from the phase 1b/2 GU-123 study investigating atezolizumab with or without BCG in BCG-U CIS found 6-mo CR rates of 42% in the atezolizumab + BCG group and 33% in the atezolizumab group [31].

The IBCG recommends that patients be counseled on the approved agent (pembrolizumab) in the context of relatively modest efficacy weighed against the risk of significant AEs. Practically speaking, this means that a single-agent ICI is currently most appropriate for patients for whom safer alternative treatment options have been exhausted.

3.4. Gene-based therapies

In 2022, the FDA approved nadofaragene firadenovec, a replication-deficient recombinant adenovirus vector–based gene therapy that delivers a copy of the human IFNα-2b gene to urothelial cells. In a single-arm, phase 3 multicentre study, the 3-mo CR was 53% for patients with BCG-U CIS treated with nadofaragene firadenovec [5]. Approximately 46% of patients with an initial CR remained free of high-grade recurrence at 12 mo, resulting in a 12-mo CR rate of 23%. In the cohort with papillary-only tumors, high-grade RFS at 3 mo was 73%, and 60% of these patients continued to be recurrence-free at 1-yr follow-up. The 24-mo CFS rate among all treated patients was 64.5% and was similar between the cohorts. No grade 4–5 TEAEs were observed.

The IBCG recognizes that despite being FDA-approved only for BCG-U CIS ± Ta or T1 papillary disease, the current NCCN guidelines also recommend nadofaragene firadenovec as a BST option for patients with high-grade papillary Ta/T1 tumors without CIS (level 2b recommendation) [11].

Cretostimogene grenadenorepvec (CG0070) is a replication-competent oncolytic adenovirus that targets bladder tumor cells with defective retinoblastoma pathway gene expression. In the phase 2 BOND-002 trial of CG0070 monotherapy in BCG-refractory (not BCG-U) CIS, the CR rate at any time was 65%; the 6-mo and 12-mo CR rates were 44% and 28%, respectively [32]. Preliminary results from the open-label, phase 3 BOND-003 trial (NCT04452591) investigating CG0070 monotherapy in 115 patients with high-risk BCG-U CIS found a CR rate of 75.7% at any time, with primarily grade 1–2 bladder-related AEs [33]. A single-arm, phase 2 trial (CORE-001) is investigating CG0070 in combination with pembrolizumab; early results revealed an overall CR rate of 85% (n = 29/34) in a small cohort of patients, with 6-mo, 9-mo, and 12-mo CR rates of 82%, 81%, and 68%, respectively [34]. The most common AEs were transient grade 1/2 local genitourinary toxicity. Four patients experienced grade 3 AEs, and no grade 4–5 AEs were reported. Although these data suggest a favorable efficacy to safety profile for CG0070, the IBCG agrees that recommendations should not be made until results are available from pivotal studies.

3.5. Intravesical immunotherapy-based agents

For novel intravesical immunotherapies, mature data are available for nogapendekin alfa inbakicept-pmln (NAI; also known as N-803), which is an interleukin-15 superagonist complex designed to enhance the immune-mediated effects of interleukin-15 and boost the immune response primed by BCG [35,36]. The phase 2/3 QUILT-3.032 trial assessed BCG combined with NAI in BCG-U NMIBC and found a CR rate at any time of 71% (median duration 26.6 mo) in the CIS cohort (n = 83); the 24-mo CFS and disease-specific survival (DSS) rates were 89% and 100%, respectively [6]. In the cohort with papillary-only tumors, the 24-mo RFS and DSS rates were 48% and 98%, respectively. The TEAEs most commonly reported were grade 1–2 events related to bladder instillation; no grade 4–5 TEAEs were reported. In April 2024, the FDA approved NAI on the basis of their assessment of 77 patients with BCG-U, high-risk NMIBC with CIS with or without Ta/T1 papillary disease. The CR rate was 62% (95% confidence interval 51–73%); 58% of patients with a CR had a DOR ≥12 mo and 40% had a DOR ≥24 mo. On the basis of these results, the IBCG agreed that NAI + BCG should be recommended to patients. However, its use will depend on BCG supply, as NAI must be combined with BCG.

EG-70 is a nanoparticle formulation of plasmids that activate both the innate and adaptive immune responses within the bladder. Preliminary results from a phase 1 study of EG-70 in BCG-U CIS (n = 20) revealed a 3-mo CR rate of 68% [37]. IBCG recommendations on EG-70 are not possible until results from pivotal trials are available.

3.6. Targeted treatments

Oportuzumab monatox (OM; Vicineum) had been studied for several years, including in a single-arm phase 3 trial that reported 3-mo, 6-mo, and 12-mo CR rates of 40%, 28%, and 17%, respectively, for patients with BCG-U CIS [38]. In the high-grade papillary-only cohort, the 3-mo, 6-mo, and 12-mo RFS rates were 71%, 58%, and 42%, respectively. The FDA did not approve this drug after Oncologic Drug Advisory Committee (ODAC) review based on consideration of its benefit-to-risk ratio, and further development of OM appears to have been halted.

Erdafitinib is a selective pan-FGFR inhibitor that is approved for locally advanced or metastatic UC in patients with *FGFR3* alterations. Preliminary results from a phase 2 study (THOR-2) found 3-mo and 6-mo CR rates of 100% and 75%, respectively, for patients with BCG-U CIS with *FGFR* alterations (n = 10) treated with oral erdafitinib [39]. Grade ≥3 TEAEs occurred in 30% of patients. In patients with BCG-treated papillary-only high-risk disease with *FGFR* alterations, erdafitinib resulted in better RFS in comparison to the investigator's choice of intravesical chemotherapy (median RFS not reached vs 11.6 mo for chemotherapy; hazard ratio [HR] 0.28; p = 0.0008) [40]. Intravesical erdafitinib has also been studied, with delivery via the TAR-210 system [41].

Enfortumab vedotin (EV) is an antibody-drug conjugate targeting Nectin-4, which is highly expressed in bladder cancer, with efficacy demonstrated in locally advanced/metastatic UC [42,43]. EV plus pembrolizumab is FDA-approved for first-line use in this disease state. A phase 1 study is evaluating an intravesical formulation of EV in BCG-U NMIBC (EV-104; NCT05014139). ABI-009, an albumin-bound rapamycin (mTOR inhibitor) nanoparticle with enhanced hydrophobic properties for intravesical use, is being evaluated in a phase 1/2 trial in BCG-U NMIBC (NCT02009332).

3.7. Miscellaneous therapies

3.7.1. Radiation-based treatment

There is increasing interest in incorporating radiation therapy (RT) in treatment for BCG-U T1 bladder cancer. Although not specific to BCG-U disease, the phase 2 RTOG 0926 trial evaluated maximal transurethral resection of bladder tumor (TURBT) followed by chemoradiation comprising 61.2 Gy in 34 daily fractions with either cisplatin or MMC/5-fluorouracil for radiosensitization in patients with recurrent high-grade T1 NMIBC [44]. The 3-yr CFS rate was 88%, and 3-yr and 5-yr OS rates were 69% and 53%, respectively. Twenty patients (59%) experienced grade 3 AEs, and two grade 4 AEs were reported. These data have been presented in abstract form only and publication of the final data is pending.

Another single-arm phase 2 trial examined the efficacy of TURBT followed by tislelizumab + RT in ten patients with BCG-U high-grade papillary-only (Ta/T1) tumors, with 12-mo and 24-mo RFS rates of 80% and 60%, respectively [45]. The 24-mo OS rate was 100%. Half of the patients experienced immune-related AEs.

The phase 1 ADAPT- BLADDER trial investigated durvalumab (n = 3), durvalumab + BCG (n = 13), and durvalumab + RT (n = 12) in patients with BCG-U NMIBC (Ta/T1/CIS) [46]. The 12-mo CR rates were 46% in the overall cohort, 73% for durvalumab + BCG, and 33% for durvalumab + RT. The ongoing, single-arm, phase 2 PREVERT trial is evaluating RT (60–66 Gy in 2-Gy fractions) with concurrent avelumab in BCG-U disease (NCT03950362). Study completion is expected in June 2024.

On the basis of the evidence available, the IBCG agreed that RT-based therapies may be an option for patients who refuse or are ineligible for RC, have no access to recommended BST options, and who cannot participate in a clinical trial.

3.7.2. *Photodynamic therapy*

Interim data from a phase 2 trial investigating photosensitizer TLD-1433-mediated photodynamic therapy (PDT) in 45 patients with BCG-U CIS (± papillary disease) revealed a 90-d CR rate of 50%, and DOR rates at 360 and 450 d of 35% and 21%, respectively [47]. Although eight (18%) serious AEs were reported, none were related to PDT. The IBCG noted that PDT may be a viable option for BCG-U NMIBC in the future.

3.7.3. *TURBT/fulguration*

The IBCG recommends against use of TURBT/surveillance alone for patients with BCG-U high-grade NMIBC given the high risks of disease recurrence and progression. For scenarios in which patients have no access to other interventions or clinical trials, the IBCG strongly recommends that patients be referred to clinicians with bladder cancer expertise for approved therapies, consideration for RC, or clinical trial enrollment.

3.8. *General recommendations for BST*

RC is the current standard for BCG-U NMIBC [10–12]. If RC is performed before progression to MIBC, the CSS rate is >90% [48]. However, for appropriately selected patients (ie, no lymphovascular invasion [LVI] or variant histological subtype, and in appropriately staged T1 patients), BST may be a safe alternative to RC for BCG-U NMIBC. One retrospective analysis of long-term survival outcomes for patients with BCG-U NMIBC found no significant differences in OS or CSS between RC and initial BST groups [49]. Similarly, there were no significant differences in OS or CSS between patients receiving immediate (or upfront) and delayed (salvage) RC following a trial of BST. Importantly, no patients with LVI or variant histological subtype received initial BST in this cohort. On multivariate analysis, ongoing smoking status was the only variable predictive of high-grade recurrence (HR 4.44; p = 0.011).

Table 3 compares pathological outcomes for patients undergoing salvage RC in key BST trials for BCG-U NMIBC to those in reference cohorts with high-risk/very high-risk NMIBC or BCG-U NMIBC who underwent upfront RC [4,5,7,49–55]. Rates of >pT2 and pN+ were similar for the groups receiving upfront RC (23–50% and 8–16%) and salvage RC following BST (8–33% and 3–12%). Thus, when using pathological outcomes as an indicator for treatment success, patients with BCG-U NMIBC treated with initial BST had similar outcomes to those for patients undergoing early RC, even for salvage RC after BST therapeutic failure.

In accordance with current MIBC guidelines [11,56,57], the IBCG recommends that progression to muscle-invasive disease (cT2+) on BST should prompt multidisciplinary management. Studies have shown that those who progress to MIBC on BCG have higher rates of disease upstaging and worse OS and CSS in comparison to patients with de novo MIBC [58]. However, better survival outcomes were observed if patients with progressive disease received neoadjuvant chemotherapy, emphasizing the need for multidisciplinary care.

In accordance with the open letter to the FDA by Kamat et al [8], the IBCG agreed that patients with BCG-U disease who experience non–muscle-invasive therapeutic failure

Table 3 – Comparison of (y)pTN stage in studies of BCG-U patients undergoing sRC following BST versus reference cohorts treated with upfront RC

BST study	*N*	mFU (mo)	sRC, *n* (%)	≥pT2, *n* (%)	pN+, *n* (%)
Pembrolizumab (KN-057) [4]	96 [a]	36.4	40 (42)	3 (8)	4 (11)
Atezolizumab (S1605) [29]	128	41	34 (27)	6 (18)	4 (12)
Nadofaragene firadenovec [5]	151	19.7 (CIS cohort) 20.2 (Ta/T1 alone cohort)	40 (25)	5 (13)	1 (3) [b]
GEM/DOCE [7] [c]	276	22.9	43 (16)	11 (26)	5 (12)
Valrubicin [50]	90	30	44 (49)	6 (14) pT3+	2 (5)
Docetaxel [51]	54	39.1	17 (31)	4 (24)	Unknown
GEM/MMC [52]	47	26	10 (21)	2 (20)	0
GEM/MMC [53]	27	22 [d]	3 (11)	1 (33)	Unknown
Reference cohort					
Upfront RC for T1HG [54]	1136	–	–	560 (50%)	184 (16)
Upfront RC for EAU VHR [55]	78	–	–	18 (23%)	6 (8)
Immediate RC at BCG-U diagnosis [49]	38	–	–	9 (24%)	Unknown

BCG-U = bacillus Calmette-Guérin–unresponsive; BST = bladder-sparing therapy; CIS = carcinoma in situ; EAU = European Association of Urology; GEM/DOCE = gemcitabine/docetaxel; GEM/MMC = gemcitabine/mitomycin C; HG = high-grade; KN-75 = KEYNOTE-57 trial; mFU = median follow-up; sRC = salvage radical cystectomy; VHR = very high risk.

[a] CIS-only cohort.

[b] CIS recurrence at 3 mo, progressed on KN-057.

[c] 38% BCG-U.

[d] Study only reported mFU for those without recurrence (n = 10; 22 mo, interquartile range 3.9–27). The median time to recurrence for 17 patients was 15.2 mo (interquartile range 1.7–32).

of BST (≤T1) and who refuse or are ineligible for RC can be considered for additional BCG-U clinical trials and BST on the basis of shared decision-making. However, since rates of progression to MIBC/mUC increase with each successive tier of failed BST (from 7% at 12 mo to 13% by 24 mo and 19% by 48 mo; unpublished data, Yair Lotan), the IBCG agreed that sequential BST options should be continually weighed against the risks of disease progression, and that RC be considered at each recurrence.

4. Discussion

To date, no RCT has been conducted in the BCG-U setting because of the lack of an effective BST for use as the comparator and the unwillingness of patients to be randomized to RC. The relative efficacy of investigational agents can only be inaccurately compared across trials; these comparisons are further confounded by different efficacy rates observed for various disease subgroups (CIS, papillary, or CIS + papillary) [59]. Therefore, the IBCG agreed that the optimal treatment should be personalized according to each patient's specific tumor characteristics (grade, stage) and physiological makeup (eg, ability/inability to hold an intravesical agent) and real-world considerations (eg, access to health care facilities, drug dosing, and costs).

The IBCG reviewed existing literature on potential biomarkers for the agents granted FDA approval, as well as those in development. Of the completed ICI trials, only two reported PD-L1 status in pretreated tumors [4,30], which did not correlate with treatment response in either trial. While baseline anti-adenovirus antibody levels in patients treated with nadofaragene firadenovec did not predict response, post-treatment titers were highly predictive of treatment response [5,60].

In the absence of direct comparative data or predictive biomarkers, and based on a review of the available evidence presented here and current guideline recommendations for BST in BCG-U NMIBC (Table 4) [10–12], the IBCG recommends the following:

1. Nadofaragene firadenovec (approved), pembrolizumab (approved), NAI (N-803) + BCG (approved), and GEM/DOCE (off-label) for patients with BCG-U CIS (Fig. 1).
2. GEM/DOCE, single-agent chemotherapy, hyperthermic MMC, NAI (N-803) + BCG, nadofaragene firadenovec and pembrolizumab (all off-label) for patients with BCG-U papillary-only tumors (Fig. 1).
3. Counsel patients with BCG-U on the therapies approved for this setting and inform them that RC is the current reference standard.
4. For those who elect not to undergo RC, counseling on the approved/off-label agents available should include a discussion of efficacy, toxicity, and quality-of-life parameters (eg, frequency of administration) to aid in informed shared decision-making.

Lastly, there is still significant room for improvement in BST outcomes, particularly with respect to the durability of response. A recent meta-analysis of 11 studies (n = 909) investigating various BST options for patients meeting the strict FDA BCG-U definition found only modest efficacy rates [59]. For patients with CIS ± Ta/T1 tumors, the CR rate was 44% at 3 mo, 38% at 6 mo, and 25% at 12 mo. This represents a modest improvement over the benchmark set by the FDA [1] and below the 50% 6-mo and 30% 12-mo thresholds previously proposed as clinically relevant [3]. Given these results, the IBCG recommends that patients continue to be offered access to clinical trials.

As more data on treatment efficacy in the BCG-U setting emerge, RCT designs that incorporate an approved agent in the control arm or randomized phase 2 trials of two or more agents would facilitate unbiased comparisons of novel investigational agents against an FDA-approved treatment. In addition, patients with non-CIS BCG-U papillary disease may also be enrolled according to appropriate stratification criteria. Finally, RCTs will allow for demonstration of additive or synergistic efficacy associated with combinatorial therapeutic strategies over their individual components.

5. Conclusions

Based on collective international expert opinion, the IBCG consensus recommendations represent an important step towards providing guidance for clinicians, patients, and stakeholders worldwide on the BST strategies available. It is expected that these consensus recommendations, in con-

Table 4 – EAU-, AUA- and NCCN-recommended treatments for patients with BCG-U NMIBC who refuse or are ineligible for radical cystectomy

EAU 2023 guidelines [10]	AUA 2024 guidelines [12]	NCCN 2024 guidelines [11]
Any of the following (although administration within the context of a clinical trial is preferred): ■ Intravesical chemotherapy ■ Chemotherapy and microwave-induced hyperthermia ■ Electromotive administration of chemotherapy ■ Intravesical immunotherapy **Weak recommendation**	● Clinical trial enrollment ● Alternative intravesical therapy (ie, nadofaragene firadenovec) ● Alternative intravesical chemotherapies (ie, gemcitabine/docetaxel) ● Pembrolizumab (for patients with CIS within 12 mo of completion of adequate BCG therapy) **Conditional recommendation (evidence strength: grade C)**	● Intravesical chemotherapy ● Pembrolizumab for: ■ BCG-U CIS ± papillary tumors ■ BCG-U, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS **(category 2B)** ● Nadofaragene firadenovec for: ■ BCG-U CIS ■ High-grade papillary Ta/T1 only tumor without CIS **(category 2b)** **All recommendations are category 2a unless otherwise specified**

AUA = American Urological Association; BCG-U: bacillus Calmette-Guérin–unresponsive; CIS = carcinoma in situ; EAU = European Association of Urology; NCCN = National Comprehensive Cancer Network.

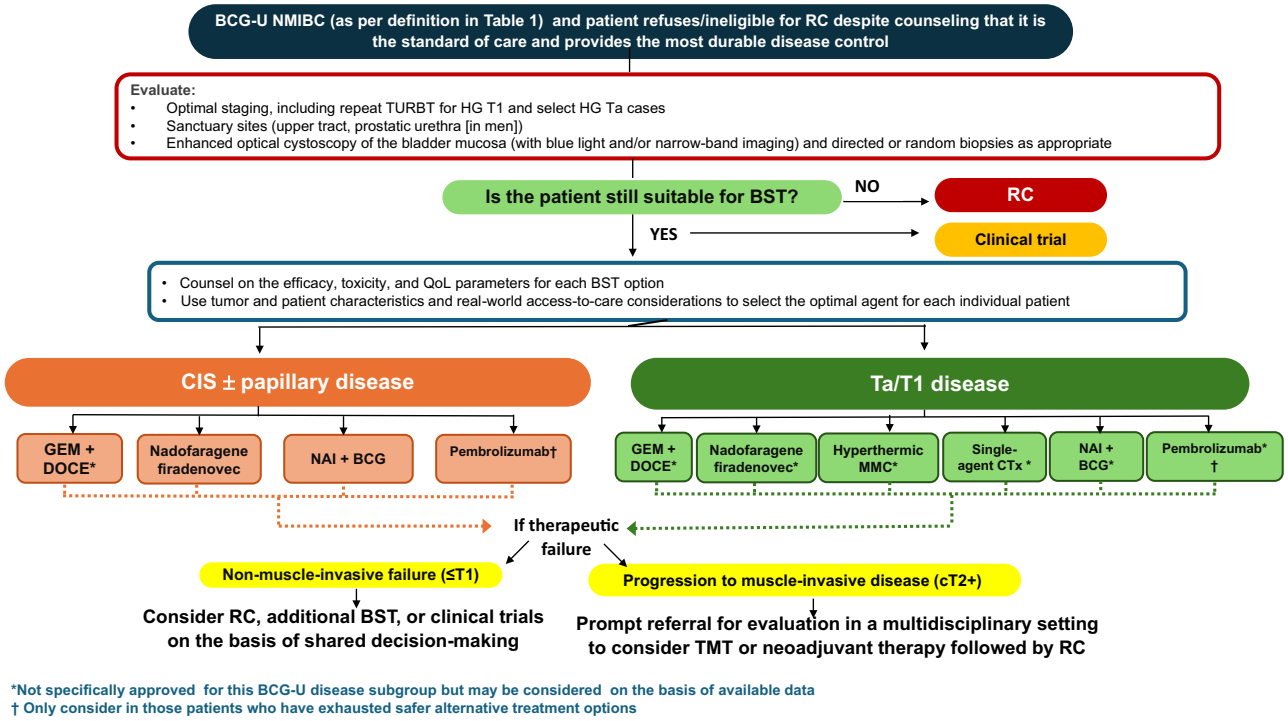

Fig. 1 – International Bladder Cancer Group recommendations for BST in patients with BCG-U NMIBC who are ineligible for or refuse RC. BCG = bacillus Calmette-Guérin; BCG-U = BCG-unresponsive; BST = bladder-sparing treatment; CIS = carcinoma in situ; CTx = chemotherapy; GEM/DOCE = gemcitabine/docetaxel; HG = high grade; MMC = mitomycin C; NAI = nogapendekin alfa inbakicept-pmln; NMIBC = non–muscle-invasive bladder cancer; RC = radical cystectomy; TUR = transurethral resection of bladder tumor; TMT = trimodal therapy.

junction with existing clinical practice guidelines, will provide patients with BCG-U disease with viable bladder-sparing alternatives to RC with acceptable oncological outcomes, at least until further evidence from RCTs becomes available for guidance.

***Author contributions*:** Ashish M. Kamat had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: All authors.
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Critical revision of the manuscript for important intellectual content: All authors.
Statistical analyses: All authors.
Obtaining funding: Kamat, Li, Hensley, Gupta, Buckley.
Administrative, technical, or material support: Kamat, Li, Hensley, Gupta, Buckley.
Supervision: Kamat.
Other: None.

***Financial disclosures*:** Ashish M. Kamat certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: Roger Li has received research support from Predicine, Veracyte, CG Oncology, Valar Labs, and Merck; has participated in clinical trial protocol committees for CG Oncology, Merck, and Janssen; has acted as a scientific advisor or consultant for BMS, Merck, Fergene, Arquer Diagnostics, Urogen Pharma, Lucence, CG Oncology, Janssen, and Thericon; and has received honoraria from UroToday and MashupMD. Shilpa Gupta has acted as a consultant for BMS, Merck, EMD Serono, Bayer, Sanofi, Guardant, Foundation Medicine, Gilead, Pfizer, and Seattle Genetics; has been a speaker for BMS, Gilead, and Astellas; and owns stock in Nektar Therapeutics and BioNTech. Hikmat Al-Ahmadie has been a consultant for AstraZeneca, Paige.AI, and Pfizer. Peter C. Black has been a consultant for AbbVie, Astellas, AstraZeneca, Bayer, BMS, Combat, EMD-Serono, Ferring, Janssen, Merck, Nonagen, Nanobot, NanOlogy, Photocure, Prokarium, Sumitomo, TerSera, Tolmar, and Verity, and shares a patent with Decipher Biosciences. Seth P. Lerner has served as a consultant/advisor for Vaxiion, Verity, Pfizer, Surge Therapeutics, C2i Genomics, BMS, Incyte, Protara, Astra Zeneca, Gilead, Urogen, and Ferring; has participated in a scientific study or trial for JBL, FKD, Viventia, Roche/Genetech, Vaxiion, QED Therapeutics, Aura Biosciences, and Surge Therapeutics; holds a health publishing role for UpToDate and Bladder Cancer Journal; and has served as a meeting participant or lecturer for Grand Rounds Urology, UroToday, Dava Oncology; and holds a patent for a TCGA classifier. Laura S. Mertens has received consultancy fees from Janssen. Carmen Mir has been a speaker for Janssen. Michael O'Donnell has been a consultant for Fidia Farmaceuticals, Merck, Theralase, Urogen, and Vaxiion; and an investigator for Photocure, SeaGen, and Urogen. Jeffrey S. Ross has financial associations with Foundation Medicine, Tango Therapeutics, and Celsius Therapeutics. Philippe E. Spiess is Vice Chair of the NCCN bladder and penile cancer panel; he has no financial disclosures. Gary Steinberg is a member of clinical trial protocol committees for Merck, BMS, Janssen, CG Oncology, Pfizer, PhotoCure, Fidia, SeaGen, Protara, and EnGene Bio; has acted as a scientific advisor/consultant for CG Oncology, PhotoCure, Merck, Taris Biomedical

(now Janssen), Fidia Farmaceuticals, Urogen, Ferring, Fergene, Bristol-Myers Squibb, AstraZeneca, Pfizer, Janssen, Epivax Therapeutics, EnGene Bio, Astellas, SeaGen, Verity Pharmaceuticals, Protara, xCures, Nonagen, Nanology, Imvax, Asieris, UroViu, Aura Biosciences, and Nucleix; and holds equity stock/options in Epivax Therapeutics, CG Oncology, and EnGene Bio. Robert S. Svatek has acted as consultant for CG Oncology and has received research support from JBL, Merck, and Pacific Edge. Roger Buckley has received honoraria from Tersera, Knight, Astellas, and Tolmar. Ashish M. Kamat has participated in clinical trials with FKD, Merck, Bristol-Myers Squibb, Photocure, SWOG, Adolor, Heat Biologics, Janssen, Taris, and Seattle Genetics; has participated in laboratory research with NIH, SPORE, AIBCCR, and PCORI; has acted as an advisory board member or consultant for TMC Innovation, Arquer Diagnostics, Asieris, Astellas, Biological Dynamics, BMS, CG Oncology, Cystotech, Eisai, Engene, Ferring, InCyte, Imvax, Imagin Medical, Janssen, Medac, Merck, Nonagen, Photocure, ProTara, Pfizer, Roche, Seattle Genetics, Sessen Bio, Theralase, US Biotest, and Urogen; is an editorial board member for European Urology Oncology, the Journal of Urology, and UroToday; is President of the International Bladder Cancer Network and the International Bladder Cancer Group; and holds a joint patent with UT MD Anderson Cancer Center on cytokine predictors of response to intravesical therapy. The remaining authors have nothing to disclose.

***Funding/Support and role of the sponsors*:** The IBCG consensus meeting was supported by funding from AstraZeneca, ImmunityBio, Merck, Astellas, EnGene, Janssen Oncology, Medac, Photocure, CG Oncology, and Ferring. The sponsors had no direct role in the study.

***Acknowledgments*:** We gratefully acknowledge the following steering committee members for their participation in the development of the consensus recommendations and the IBCG consensus meeting: Dr. Anaya Choudhury (University of Manchester, The Christie NHS Foundation Trust, Manchester, UK), Dr. Sia Daneshmand (University of South California Keck School of Medicine, Los Angeles, CA, USA), Dr. Colin Dinney (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Dr. Bishoy Faltas (Weill Cornell Medical College, New York City, NY, USA), Dr. Thomas Flaig (University of Colorado School of Medicine, Aurora, CO, USA), Dr. Daniel Grass (H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA), Dr. Petros Grivas (University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, Seattle, WA, USA), Dr. Donna Hansel (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Dr. Comron Hassanzadeh (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Dr. Wassim Kassouf (McGill University, Montreal, Canada), Dr. Janet Kukreja (University of Colorado Anschutz Medical Campus, Denver, CO, USA), Dr. Arturo Mendoza-Valdés (Hospital Medica Sur, Mexico City, Mexico), Dr. Marco Moschini (URI IRCCS Ospedale San Raffaele, Milan, Italy), Dr. Kent Mouw (Dana-Farber Cancer Institute & Brigham and Women's Hospital & Harvard Medical School, Boston, MA, USA), Dr. Neema Navai (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Dr. Andrea Necchi (Vita-Salute San Raffaele University and IRCCS San Raffaele Hospital, Milan, Italy), Dr. Jonathan Rosenberg (Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA), Dr. Arlene Siefker-Radtke (The University of Texas MD Anderson Cancer Center, Houston, TX, USA), Dr. John Taylor (University of Kansas Cancer Center, Kansas City, KS, USA), Dr. Stephen Williams (University of Texas Medical Branch, Galveston, TX, USA), and Dr. Alexandre Zlotta (Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Canada). We also acknowledge the following bladder cancer patient advocates for their participation and valued feedback on the consensus recommendations: Toby Shor, Rick Bangs (Bladder Cancer Advocacy Network), Stephanie Chisolm (Bladder Cancer Advocacy Network), and Melvyn Klein. We thank Prem Parameswaran and Allison Witty for their support in preparing for and implementing the IBCG consensus meeting, and Julie Tasso for her editorial services and assistance in the preparation of this manuscript.

Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eururo.2024.08.001.

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