End Points for the Next-Generation Bladder-Sparing Perioperative Trials for Patients With Muscle-Invasive Bladder Cancer

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DOI https://doi.org/10.1200/JCO-25-01608

ABSTRACT

PURPOSE The evolving treatment landscape of muscle-invasive bladder cancer (MIBC) increasingly warrants novel trial design to evaluate perioperative strategies aimed at bladder preservation. To establish standardized outcome measures for evaluating organ preservation strategies in MIBC, the International Bladder Cancer Group (IBCG) and the Global Society of Rare Genitourinary Tumors (GSRGT) assembled an international, multidisciplinary consensus panel.

METHODS The IBCG and GSRGT gathered global bladder cancer experts and patient advocates to establish a framework for risk-adapted bladder-sparing treatment approaches for MIBC. Working groups reviewed the literature and developed draft recommendations, which were discussed at a live meeting in December 2024 in Milan. This was followed by voting by the members using a modified Delphi process. Recommendations achieving ≥75% agreement during the meeting were further refined and presented.

RESULTS Clinical complete response (cCR) definition should encompass the absence of high-grade malignancy on pathology and malignant cells on urine cytology and no evidence of local or metastatic disease on cross-sectional imaging. Although cCR remains immature as a primary or coprimary end point in registrational trials, it could serve as a suitable end point in early-phase studies and risk-adapted investigations. Event-free survival (EFS) remains the preferred primary end point as it could reliably capture the durability of clinically meaningful benefit after omittance of surgical consolidation or chemoradiation. Given the composite nature of EFS, events should be prespecified, evaluated in an intention-to-treat approach, and meticulously collected. Continuous assessment of individual patient preferences should begin at the outset of perioperative therapy discussions, with informed decision making prioritized throughout.

CONCLUSION The consensus definition of cCR and the framework presented in this study can serve as a foundation for thorough testing of risk-adapted bladder-sparing treatment paradigms for MIBC.

ACCOMPANYING CONTENT

Appendix

Accepted July 31, 2025
Published September 11, 2025

J Clin Oncol 00:1-9

View Online Article

INTRODUCTION

Neoadjuvant chemotherapy followed by radical cystectomy (RC) is the most widely used standard-of-care option for the management of patients with muscle-invasive bladder cancer (MIBC).[1,2] Multiple phase II studies with immune checkpoint inhibitors (ICI), either as monotherapy or combined, demonstrated comparable pathologic complete response (pCR) rates of 35%-40%[3-13] until the NIAGARA trial, the first phase III trial testing the addition of perioperative (neoadjuvant and adjuvant) durvalumab to standard-of-care chemotherapy followed by RC. The trial

showed a significant event-free survival (EFS) and overall survival (OS) benefit in favor of the perioperative regimen.[14] Further clinical trials are underway testing novel combinations of ICI with antibody-drug conjugates (ADC), targeted therapies, or other compounds.

RC currently represents the mainstay treatment in these trials and in standard of care. Removal of the bladder inherently reduces the risk of local recurrences, surgically consolidates treatment-refractory residual disease, and reliably risk-stratifies patients, informing the need for adjuvant treatment. However, at the individual patient level, RC can be associated with significant morbidity with substantial implications for functional independence and quality of life, as well as the risk of perioperative mortality.[15] Given the unprecedented activity of novel systemic therapies in metastatic urothelial cancer which are now being moved to organ-confined stages, whether RC is required for all patients is now in question. While retrospective series, and recent prospective studies, demonstrate that durable bladder-intact EFS (BI-EFS) is achievable in a subset of patients treated with neoadjuvant systemic therapy, followed by transurethral resection of the bladder tumor (TURBT), larger and more definitive studies are needed.

Advancing a risk-adapted nonradiation-based bladder-sparing treatment for MIBC requires the development of precise and standardized definitions for clinical complete response (cCR).[16,17] Therefore, the International Bladder Cancer Group (IBCG) and the Global Society of Rare Genitourinary Tumors (GSRGT) held a consensus meeting in Milan, Italy, on December 13, 2024, focusing on establishing a uniform definition of cCR and a general framework to advance definitive testing of a risk-adapted bladder-sparing strategy for MIBC treatment.

METHODS

Consensus Panel Assembly

The participants of the consensus panel represented a diverse and balanced group of individuals with expertise in clinical management of bladder cancer and clinical trial development. The panel included experts from the core disciplines involved in bladder cancer management and research, including patient advocates from the Bladder Cancer Advocacy Network and the World Bladder Cancer Patient Coalition. Although not part of the consensus panel, representatives from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) also joined and provided valuable input to the discussion.

Development of Recommendations

All recommendations included in this study are based on rigorous and balanced discussions of the available evidence in the literature and, when such evidence was lacking, on the clinical expertise/consensus of the panelists. Members of the IBCG and of the consensus panel were first sent an anonymous survey to identify key discussion points and areas where consensus is lacking within the urologic oncology community pertinent to the goals of the study (N = 64 participants, Appendix Table A1, online only). Subsequently, an IBCG and GSRGT Consensus Meeting was held in Milan, Italy, and broadcasted online on December 14, 2024, allowing a detailed discussion on these areas.[18] Specifically, panel members participated in a modified Delphi process.[19] An anonymous postmeeting poll pertaining to select key statements representing the discussions at the consensus meeting and the objectives of the consensus definition, including cCR, EFS, OS, and their use in ongoing and future research efforts, was developed during the consensus meeting via live voting and sent to the meeting panelists and participants after the meeting (N = 59, Appendix Table A2). Consensus was defined as achieving ≥75% agreement. These recommendations formed the basis of this study. When additional practice-changing data and/or clinical trial results became available in the time between the live meeting and manuscript submission date, the authors considered and incorporated new evidence into the recommendations. All authors reviewed, edited, and agreed upon the final recommendations put forth in this study.

Conflict of Interest Management

Panelists, all of whom are coauthors of this study, have individually declared all potential and actual financial relationships and competing interests relevant to the topics discussed as part of the development of this study. Those with industry employment or significant financial interests that may impair unbiased contributions were recused from discussions and development of this consensus report. Guideline development procedures, including in-person and virtual attendance, were funded solely by IBCG and GSRGT. No for-profit or industry funding was involved.

RESULTS

Panel recommendations on key components of clinical trial designs exploring a risk-adapted bladder-sparing approach in MIBC are summarized in Table 1. A simplified schema of standard-of-care management of MIBC and next-generation bladder preservation approaches is depicted in Figure 1.

Patient Selection in Perioperative Trials in MIBC

Cisplatin-based regimens comprise the cornerstone of standard-of-care neoadjuvant treatment in clinical stage T2-4N0-1M0 MIBC with pure or predominant (comprising ≥50% of the tumor specimen) urothelial carcinoma histology. In the design of bladder-sparing trials, specifically for those using novel agents, cisplatin eligibility and the role of standard neoadjuvant therapy should still be considered. In clinical practice, a large proportion of patients with MIBC are not eligible for cisplatin or refuse to receive

TABLE 1. Key Components of Design for Clinical Trials Implementing Bladder Preservation After Clinical Complete Response to Systemic Therapy

Key Component of Trial Design	
Eligibility	Clinical stage T2-4N0-1M0 MIBC with pure or predominant urothelial carcinoma histology[a] Eligibility pertaining to the systemic treatment type[b] Suitability and acceptance of radical cystectomy at the time of enrollment Unsuitability or refusal of radical radiotherapy at the time of enrollment in nonradiotherapy-based bladder-sparing approaches Prioritize informed decision making by the patient on prospects of bladder preservation at the time of enrollment
End points	
Clinical complete response	
Definition	No evidence of high-grade malignancy on bladder biopsy pathology (including all visually abnormal sites in addition to reTURBT/biopsy of the known site of MIBC before neoadjuvant chemotherapy) AND Absence of malignant cells on urine cytology AND No definitive evidence of local or metastatic disease on cross-sectional imaging
Utilization	Immature as a primary or coprimary end point for registration late-phase clinical trials Appropriate primary end point in early phase single-arm trials (ie, phase I/II) Appropriate intermediate end point to facilitate individualized risk-adapted strategies
Event-free survival	
Definition	Event defined as high-grade tumor persistence, recurrence, or progression during or after perioperative therapy, and receipt of any additional standard-of-care treatment, including radical cystectomy, radiotherapy, or intravesical therapy
Utilization	Adequate primary end point for both early- and late-phase bladder preservation trials
Overall survival	Secondary end point
Patient-reported outcomes	Secondary end point
Random assignment	Randomized trials testing newer strategies against the standard-of-care approach are still the mainstay for setting new treatment options
Stratification	Tumor stage and completeness of diagnostic TURBT can be accounted for as stratification factors within trials

Abbreviations: MIBC, muscle-invasive bladder cancer; TURBT, transurethral resection of bladder tumor.
[a]Predominantly urothelial histology defined ≥50% of the tumor specimen comprising conventional urothelial histology.
[b]Cisplatin eligibility should be considered in trial design. Renal function–based cisplatin eligibility defined as ≥50-60 mL/min using the Cockcroft Gault formula.

such chemotherapy.[20] The consensus panel recommends that patients with borderline creatinine clearance, that is, of 50-60 mL/min, receive neoadjuvant cisplatin-based chemotherapy, alone or in combination with durvalumab (NIAGARA trial data with level I evidence), tested in clinical trials. Importantly, the evolving neoadjuvant treatment landscape of MIBC, now incorporating new therapeutics, necessitates continuous attention to the eligibility of both conventional and new therapies either as monotherapy or as part of combination regimens.

The consensus panel recommends that patients who are fit for RC should be offered enrollment in clinical trials exploring risk-adapted bladder-sparing approaches, therefore defining a patient population distinct from the typical RC-unfit or RC-refusing population, for which trimodality therapy with maximum TURBT followed by chemoradiation protocols represents the standard-of-care option. Multidisciplinary discussions between urologists, radiation oncologists, and medical oncologists are of utmost importance in assessing patient eligibility. Patients pursuing clinical trials exploring risk-adapted nonradiation-based bladder-sparing treatment approaches should be deemed unsuited for, or have declined, conventional trimodality therapy after shared and informed decision making.

Definition of cCR

Risk-adapted bladder-sparing treatment approaches for MIBC, in which the decision to integrate definitive locoregional therapy is based on real-time assessment of an individual patient's response to systemic therapy, require adjudication of cCR. In a well-selected population of patients based on the achievement of complete tumor disappearance on cross-sectional imaging and biopsy, retrospective cohort studies and a meta-analysis demonstrated the potential for favorable long-term outcomes.[21-23] According to recent studies, cCR has been defined as a state where the patient meets varying definitions and combinations of the following criteria: negative urinary cytology, negative cross-sectional imaging, and negative pathology results from repeat post-neoadjuvant chemotherapy TURBT (reTURBT) with mapping biopsies.[23-28] In patients with cT2-cT3N0M0 MIBC bearing at least one mutation in *ATM*, *RB1*, *FANCC*, or *ERCC2* genes, RETAIN-1 and RETAIN-2 studies tested active surveillance (AS) after cCR (by computed tomography, reTURBT, and urinary cytology) after neoadjuvant-accelerated methotrexate, vinblastine, doxorubicin, and cisplatin, alone or in combination with nivolumab, respectively, and showed a 2-year metastasis-free survival (MFS) of 72.9% and 77.4%, respectively.[26,27] In parallel, the HCRN GU16-257 trial tested

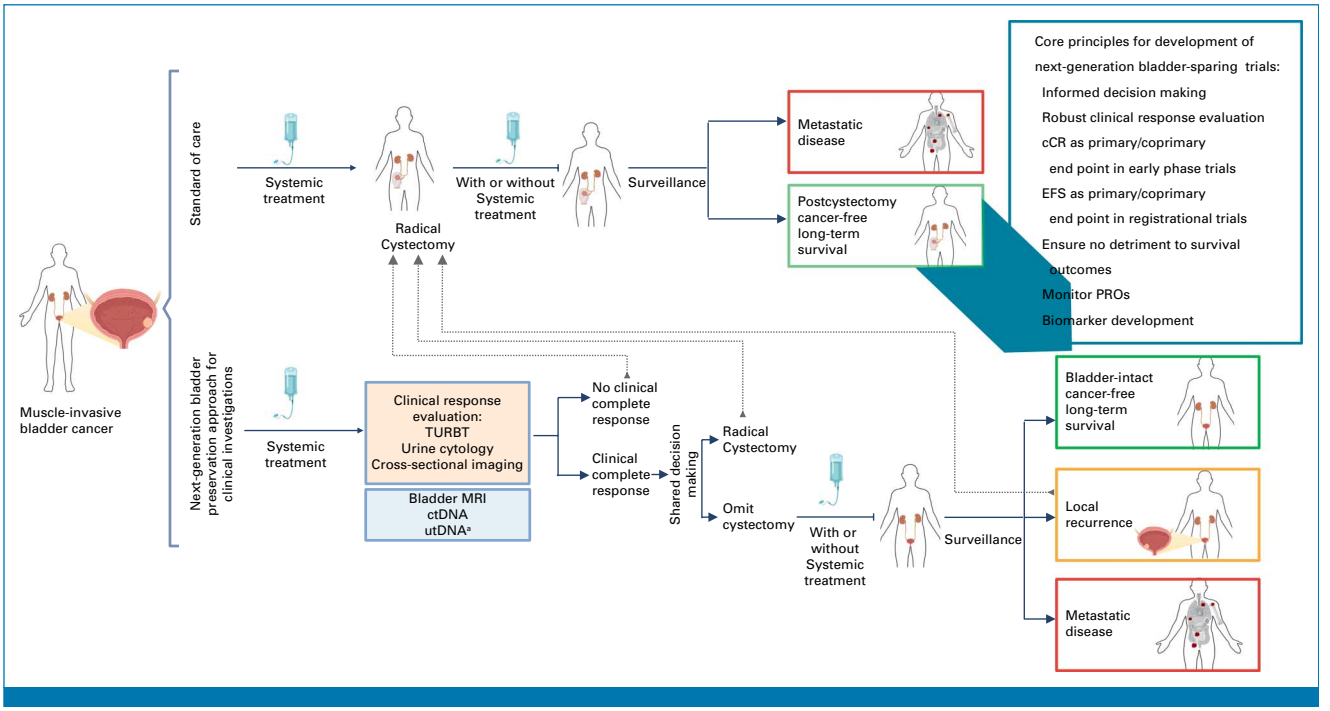

FIG 1. A simplified overview of standard-of-care treatment for surgically fit and systemic treatment–eligible patients with muscle-invasive bladder cancer and next-generation bladder preservation strategies. Created using Biorender.com. [a]Currently being tested prospectively. cCR, clinical response; ctDNA, circulating tumor DNA; EFS, event-free survival; MRI, magnetic resonance imaging; PROs, patient-reported outcomes; TURBT, transurethral resection of bladder tumor; utDNA, urinary tumor DNA.

the positive predictive value of a uniformly assessed and stringently defined cCR for 2-year MFS in patients pursuing a risk-adapted bladder-sparing approach. In this study, the cCR rate after nivolumab, gemcitabine, and cisplatin was 43%, and cCR predicted treatment benefit with a positive predictive value of 0.97 (95% CI, 0.91 to 1.0).[28] Consistent with the cCR definition used in HCRN GU16-257, the consensus panel recommends that the cCR definition in clinical trials should meet all the following criteria: no evidence of high-grade malignancy on bladder biopsy (including pTa/pT1/pTis), including all visually abnormal sites in addition to reTURBT or biopsy of the known site of MIBC before neoadjuvant therapy, the absence of malignant cells on urine cytology, and no definitive evidence of local or metastatic disease at cross-sectional imaging. In addition, the panel recommends that baseline tumor stage and completeness of diagnostic reTURBT can ideally be accounted for as stratification factors within trials.

Notably, despite significant advancements, imaging and biopsy sampling techniques continue to bear a considerable degree of subjectiveness and interobserver variability. Accordingly, cross-sectional imaging and repeat biopsy techniques should follow a uniform methodology, such as prespecified bladder mapping as part of TURBT. Importantly, it is known that TURBT remains relatively inaccurate in predicting true pathologic response and thus must be coupled with other methodologies.[29] Recently, bladder magnetic resonance imaging (MRI) has shown promise in overcoming challenges associated with interobserver variability when predicting major tumor response.[30,31] Most panelists suggested that pelvic MRI should be the preferred imaging methodology over computed tomography with incorporation of the Vesical Imaging-Reporting and Data System assessment when feasible; however, consensus was not reached on this point. Investigations of the role of radiomics and tissue-based or liquid molecular biomarkers like circulating tumor DNA (ctDNA) or urinary tumor DNA (utDNA) are currently underway, with preliminary evidence suggesting prognostic power (robust for ctDNA) and a potential additional/complementary role in identifying patients with cCR.[32,33] However, these data remain immature at the time of consensus development. Thus, the panel did not recommend that they should be incorporated into the current definition of cCR. However, this topic merits revisiting in the near future to refine this consensus definition, given the rapid development and availability of new biomarkers, such as ctDNA, utDNA, and others, and the continuous improvement of more refined imaging-based tools. From a clinical trial management standpoint, investigators should consider central data collection and response assessment; however, these procedures should not delay therapy decision making.

cCR as an End Point

As in any malignancy, the choice of appropriate primary end point for regulatory purposes in MIBC needs to be considered

in the context of the specific clinical/therapy setting, phase of drug development, intended therapeutic indication, study population, and methodologic study design aspects. For exploratory purposes in single-arm early-phase trials, it is critical that the chosen primary efficacy end point convincingly allows attribution of the treatment effect. For such cases in MIBC, cCR rate has the potential to serve this purpose as a pharmacodynamic end point. The consensus panel recommends cCR as an appropriate primary end point in early-phase single-arm trials. Importantly, the validity of cCR as a surrogate for time-to-event end points, thus its ability to capture clinically meaningful benefit over time, is yet to be established for use in confirmatory settings. Accordingly, in registrational and late-phase trials, the consensus panel recommends against use of cCR as a primary or coprimary end point.

A commonly cited barrier to advancing a risk-adapted bladder-sparing approach to the treatment of MIBC has been the imperfect correlation between cCR and pCR.[34] However, a more relevant consideration is the correlation between cCR and longer-term end points that capture how patients feel, function, or survive. Therefore, cCR remains a critically valuable tool to guide treatment decisions if it can identify (1) patients capable of achieving a durable survival benefit after omitting RC (ie, those who have truly achieved an underlying pCR) or have non–muscle-invasive bladder recurrences that can be managed locally or (2) patients whose survival is not compromised in the setting of a later RC for local (eg, muscle-invasive) recurrence after an initial cCR. Notably, salvage surgery plays a key role in the success of organ-sparing approaches that have been adopted into standard practice for many solid tumors, including after trimodality therapy for MIBC.

The panel also explored whether cCR may serve as a biomarker, an end point, or both, concluding that its role depends on the context of use. While pretreatment biomarkers have been widely studied to personalize therapy, on-treatment response measures like cCR are currently underutilized in guiding individualized bladder cancer treatment. Based on current evidence, the panel recommends using cCR to guide risk-adapted bladder-sparing treatment strategies for MIBC in prospective clinical trials.

The panel emphasizes that trials integrating cCR as an end point or a biomarker should follow rigorous biomarker development principles and use standardized assessments. Biomarker development in studies implementing cCR is fundamental to advancing the risk-adapted strategies. Investigators should evaluate determinants of response with the same rigor that has assessed pCR in the RC setting.[35-39]

Recognizing the potential for cCR to be used to screen the activity of new regimens, the panel recommends the adoption of cCR as an end point in single-arm phase II trials designed to evaluate novel therapies within a risk-adapted, bladder-sparing framework. In addition to examining cCR as an end point, these trials should also aim to prospectively examine the relationship between cCR and long-term outcomes, such as EFS and BI-EFS.

Survival End Points in a Risk-Adapted Bladder-Sparing Paradigm

Time-to-event end points, such as EFS, BI-EFS, MFS, disease-specific survival, or OS, comprise the pillars of determining whether a treatment is associated with long-term remission or cure across cancers, including MIBC. The panel recommends that the event definition used in EFS estimations should capture any high-grade tumor persistence, recurrence, or progression during or after systemic therapy, along with the receipt of any additional standard-of-care treatment, including RC or bladder radiotherapy and intravesical therapy. This EFS definition incorporates and extends the BI-EFS definition conventionally used in trimodality therapy trials.[40] The consensus panel recommends using EFS in the intent-to-treat population as an adequate primary end point for the next-generation trials aimed at bladder preservation in patients with cCR, including those with registrational intent. As the cCR alone does not inherently capture the durability of response or survival, EFS will provide insight into the clinically relevant time period for patients in whom surgical consolidation or chemoradiation is omitted. Investigators should be aware that, because EFS is a composite end point, it can be challenging to determine which specific events drive an observed treatment effect. Furthermore, the thresholds to treat different events at the individual level will be subjective. To address this, objective triggers for meeting the EFS event definition should be prespecified and meticulously collected throughout a clinical trial, specifically with regard to the nonmetastatic relapse events occurring in the bladder. Patients should still be censored at the time of secondary urothelial cancer occurrence in nonbladder sites such as renal pelvis or ureter. Future clinical trials are expected to adopt event definitions that are broadly aligned, yet study-specific. Investigators should therefore reconcile their strategies, so findings can be meaningfully compared.

MFS is another relevant end point for potential studies evaluating the validity of approaches that limit definitive locoregional therapy to the bladder. In comparative trials where one arm defers definitive local therapy, such as the NEOBLAST trial (ClinicalTrials.gov identifier: NCT06537154) or studies evaluating intravesical drug delivery after cCR, local recurrences are expected to occur more frequently in the bladder-sparing arm. However, if these non-MIBC (NMIBC) recurrences can be reliably detected and effectively salvaged, their clinical consequence may be limited, particularly as many patients may avoid radical treatment altogether or experience additional months or years with their bladder intact before requiring definitive therapy. In this context, MFS becomes a meaningful measure of long-term disease control as it reflects the ability to prevent systemic progression while tolerating manageable local

events. Accordingly, the advantage in using MFS is that it is a clinically meaningful differentiator between a disease that can be (or has been) cured despite an event and the development of metastases which results in a far lower probability of cure.

However, there are still critical uncertainties regarding NMIBC recurrences and risk of metastasis development and, at present, MFS remains immature for registrational trials. In RETAIN-1, AS was recommended in 36% of patients and 17% remained alive and metastasis-free with an intact and unirradiated bladder. Ten of 25 per-protocol AS patients (40%) developed NMIBC recurrence, with three patients developing metastatic disease and three undergoing RC.[26] In the RETAIN-2 study, in the AS group as of this manuscript writing (median follow-up 18.4 months), approximately 30% of patients with recurrent NMIBC developed metastatic disease,[27] highlighting the fact that recurrent NMIBC can be a harbinger of poor outcomes in bladder-sparing paradigms and requires prompt and aggressive bladder-directed management.

Furthermore, future investigations should evaluate systemic therapies in this setting to eradicate potentially coexisting micrometastatic disease. In the HCRN GU16-257 study, among the 33 cCR patients, nine (27%) underwent RC, nine (27%) developed a local NMIBC recurrence, and two patients developed distant metastases. Another similar study is ongoing in the United States, and results are eagerly awaited (Alliance A031701; ClinicalTrials.gov identifier: NCT03609216).[25]

Methodologic Considerations for Future Clinical Trial Design

FDA approvals in early, curative-intent settings generally rely on randomized trials and are based on established clinical benefit time-to-event end points, such as disease-free survival, although there may be rare scenarios where a single-arm trial using a response-based end point is considered acceptable (eg, Bacillus Calmette-Guérin–unresponsive NMIBC with carcinoma in situ or deficient mismatch repair/microsatellite instability-high locally advanced rectal cancer) because of the lack of feasibility of conducting a randomized trial.[41,42]

Per international guidelines, end points must be valid and reliable measures of clinically relevant treatment benefits (ICH E9).[43] A clinical trial evaluating an investigational therapy in a potentially curable population should therefore ensure robust assessment of durability of response and missed opportunities for cure. EFS captures the durability of response and survival; however, interpretation of EFS, as defined by the panel, is challenging if the decision to proceed to RC is subjective. The panel thus recommends that studies with EFS as an end point should ensure that criteria for RC are clearly prespecified in the protocol and minimize deviations from the protocol. A thorough assessment of all potential patient and physician perspectives in these situations should be pursued by the investigators to minimize participant attrition.

OS remains the most convincing efficacy end point in confirmatory settings in MIBC and a gold standard end point for therapeutic trials in general. In nonmetastatic curative settings where EFS is the primary end point, it is critical to ensure that no detriment in OS is observed as a secondary end point. With perioperative approaches like in the NIAGARA trial, questions remain regarding the individual impact of the neoadjuvant and adjuvant components of the intervention on the improvement of OS as the study was not designed to answer this fundamental question. Furthermore, OS might be confounded by access to therapies and the activity of the therapeutics used in these multistage therapeutic settings. Novel study designs using a second random assignment or inclusion of a third arm could be considered in neoadjuvant-adjuvant settings to establish the contribution of different elements of the treatment sequence.

Notably, a response-based end point, such as cCR, has numerous challenges associated with its use, including but not limited to definition, assessment methods, and trial-level association with later oncologic outcomes. Investigators and sponsors are encouraged to meet with representatives of regulatory agencies to discuss registrational trial designs early in the design phase. The consensus panel recommends that the ideal design would be a randomized noninferiority trial with a carefully formulated recurrence and RC-free end point, understanding that there are feasibility concerns with randomly assigning to RC or no RC and accruing the very large number of patients that a noninferiority approach would require. It is worth noting, for the design of such studies, that the regulatory agencies consider response-based end points or OS as primary end points in registrational trials.[44,45] Limiting trials to patients who have a tumor biomarker of response to neoadjuvant therapy would potentially maximize the benefit-risk for participants in bladder-sparing trials. However, the relatively modest sensitivity might have limited biomarker use to date in perioperative clinical trials.

It remains critically important to emphasize that bladder-sparing strategies based on cCR, as discussed herein, are intended solely for clinical trial development and conduct, require further validation in ongoing trials, and should not guide routine clinical decision making given the need to further evaluate this approach. Uncertainties remain regarding the treatment of patients in real-world practice, where it is common for patients to refuse RC and radical radiotherapy after cCR with neoadjuvant chemotherapy. The panel consensus was that a reTURBT and observation in lieu of surgical or radiation-based consolidation should not serve as a standard-of-care approach outside of clinical trials. Clinical trial enrollment should be strongly encouraged in this patient population. The consensus panel recommends that clinical trial designs may implement maintenance/

consolidation therapies as opposed to observation for this patient population. This is especially relevant since an area of uncertainty remains with regard to the optimal management of patients undergoing bladder preservation after cCR who develop NMIBC recurrences, and data on the reliability of salvage RC versus intravesical or alternative therapies should be collected within trials.

Patient-Reported Outcomes as End Points in the Perioperative Setting

Careful evaluation and reporting of patient-reported quality-of-life outcomes with relevant tools and prespecified statistical analysis plans should ideally be a secondary end point in perioperative clinical trials evaluating bladder-preserving strategies. Novel patient-reported outcome measures tailored to assess the clinical, psychosocial, and financial burdens of bladder cancer diagnosis and its surgical and therapeutic management strategies are currently underway. Longitudinal assessment of patient experience is strongly encouraged in studies investigating the impact of undergoing or deferring surgical consolidation or chemoradiation.[46]

Involving Patients Into the Decision-Making Process

The literature suggests that prioritization of cure, quality of life, functional preservation, or cosmetic outcomes varies substantially between individuals.[47] The panel recommends eliciting individual patient priorities throughout the disease course and enrollment into bladder preservation clinical trials. All counseling should be enacted according to principles of informed and shared decision making. The consensus panel emphasizes the importance of timely discussions regarding bladder-preserving approaches with all patients with MIBC. These discussions should commence before the initiation of systemic treatment for all patients starting neoadjuvant therapy to allow sufficient time for the patient and the provider to engage in informed decision making for situations where bladder preservation could serve as an option depending on the response to neoadjuvant treatment. It is also essential to recognize that not all patients will have cCR and timely sequence to definitive locoregional therapy must be ensured for patients who do not achieve cCR as delays beyond 12 weeks to RC are associated with worse outcomes.[48]

In the emerging paradigm of a bladder-sparing approach after cCR with either systemic or intravesical maintenance therapy or observation, instead of any radical locoregional treatment to the bladder, the potential for NMIBC recurrences and their management, and their impact on patient-reported outcomes have emerged as a critical issue. Future challenges include identifying patients who benefit from further bladder-sparing strategies versus definitive salvage treatment and elucidating patients' understanding of complete remission, duration of trials for comprehensive capture of outcomes, surveillance costs and therapy/monitoring patient burden, loss of bladder function secondary to treatment in a number of patients, affordability and accessibility of personalized approaches, and personalized risk/benefit calibration.[49] Accordingly, in the development of clinical trials incorporating bladder-preserving strategies, there is a pressing need for shared decision making and patient advocacy groups should be involved as early as possible in the clinical trial conception and design.

In conclusion, the IBCG-GSRGT provides new and well-defined consensus recommendations informing standardized approaches for the development of next-generation clinical trials aimed at advancing the MIBC field through the evaluation of bladder preservation after cCR with highly effective therapy and within personalized, response-driven adaptive approaches.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-01608.

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ACKNOWLEDGMENT

We thank the representatives from the US Food and Drug Administration and the European Medicines Agency for attending the IBCG and GSRGT Consensus Meeting and for their invaluable contributions to the development of this consensus report.

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End Points for the Next-Generation Bladder-Sparing Perioperative Trials for Patients With Muscle-Invasive Bladder Cancer

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

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Patents, Royalties, Other Intellectual Property: NOVEL METHOD Publication number: 20240156912 Abstract: The invention relates to a method of expanding a population of regulatory T cells in a tissue or organ of a subject, wherein said method comprises administration of IL-2 and a targeting moiety specific for said tissue or organ, and wherein said tissue or organ is the lung. The invention further relates to populations of regulatory T cells produced according to the method and the production of said population in vivo. Also provided is a pharmaceutical composition comprising IL-2 and a targeting moiety as defined herein as well as a method of treating a disease or disorder mediated by inflammation or for the reduction of inflammation which comprises the methods defined herein or administration of a pharmaceutical composition as defined herein. Type: Application Filed: March 10, 2022; Publication date: May 16, 2024; Inventors: Adrian LISTON, James DOOLEY, Oliver BURTON, Lubna KOUSER, Ntombizodwa MAKUYANA, Stephanie LIENART (I), NOVEL METHOD

Publication number: 20220220180. Abstract: The invention relates to a method of expanding a population of regulatory T cells in a tissue or organ of a subject, wherein said method comprises administration of IL-2 and a targeting moiety specific for said tissue or organ and wherein said tissue or organ is the central and/or peripheral nervous system. The invention further relates to populations of regulatory T cells produced according to the method and the production of said population in vivo. Also provided is a pharmaceutical composition comprising IL-2 and a targeting moiety as defined herein as well as a method of treating a disease or disorder mediated by inflammation or for the reduction of inflammation which comprises the methods defined herein or administration of a pharmaceutical composition as defined herein. Type: Application Filed: March 4, 2022; Publication date: July 14, 2022; Inventors: Matthew Holt, Adrian Liston, James Dooley (I)
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Consulting or Advisory Role: Cardinal Health
Research Funding: Pfizer, Merck

Bogdana Schmidt
Consulting or Advisory Role: ImmunityBio, UroGen Pharma, Janssen
Speakers' Bureau: Ferring

Lawrence H. Schwartz
Consulting or Advisory Role: Bristol Myers Squibb/Celgene, Merck
Research Funding: Merck Sharp & Dohme (Inst), Boehringer Ingelheim (Inst)
Patents, Royalties, Other Intellectual Property: Varian Medical Systems

Guru P. Sonpavde
Employment: Myriad Genetics (I), Exact Sciences (I)
Honoraria: UpToDate, Onviv, PrecisCa, Ideology Health, PeerView, Grand Rounds in Urology
Consulting or Advisory Role: Genentech, Merck, Janssen, Bristol Myers Squibb, Exelixis, EMD Serono, Astellas Pharma, Bicycle Therapeutics, Pfizer, Seagen, Gilead Sciences, Scholar Rock, G1 Therapeutics, Loxo/Lilly, Syapse, Lucence, Vial, Kura Oncology, Loxo/Lilly, Daiichi Sankyo/Astra Zeneca, Aktis Oncology, Ellipses Pharma, GlaxoSmithKline
Speakers' Bureau: Research to Practice, Medscape, Gilead Sciences, Seagen, Natera, Exelixis, Informação Brasileira de Oncologia, Janssen Oncology, Bayer, Merck, AVEO, Pfizer, Astellas Pharma, AstraZeneca
Research Funding: Gilead Sciences (Inst), Bristol Myers Squibb (Inst), EMD Serono (Inst), Jazz Pharmaceuticals (Inst), Bayer (Inst), Sumitomo Pharma Oncology (Inst), Blue Earth Diagnostics (Inst), Exelixis (Inst)
Travel, Accommodations, Expenses: Bristol Myers Squibb, Astellas Pharma
Other Relationship: Bristol Myers Squibb, QED Therapeutics, Elsevier, Mereo BioPharma, G1 Therapeutics, Merck

Marie-Pier St Laurent
Honoraria: Bayer, EMD Serono
Consulting or Advisory Role: AbbVie, Janssen, EMD Serono

Philippe E. Spiess
Leadership: NCCN, Global Society of Rare Genitourinary Tumors, Société Internationale d'Urologie Journal, President of Global Society of Rare GU Tumors
Honoraria: UptoDate
Other Relationship: NCCN
Uncompensated Relationships: Moffitt Cancer Center

Ashish M. Kamat
Leadership: International Bladder Cancer Group (IBCG), World Bladder Cancer Patient Coalition, American Urological Association
Consulting or Advisory Role: Merck, Janssen, Astellas Pharma, Cystotech, Imvax, ImmunityBio, Vivet Therapeutics, enGene, CG Oncology, Ferring, Genentech, Nonagen Bioscience, Pfizer, Seagen, Theralase, Valar Labs, Aspira Women's Health (I), Atonco Pharma, Biological Dynamics, Bristol Myers Squibb, Eisai, Imagin Medical, Incyte, Medac, Photocure, Protara Therapeutics, Roche, Sesen Bio, Urogen pharma, US Biotest
Research Funding: FKD Therapies (Inst), Photocure (Inst), SWOG (Inst), Patient-Centered Outcomes Research Institute (PCORI) (Inst), enGene (Inst), Arquer Diagnostics (Inst), Seagen (Inst)
Patents, Royalties, Other Intellectual Property: Patent: CyPRIT (Cytokine Predictors of Response to Intravesical Therapy) joint with UT MD Anderson Cancer Center
Other Relationship: European Urology Oncology, Journal of Urology, UroToday

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Premeeting Poll Results

Question	Participants, No.	Agree, No. (%)	Disagree, No. (%)	Abstain, No.
Novel bladder-preservation approaches with experimental perioperative therapies should rely on stringent definition of cCR	64	62 (98)	1 (2)	1
Within clinical trials, cCR definition should include the combination of all of these factors: Negative cross-sectional imaging, negative urine cytology, negative biopsy	64	59 (94)	4 (6)	1
Any residual nonmuscle-invasive tumor (including carcinoma in situ, pTa, pT1, either high-grade or low grade) should disqualify for cCR	64	45 (70)	19 (30)	0
Tumor stage and completeness of diagnostic, pretherapy TURBT should be accounted for in the cCR definition	64	47 (75)	16 (25)	1
Pelvic MRI and VI-RADS use should be preferred over CT scan for tumor staging and response assessment	64	39 (72)	15 (28)	10
Tumor and liquid biomarkers are still immature to be incorporated into the definition of cCR	64	50 (86)	8 (14)	6
All patients diagnosed with MIBC should be offered an inclusion in clinical trials of perioperative therapy	64	47 (77)	14 (23)	3
A calculated value of GFR between 50 and 60 (using Cochroft-Gault) should not disqualify patients to receive standard neoadjuvant chemotherapy	64	54 (98)	1 (2)	9
Opportunities for bladder preservation, depending on the response to neoadjuvant therapy should be discussed a priori with the patients (ie, prior to starting treatment)	64	57 (91)	6 (10)	1
Opportunities for bladder preservation, depending on the response to neoadjuvant therapy, should be offered to patients who are qualified for radical cystectomy	64	50 (83)	10 (17)	4
Opportunities for bladder preservation, depending on the response to neoadjuvant therapy, should be offered to patients who are unsuited for or elect not to undergo radical radiotherapy	64	51 (88)	7 (12)	6
Opportunities for bladder preservation, depending on the response to neoadjuvant therapy, should be considered if a maintenance/consolidation therapy is offered within trials	64	55 (90)	6 (10)	3
Cisplatin eligibility and the role of standard neoadjuvant therapy should be considered in the design of bladder-saving perioperative trials using experimental therapies	64	54 (90)	6 (10)	4
Neoadjuvant cisplatin-based chemotherapy, followed by reTURBT and observation, should be considered the standard-of-care approach for patients who refuse cystectomy after the neoadjuvant course and refuse or are unsuited for radical radiotherapy	64	37 (62)	23 (38.)	4
Based on the results of the NIAGARA study, neoadjuvant durvalumab plus gemcitabine-cisplatin chemotherapy, followed by reTURBT and maintenance durvalumab, should be considered the standard-of-care approach for patients who refuse cystectomy after the neoadjuvant course and refuse or are unsuited for radical radiotherapy	64	33 (58)	24 (42)	7
cCR end point is ready to be used as a coprimary end point for the next generation of bladder-sparing perioperative trials aimed at registrational purposes	64	42 (68)	20 (33)	2
EFS should capture any type of tumor persistence, recurrence, or progression during/following perioperative therapy, along with the received of any additional standard-of-care treatment	64	59 (95)	3 (5)	2
cCR and EFS are adequate coprimary end points for setting new standards with the next-generation bladder-saving perioperative trials	64	43 (69)	19 (31)	2
Evaluation and reporting of patient-reported outcomes (in addition to survival) should be a required secondary end point of clinical trials of perioperative and bladder-preserving therapies	64	60 (95)	3 (5)	1

NOTE. Consensus was defined as achieving ≥75% agreement.
Abbreviations: cCR, clinical complete response; CT, computed tomography; EFS, event-free survival; GFR, glomerular filtration rate; MIBC, muscle-invasive bladder cancer; MRI, magnetic resonance imaging; TURBT, transurethral resection of the bladder tumor; VI-RADS, vesical-imaging reporting and data system.

TABLE A2. Postmeeting Survey Results

Question	Participants, No.	Agree, No. (%)	Disagree, No. (%)	Abstain, No.
cCR, defined as negative urinary cytology, negative cross-sectional imaging, and negative biopsy, is still immature as an end point (either primary or coprimary) for registration trials, as it still requires validation with prospective trials	59	44 (75)	15 (25)	0
cCR can be used as a primary end point to screen the activity of novel treatment strategies for MIBC in single-arm phase II trials	59	50 (85)	9 (15)	0
cCR can be used as an intermediate end point to facilitate individualized risk-adapted approaches to bladder-sparing treatment for MIBC in prospective clinical trials	59	55 (96)	2 (4)	2
In next-generation trials aimed at bladder preservation with novel systemic and/or intravesical therapies, EFS should capture any type of high-grade tumor persistence, recurrence, or progression during/following perioperative therapy, along with the receipt of any additional standard-of-care treatment, including bladder radiotherapy, intravesical therapy, systemic therapy, and radical cystectomy, as an event	57	54 (95	3 (5)	2
EFS, defined as above, is an adequate primary end point for the next-generation bladder-sparing trials aimed at registrational purposes	58	49 (85)	9 (16)	1
In patients who achieve a cCR after neoadjuvant therapy, who are offered observation or maintenance therapy within trials, timely radical cystectomy is recommended at the first occurrence of high-grade tumor relapse within the bladder	55	39 (71)	16 (30)	4

NOTE. Consensus was defined as achieving ≥75% agreement.

Abbreviations: cCR, clinical complete response; EFS, event-free survival; MIBC, muscle-invasive bladder cancer.