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Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of urothelial cancer

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ABSTRACT

A number of immunotherapies have been developed and adopted for the treatment of urothelial cancer (encompassing cancers arising from the bladder, urethra, or renal pelvis). For these immunotherapies to positively impact patient outcomes, optimal selection of agents and treatment scheduling, especially in conjunction with existing treatment paradigms, is paramount. Immunotherapies also warrant specific and unique considerations regarding patient management, emphasizing both the prompt identification and treatment of potential toxicities. In order to address these issues, the Society for Immunotherapy of Cancer (SITC) convened a panel of experts in the field of immunotherapy for urothelial cancer. The expert panel developed this clinical practice guideline (CPG) to inform healthcare professionals on important aspects of immunotherapeutic treatment for urothelial cancer, including diagnostic testing, treatment planning, immune-related adverse events (irAEs), and patient quality of life (QOL) considerations. The evidence- and consensus-based recommendations in this CPG are intended to give guidance to cancer care providers treating patients with urothelial cancer.

BACKGROUND

Urothelial cancer (a term that encompasses cancers of the bladder, urethra, and upper urinary tract) represents a significant public health concern as the sixth most common type of cancer in the US. In the year 2021, an estimated 83,730 new cases of bladder cancer and 4,190 new cases of cancers of the ureter and other urinary organs will be diagnosed in the US, leading to approximately 18,160 deaths.[1] There is a clear and unmet need for additional therapeutic options that may provide effective disease control outcomes without compromising quality of life (QOL) for patients with urothelial cancer.

For several decades, standard of care (SOC) therapies for urothelial cancer included surgery, chemotherapy, radiotherapy, and intravesical Bacillus Calmette-Guérin (BCG), a form of immunotherapy comprising an attenuated bacterial pathogen to promote antitumor immune responses. In recent years, however, the US Food and Drug Administration (FDA) has approved a number of immune checkpoint inhibitors (ICIs) for the treatment of urothelial cancer arising from the bladder or other areas of the urinary tract. The ICIs approved for the treatment of urothelial cancer at the time of manuscript preparation include anti-programmed cell death protein-1 (PD-1) agents (nivolumab and pembrolizumab) and anti-programmed death-ligand 1 (PD-L1) agents (atezolizumab, avelumab, and durvalumab). The disease states for which the FDA has approved ICI therapy include non-muscle-invasive bladder cancer (NMIBC) and locally advanced or metastatic urothelial cancer (mUC) (including bladder, urethra, and upper tract urothelial cancers).[2] Trials are ongoing investigating ICIs in earlier disease stages of NMIBC, mUC, and muscle-invasive bladder cancer (MIBC), as well as in the context of novel combination regimens, such as in combination with anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) agents (ipilimumab), chemotherapies, or targeted agents.

Due to the recent clinical adoption of ICIs for bladder cancer, many uncertainties remain regarding the optimal use of these agents, both as monotherapies and in combination with existing or emerging modalities.[3–6] Of note, although antibody-drug conjugates (ADCs) such as enfortumab vedotin (EV) or vicinium are derived from key protein constituents of humoral immunity, they were not defined as

immunotherapies for the purposes of this manuscript since their primary mechanism of action includes direct cytotoxicity akin to classical chemotherapies as opposed to immune-mediated anti-tumor effects.[7 8]

The Society for Immunotherapy of Cancer (SITC) previously convened an expert panel to develop a clinical practice guideline (CPG) in 2017 titled, "The Society for Immunotherapy of Cancer consensus statement on immunotherapy for the treatment of bladder carcinoma."[9] However, immunotherapeutic options for the treatment of urothelial cancer have expanded substantially since the publication of the 2017 guideline. Therefore, in 2020, SITC convened an expert panel to generate updated and expanded evidence- and consensus-based recommendations for the treatment of urothelial cancer with immunotherapy. The expert panel discussed and made recommendations on topics including diagnostic testing, treatment planning, emerging data on investigational immunotherapies, the management of immune-related adverse events (irAEs), and patient QOL. The recommendations in this manuscript are not intended to replace sound clinical judgment and unique patient-based decisions, but to provide healthcare professionals with current, evidence-based guidance on the use of immunotherapy for the treatment of urothelial cancer. The panel focused solely on drugs approved by the FDA; regulatory status, availability, or common clinical practices may differ in other regions. The full series of SITC CPGs can be found on the SITC website (https://www.sitcancer.org/guidelines).

GUIDELINE DEVELOPMENT METHODS

The Institute of Medicine's (IOM) Standards for Developing Trustworthy Clinical Practice Guidelines were used as a model to develop the recommendations in this manuscript. IOM standards dictate that guideline development is led by a multidisciplinary expert panel using a transparent process where both funding sources and conflicts of interest are readily reported. This CPG is intended to provide guidance and is not a substitute for the professional judgment of individual treating physicians.

Conflict of interest management

As outlined by IOM standards, all financial relationships of expert panel members that might result in actual, potential, or perceived conflicts of interest were individually reported. Disclosures were made prior to the onset of manuscript development and updated on an annual basis. In addition, panel members were asked to articulate any actual or potential conflicts at all key decision points during guideline development, so that participants would understand all possible influences, biases, and/or the diversity of perspectives on the panel. Although some degree of relationships with outside interests are to be expected among experts, panel candidates with significant financial connections that may compromise their ability to fairly weigh evidence (either actual or perceived) were not eligible to participate in guideline development.

Recognizing that guideline panel members are among the leading experts on the subject matter under consideration and guideline recommendations should have the benefit of their expertise, any identified potential conflicts of interests were managed as outlined in SITC's disclosure and conflict of interest resolution policies. As noted in these policies, panel members disclosing a real or perceived potential conflict of interest may be permitted to participate in consideration and decision-making of a matter related to that conflict, but only if deemed appropriate after discussion and agreement by the expert panel.

The financial support for the development of this guideline was provided solely by SITC. No commercial funding was received.

Recommendation development

Panel recommendations are based on literature evidence, where possible, and clinical experience, where appropriate.[10] Consensus for the recommendations herein was generated by open communication and scientific debate in small- and whole-group settings, surveying and responses to clinical questionnaires, as well as formal voting in consensus meetings.

For transparency, a draft of this CPG was made publicly available for comment during the development process and prior to publication. All comments were evaluated and considered for inclusion into the final manuscript according to the IOM standard.

Evidence rating

The evidence- and consensus-based recommendations of the panel were refined throughout the development process in order to obtain the highest possible agreement among the experts, however, the minimum threshold was defined as 75% approval among the voting members. Evidence supporting panel recommendations was graded according to the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group "The Oxford Levels of Evidence 2" (2016 version). A summary of the OCEBM grading scale may be found below (table 1). The level of evidence (LE) for a given recommendation is

Table 1 Summary of "The Oxford Levels of Evidence 2." (adapted from OCEBM Levels of Evidence Working Group)

Level 1	Level 2	Level 3	Level 4	Level 5
Systematic review or meta-analysis	Randomized trial or observational study with dramatic effect	Non-randomized, controlled cohort, or follow-up study	Case series, case–control, or historically controlled study	Mechanism-based reasoning

expressed in parentheses following the recommendation (eg, LE: 1). Recommendations without an associated LE were based on expert consensus.

DIAGNOSTIC TESTS AND BIOMARKERS FOR UROTHELIAL CANCER IMMUNOTHERAPY

Biomarkers to predict response to intravesical BCG therapy have remained elusive, with most candidate biomarkers reported from single institutional series lacking subsequent validation.[11 12] The exception is the UroVysion Bladder Cancer Kit (UroVysion Kit), a fluorescence in situ hybridization (FISH) test. A prospective, multicenter validation study in 150 patients confirmed findings from a previous 200 patient single-center study[13] that the UroVysion Kit can stratify the risk of recurrence in patients with high-risk NMIBC receiving BCG therapy.[14] However, the test's performance characteristics and its variance over time make it unsuitable for guiding individual patient management. Instead, the test could possibly be suitable for use in a clinical trial to help randomize patients with a positive UroVysion Kit result after induction BCG to receive additional BCG versus an experimental treatment.[15]

Predicting response to immune checkpoint blockade in patients with mUC is particularly important since only approximately 20% of patients demonstrate an objective response to therapy.[16] Biomarker discovery in this domain has focused mostly on PD-L1 expression by immunohistochemistry (IHC), tumor mutational burden (TMB) by next-generation sequencing (NGS), and RNA-based signatures.[17–19] Only PD-L1 IHC has demonstrated prognostic value,[20–22] although data are lacking to support the predictive power of PD-L1 expression for clinical benefit with immunotherapy for platinum-refractory disease. Additionally, methodological limitations, including poor concordance among approved assays, have led to some confusion about the definition of "PD-L1 positivity," especially given multiple different scoring systems that include protein expression on tumor and/or immune cells.[23] Four different PD-L1 IHC assays have been approved by the FDA: the companion diagnostics VENTANA PD-L1 (SP142) for atezolizumab and IHC 22C3 pharmDx for pembrolizumab, and the complementary diagnostics VENTANA PD-L1 (SP263) for durvalumab and IHC 28-8 pharmDx for nivolumab. At present, there is no role for PD-L1 testing for immunotherapy selection for platinum-refractory disease.

In some of the single-arm, early phase trials of ICIs in the platinum-refractory disease population, patients with PD-L1-positive tumors demonstrated higher response rates and longer survival than those with PD-L1-negative tumors, measured by immune cell (IC) PD-L1 expression or by tumor cell (TC) PD-L1 expression (SP142 for atezolizumab, SP263 for durvalumab, IHC 73-10 pharmDx for avelumab, IHC 28-8 for nivolumab).[19 24–27] However, two large phase III, randomized, controlled trials, IMvigor211[28] and KEYNOTE-045,[29] demonstrated that PD-L1 expression by IHC was not significantly associated with overall survival (OS), progression-free survival (PFS), overall response rate (ORR), or duration of response (DOR) in patients with platinum-refractory mUC treated with ICIs.

The phase II, single-arm KEYNOTE-052 trial of first-line pembrolizumab for cisplatin-ineligible patients with mUC showed an improved ORR in patients with high PD-L1 expression by IHC 22C3 assay (defined as combined positive score (CPS)≥10).[30] However, there was no significant correlation between response rates and PD-L1 expression in the IMvigor210 trial of atezolizumab using the SP142 assay (NCT02108652).[31] When both of these treatments received accelerated approval by the FDA for the first-line treatment of cisplatin-ineligible patients with mUC in 2017, the labels did not restrict treatment to patients based on PD-L1 testing results. However, in June 2018, based on the Data and Safety Monitoring Committee review of the IMvigor130[32] and KEYNOTE-361 trials,[33] which compared checkpoint blockade to either standard carboplatin-based or cisplatin-based chemotherapy, both the FDA and the European Medicines Agency (EMA) issued label changes indicating that cisplatin-ineligible patients should only receive first-line atezolizumab or pembrolizumab if their tumors were PD-L1-positive, as determined by approved companion diagnostic assays (at the time of writing, SP142 for atezolizumab and IHC 22C3 for pembrolizumab). The FDA stipulated that carboplatin-ineligible patients may be eligible for ICI therapy regardless of PD-L1 expression. The data that led to these label changes are outlined in further detail in the **Advanced/metastatic urothelial carcinoma** section.

Importantly, both IMvigor130 and KEYNOTE-361 pooled cisplatin-eligible and -ineligible patients in the primary analysis. Exploratory analysis of IMvigor130 showed evidence for benefit with single-agent atezolizumab for cisplatin-ineligible patients with PD-L1-expressing ICs in 5% of the tumor area by SP142.[34] However, CPS≥10 did not enrich for response to pembrolizumab in the choice-of-carboplatin population in exploratory analysis of KEYNOTE-361.[35] Based on the available data, in the first line, chemotherapy-naive setting, atezolizumab and pembrolizumab remain treatment options for patients with PD-L1-positive tumors deemed ineligible for cisplatin-based chemotherapy (in the US, based on the specific label) and for patients deemed ineligible for any platinum chemotherapy. It is important to note, however, that the evaluation of risks versus benefits for cisplatin-based chemotherapy is defined somewhat arbitrarily and includes considerations that involve patient comorbidities and the clinical disease state for which a patient is being treated.[36] Notwithstanding clinical trials, harmonized definitions are needed to develop therapies for unmet need populations.

Initial chemotherapy followed by maintenance PD-(L)1 blockade results in significantly improved outcomes, demonstrated in randomized trials described in the **Advanced/metastatic urothelial carcinoma** section, and

has largely supplanted the use of pembrolizumab or atezolizumab for the first-line treatment of mUC.[37 38] The OS benefit with maintenance avelumab was observed regardless of PD-L1 status, suggesting that PD-L1 testing does not currently offer clinical utility after chemotherapy in mUC.[38 39]

Evaluation of candidate predictive biomarkers for benefit with checkpoint blockade in adjuvant disease settings is pending the completion of prospective randomized trials.[40–43] The first of these data were reported in abstract format from the phase III open-label IMvigor010 trial, which tested adjuvant atezolizumab versus observation after radical cystectomy or (nephro)ureterectomy for muscle-invasive urothelial carcinoma.[44] No significant difference was observed in disease-free survival (DFS) in the entire study cohort or in patients with PD-L1-positive (IC2/3) tumors. Improvement in DFS in the CheckMate 274 study with adjuvant nivolumab versus placebo after radical cystectomy or (nephro)ureterectomy for muscle-invasive urothelial carcinoma in both the intent-to-treat (ITT) population and in the subset of patients with PD-L1-positive tumors (determined by the IHC 28-8 assay) has also been reported. Notably, although CheckMate 274 demonstrated clinical benefit with adjuvant nivolumab in the all-comers population, the DFS hazard ratio (HR) was smaller for the group of patients with PD-L1-positive tumors than for the ITT population (0.53 [95% CI 0.34 to 0.84] vs 0.70 [95% CI 0.54 to 0.89], respectively).[45]

Tumors with high microsatellite instability (MSI-H), which is a biomarker of mismatch repair deficiency (dMMR), may benefit from ICIs regardless of primary tumor origin.[46 47] Pembrolizumab received accelerated approval by the FDA for the treatment of patients with unresectable or metastatic, MSI-H (typically measured by PCR assay or NGS) or dMMR (typically measured by IHC or NGS) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options based on data from five pooled trials (KEYNOTE-016, KEYNOTE-164, KEYNOTE-012, KEYNOTE-028, and KEYNOTE-158).[3] dMMR is present in approximately 1% of bladder cancers[48 49] and 7%–14% of upper tract urothelial carcinomas, where it is more commonly seen in the context of Lynch syndrome, which occurs due to germline defects.[49–51] Since bladder cancer and upper tract urothelial carcinoma are also enriched for *FGFR3* alterations and erdafitinib (a pan-fibroblast growth factor receptor (FGFR) inhibitor) represents an alternative therapy for post-platinum urothelial carcinoma, it remains to be determined if both *FGFR3* testing and MSI-H/dMMR testing could be used in conjunction to optimally guide treatment selection and therapy sequence. The optimal sequence of ICI versus FGFR inhibition in patients with urothelial carcinoma with *FGFR3* alterations remains undefined but is being explored in prospective studies, including the THOR trial (NCT03390504).

Exploratory analyses of clinical trials in urothelial cancer have suggested that tumors with high TMB may respond better to immunotherapy than tumors with low TMB,[18 21 22 40] but data are still lacking on the use of TMB for clinical decision-making in urothelial cancer. However, the FDA has granted accelerated approval to pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with high TMB (≥10 mutations/megabase (mut/Mb)) that have progressed following prior treatment and who have no satisfactory alternative treatment options. This approval was based on the single-arm, phase II KEYNOTE-158 (NCT02628067) trial, which examined 1,050 patients with various solid tumors, and measured TMB using the FoundationOne CDx assay.[52] As with MSI-H/dMMR testing, TMB status could potentially aid in the selection of one treatment over another in platinum-refractory mUC. However, it is important to note that with the potential approval and use of PD-(L)1 inhibitors in earlier settings, this biomarker is likely to have less impact on treatment selection in the future.

Panel recommendations

- Currently, the evidence does not support routine use of biomarkers to guide BCG therapy in NMIBC. Cystoscopy (with biopsy/transurethral resection (TUR) of bladder tumor as needed), urine cytology, and periodic upper tract imaging should be used to detect recurrence.
- PD-L1 expression by IHC should be used to guide therapy in patients with mUC who are cisplatin-ineligible but eligible for carboplatin. Patients with PD-L1 negative tumors should receive carboplatin-based combination chemotherapy in this setting, while those with PD-L1 positive tumors can receive either immune checkpoint blockade or carboplatin-based chemotherapy (LE: 2). Clinical trial data otherwise does not currently support the use of PD-L1 expression to select patients with platinum-refractory disease for therapy.
- MSI-H/dMMR testing should be considered in patients with upper tract and bladder urothelial cancer, especially for patients of younger age and/or with relevant personal or family history to rule out Lynch syndrome, which has implications for genetic counseling (LE: 3). The presence of MSI should not change the use of ICIs in advanced urothelial cancer.

NON-MUSCLE-INVASIVE BLADDER CANCER

The SOC for intermediate- and high-risk NMIBC is BCG induction followed by maintenance. Depending on risk category and BCG availability, however, intravesical chemotherapy may be used for induction and the length of maintenance therapy varies. For BCG-unresponsive high-risk NMIBC, pembrolizumab is approved and may be offered to patients after a balanced discussion of risks and benefits. A treatment algorithm depicting management options for different NMIBC risk categories is shown in table 2.

Table 2 NMIBC immunotherapy treatment algorithm

NMIBC risk category	Management		
Low-risk	BCG not recommended		
Intermediate-risk (BCG available)	BCG†-induction and 1-year maintenance		
Intermediate-risk (BCG unavailable)	Intravesical chemotherapy	If recurrence occurs	BCG†
High-risk*	BCG† induction and 3 years maintenance	If BCG-unresponsive high-risk CIS NMIBC with or without papillary tumors	Pembrolizumab

Individual rows represent treatment decision options that can be followed from left to right horizontally in adjacent columns.
*Including NMIBC high-risk cases with CIS or papillary tumors.
†BCG should not be administered to patients with active infection or gross hematuria, but BCG may be administered to patients experiencing asymptomatic bacteriuria. Best supportive measures should be employed to ensure that patients receive a full, adequate course of BCG.

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; NMIBC, non-muscle-invasive bladder cancer.

First-line NMIBC

BCG is a live, attenuated strain of *Mycobacterium bovis* that is administered intravesically as a therapy for NMIBC. BCG has been an important option for the management of NMIBC for more than four decades. BCG treatment depends on the risk category of NMIBC. Low-risk disease is defined as single, primary, low-grade tumors (G1, Ta).[53] For patients with low-risk NMIBC, the SOC treatment is TUR followed by intravesical chemotherapy, without the use of BCG or other immunotherapies.[54] The International Bladder Cancer Group (IBCG) defines intermediate-risk bladder cancer as multiple and/or recurrent low-grade Ta tumors, with specific factors including number of tumors (> one), size of tumors (>3 cm), timing of recurrence (within 1 year), rate of recurrence (> one per year), and prior treatment.[55] High-risk NMIBC is defined as any T1, high-grade (G3) or CIS disease.[53]

In SWOG-8795 (also identified as INT-0094 or EST-1888), 447 patients with NMIBC were administered BCG or mitomycin C as adjuvant therapy following surgical resection. Among the study population, 377 patients had Ta/T1 NMIBC, and median follow-up was 2.5 years. In patients with Ta/T1 NMIBC, mitomycin C treatment led to a recurrence-free survival (RFS) rate of 43%, while those treated with BCG exhibited an RFS rate of 54% (HR 1.41; 95% CI 1.06 to 1.88; p=0.017). It was also noted that local and systemic adverse events (AEs) of grade 1 or 2 were more common in patients treated with BCG (p=0.003).[56]

During the Nijmegen study, 437 patients were treated with TICE-BCG, the *Rijksinstituut voor Volksgezondheid en Milieuhygiene* (RIVM) strain of BCG, or mitomycin C as adjuvant therapy following surgical resection of NMIBC (for papillary lesions, n=387) or biopsy (for CIS, n=50). Despite the fact that the BCG regimen used was suboptimal (ie, no maintenance therapy was given) and the cohort in the mitomycin C arm received monthly maintenance, at 2-year follow-up, the estimated rate of DFS for patients with papillary lesions was similar across groups, at 65% (95% CI 60% to 70%) for mitomycin C treatment, 54% (95% CI 49% to 59%) for TICE-BCG treatment, and 62% (95% CI 57% to 67%) for RIVM-BCG treatment. The differences between treatment arms were not statistically significant.[57]

An analysis of six pooled phase II clinical trials in which 119 patients with CIS received TICE-BCG as first-line therapy (6 weekly instillations for induction, 12 monthly instillations for maintenance) found an ORR of 75.6%, and complete response (CR) rate of 45.4% at a median follow-up of 47 months. The median PFS was estimated at ≥48 months.[58] On the basis of the clinical trials discussed above, in August 1998, the FDA approved the use of TICE-BCG for the first-line and adjuvant treatment of CIS, and for the adjuvant treatment of Ta and/or T1 papillary tumors of the bladder following TUR.[59] Several meta-analyses have subsequently concluded that BCG prevents, or at least delays, progression to invasive disease in high-risk or intermediate-risk disease. The largest of these meta-analyses analyzed 24 trials (n=4,863 patients) and showed a 27% reduction in the odds of progression (9.8% vs 13.8%; odds ratio (OR) 0.73; p=0.001) in patients treated with maintenance BCG compared with either TUR alone or TUR with chemotherapies other than mitomycin C.[60–62] The meta-analyses illustrated that BCG is only superior to mitomycin C in situations where BCG maintenance is provided.[60 62]

Historically, there have been efforts to administer BCG in conjunction with recombinant interferons. However, a meta-analysis demonstrated that BCG alone was associated with lower risk of recurrence in comparison to BCG with interferon-α-2a (relative risk (RR) 0.57; 95% CI 0.39 to 0.82) and to BCG with interferon-α-2b (RR 0.42; 95% CI 0.30 to 0.59).[63]

The standard BCG dosing regimen contains an induction and a maintenance phase, with induction consisting of BCG instillation once a week for 6 weeks and maintenance consisting of repeat instillations at set time intervals (at 3, 6, 12, 18, 24, 30, and 36 months postinduction). Maintenance instillations occur once a week for 3 weeks at each time interval. This dosing regimen (the '6+3

regimen') is supported by the results of EORTC-30962 (NCT00002990), a phase III clinical trial that randomized patients to receive full-dose or one-third-dose BCG with 1 year or 3 years of maintenance instillations. In this trial, no differences in toxicity were identified between one-third-dose and full-dose BCG. Further, for intermediate-risk patients (defined as lower than pT1 and lower than G3 in this study), no significant difference in the 5-year DFS rate was observed between 1 year and 3 years of maintenance. For high-risk patients (at least pT1 or G3 disease), 3 years of maintenance was superior to 1 year of maintenance by percentage of disease-free patients at 5 years for patients receiving full-dose BCG (HR 1.61; 95% CI 1.13 to 2.30; p=0.0087).[64]

A complicating factor is that BCG is currently subject to ongoing global shortages, which has impacted the ability of healthcare providers to provide BCG therapy to patients.[65 66] In light of this ongoing shortage, several professional and advocacy societies have modified their guidelines for management of NMIBC and advocated a risk-stratified approach toward BCG administration.[67–70] For this reason, current guidelines recommend a risk-stratified schedule of maintenance instillations: while patients with high-risk disease should receive a full 3-year course of maintenance, patients with intermediate-risk disease may receive shortened courses of 1 year of maintenance therapy.[68 71 72]

BCG treatment is associated with a number of potential AEs, which are cumulative over the course of BCG therapy, including cystitis, dysuria, frequency of urination, and, more rarely, infections or systemic side effects. Vigilance is important, since these symptoms overlap with other common AEs in patients receiving treatment for bladder cancer, including urinary tract infections, sensitivity related to urinary catheterization, or overactive bladder. AEs stemming from BCG therapy may be addressed through temporary withholding of BCG, conventional treatments (including systemic steroids,[73 74] non-steroidal anti-inflammatory drugs (NSAIDS),[74] antituberculosis antibiotics,[75] and quinolone antibiotics[76 77]), or permanent withdrawal of BCG for severe toxicity.[78] A proinflammatory response to BCG, leukocyturia, is associated with both an increase in self-reported AEs[79 80] and response to BCG.[81] It may be the case that the occurrence of systemic side effects is indicative of an immune response to BCG and thus could be used as a marker of response to therapy, although more data is required on this subject.

One well-studied method to reduce BCG-related toxicity is dose reduction. Clinical trials have demonstrated that reduced-dose BCG may be efficacious, with significantly less toxicity than full-dose BCG. Long-term follow-up of 499 patients in one prospective trial found that while patients with multifocal tumors derived more benefit from the standard dose than the reduced dose (p=0.0151), the cause-specific survival at 5 years did not differ between the two arms (p=0.76). Patients who received reduced doses of BCG were significantly less likely to experience grade ≥3 toxicity (p<0.001).[82] However, in the EORTC-30962 trial, there were no differences in toxicity between the one-third-dose and full-dose arms.[64] Reduced dosing frequency, however, leads to inferior outcomes. The NIMBUS study (NTR4011) evaluated reduced frequency instillation in a randomized trial of 824 BCG-naive patients. Patients who received reduced frequency instillation experienced an increased rate of recurrence, at 27% compared with 12% for patients receiving standard BCG treatment (HR 0.40; 95% CI 0.24 to 0.67).[83] While research is ongoing regarding possible alternative dosing regimens, the 6+3 regimen remains the gold standard based on current data.

BCG-unresponsive NMIBC

BCG-unresponsive NMIBC is a term that encompasses both BCG-refractory and BCG-relapsing (within 6 months of last BCG exposure) NMIBC, as defined by the IBCG.[84] The FDA has also issued guidance on BCG-unresponsive NMIBC with more specific criteria, defined as at least one of the following: (1) persistent or recurrent CIS (with or without recurrent Ta/T1 disease) within 12 months of completion of adequate BCG therapy, (2) recurrent high-grade Ta/T1 disease within 6 months of completion of adequate BCG therapy, or (3) T1 high-grade disease at the first evaluation following BCG induction. Adequate BCG therapy is defined as at least 5 of 6 doses of an initial induction course with at least 2 additional doses (either of maintenance therapy or of a second course of induction).[85] Multiple clinical trials have been conducted using this guidance to define this at-risk patient population, for which the only FDA-approved systemic immunotherapy is pembrolizumab.

Pembrolizumab is approved for the treatment of high-risk, BCG-unresponsive CIS at a dose of 200 mg every 3 weeks or 400 mg every 6 weeks (an alternative treatment schedule approved across multiple indications) for up to 24 months. The approval is based on favorable outcomes for patients in cohort A of the phase II KEYNOTE-057 trial (NCT02625961), who had high-risk, BCG-unresponsive CIS with or without papillary disease and were treated with pembrolizumab every 3 weeks for up to 24 months. Patients were required to undergo full resection of papillary disease prior to their first dose of pembrolizumab. The primary endpoint of CR was assessed at 3 months, and a key secondary endpoint was DOR.[86] At first analysis, 41 of 102 patients achieved CR at 3 months (40.2%; 95% CI 30.6% to 50.4%) and the median DOR of those patients who achieved CR was 12.7 months.[87] At the 12-month landmark analysis for DOR (which occurred approximately 15 months from the start of pembrolizumab therapy), the rate of patients with observed DOR ≥12 months was 46% (18 of 39 initial complete responders) and 19% of all treated patients.[42] None of the patients developed muscle-invasive or metastatic disease while on protocol treatment. Based on these data, in January 2020, the FDA approved the use of pembrolizumab for the treatment of BCG-unresponsive, high-risk CIS (with or

without papillary tumors).[3] Cohort B of KEYNOTE-057, which focuses on patients with fully resected papillary disease only (without concomitant CIS), was ongoing at the time of publication with a primary endpoint of RFS.[86]

Investigational strategies to overcome BCG-unresponsiveness include concomitant immunomodulation with recombinant cytokines. As an example, N-803 is a mutant IL-15-based immunostimulatory fusion protein complex (IL-15RαFc) that selectively promotes proliferation and activation of natural killer (NK) cells and $CD8^+$ T cells. In one cohort of a phase II/III trial that enrolled 80 patients with BCG-unresponsive CIS for intravesical administration of N-803 with BCG, the CR rate at any time was 72% (n=51/71) and the probability of maintaining CR for 12 months was 59%, with a median CR duration of 19.2 months (range 7.6–26.4) months.[88]

A recent phase III, open-label, multicenter US trial (NCT02773849) showed antitumor efficacy with intravesical nadofaragene firadenovec (rAD-IFNα2b), a replication-defective adenoviral gene transfer vector that delivers interferon-α-2b expression to the bladder epithelium. In the trial, patients with BCG-unresponsive CIS with or without Ta/T1 disease achieved a CR rate at 3 months of 53.4% (95% CI 43.3% to 63.3%) with 45.5% of these remaining free of high-grade recurrence at 12 months. A similar trend of durable response and RFS was observed in patients with papillary high-grade Ta/T1 BCG-unresponsive NMIBC, with 43.8% of patients remaining recurrence-free at 12 months. Progression to muscle invasion occurred in 5% of the CIS cohort and 6% of the high-grade Ta/T1 cohort. Among the patients with CIS, 29% underwent cystectomy by 12 months, as did 21% of those with high-grade Ta/T1 disease. The cystectomy-free survival at 24 months for the whole cohort was 64.5%. Of patients who underwent cystectomy, 3 of 32 (9.3%) in the CIS cohort were found to have pT2 or higher stage disease.[89] While nadofaragene firadnovec is not FDA-approved for the treatment of BCG-unresponsive NMIBC, at the time of writing, it has been granted priority review by the agency and previously received Fast Track and Breakthrough Therapy Designations.

Panel recommendations

- BCG is recommended for all eligible patients with high-risk NMIBC (including cases with CIS or papillary tumors) (LE: 1).
- BCG is also recommended for patients with intermediate-risk NMIBC. However, due to global shortages of BCG, and when BCG is unavailable, the panel recommends intravesical chemotherapy as the first-line therapy for intermediate-risk NMIBC (LE: 1).
- If patients experience recurrence of intermediate-risk NMIBC after a course of intravesical chemotherapy, the panel recommends BCG as second-line intravesical therapy (LE: 1).
- BCG is not recommended for the treatment of patients with low-risk NMIBC (LE: 1).
- BCG should not be administered to patients with active infection or gross hematuria, but BCG may be administered to patients experiencing asymptomatic bacteriuria.
- Best supportive measures should be employed to ensure that patients receive a full, adequate course of BCG.
- Pembrolizumab is approved for the treatment of high-risk BCG-unresponsive CIS with or without papillary tumors (LE: 2).

MUSCLE-INVASIVE BLADDER CANCER

While ICI therapy has not been approved for the treatment of MIBC, a number of ongoing clinical trials are examining the use of ICIs for this disease state. A selection of these trials are summarized in table 3.

Phase III trials of neoadjuvant therapy for MIBC

Neoadjuvant cisplatin-based chemotherapy is the current SOC in MIBC. While there are no immunotherapies currently approved as neoadjuvant therapy for localized MIBC, immunotherapy, alone and in combination with chemotherapy, has shown efficacy in MIBC in phase II trials.[40 41 90]

Based on the phase II data, there are several ongoing randomized phase III trials evaluating the role of perioperative immunotherapy in MIBC and results from these trials may establish the utility of this approach. For cisplatin-eligible MIBC, three randomized phase III trials are active at the time of manuscript preparation: KEYNOTE-866 (pembrolizumab, gemcitabine, and cisplatin vs gemcitabine and cisplatin), NIAGARA (durvalumab, gemcitabine, and cisplatin vs gemcitabine and cisplatin), and ENERGIZE (nivolumab, gemcitabine, and cisplatin with or without linrodostat vs gemcitabine and cisplatin). For cisplatin-ineligible MIBC, KEYNOTE-905 is evaluating pembrolizumab with or without EV followed by radical cystectomy versus radical cystectomy alone and the PIVOT IO 009 (NCT04209114) trial is evaluating nivolumab with or without bempegaldesleukin (NKTR-214) followed by radical cystectomy versus radical cystectomy alone. In these trials, immunotherapy agents are continued after radical cystectomy as well. Further, the KEYNOTE-B15 phase III trial, which will examine EV with pembrolizumab versus gemcitabine with cisplatin in patients with cisplatin-eligible MIBC, is anticipated to begin enrollment soon.

Phase III trials of adjuvant therapy for MIBC

Atezolizumab was tested in a randomized phase III trial as adjuvant therapy after radical surgery in patients with muscle-invasive (including node-positive) urothelial carcinoma. This trial, IMvigor010, enrolled patients with ≥ypT2 disease and/or nodal involvement at radical surgery after neoadjuvant chemotherapy or ≥ypT3 disease and/or nodal involvement if they did not receive prior neoadjuvant chemotherapy. Patients were randomized after radical surgery to receive either atezolizumab for

Table 3 Ongoing phase III clinical trials of immunotherapy for MIBC

Trial	Immunotherapy and control arms	Agent description	Primary outcome(s) for assessment
Neoadjuvant/adjuvant, cisplatin-eligible			
KEYNOTE-866 (NCT03924856)	Pembrolizumab+gemcitabine+cisplatin	ICI, chemotherapy	pCR rate, EFS
	Placebo+gemcitabine+cisplatin	Chemotherapy	
KEYNOTE-B15/EV-304 (NCT04700124)	Pembrolizumab+EV	ICI, ADC	pCR rate, EFS
	Gemcitabine+cisplatin	Chemotherapy	
NIAGARA (NCT03732677)	Cisplatin+gemcitabine+durvalumab	ICI, chemotherapy	pCR rate at time of surgery, EFS
	Cisplatin+gemcitabine	Chemotherapy	
ENERGIZE CA017078 (NCT03661320)	Gemcitabine+cisplatin	Chemotherapy	pCR rate, EFS
	Placebo+nivolumab+cisplatin+gemcitabine	ICI, chemotherapy	
	Linrodostat+nivolumab+cisplatin+gemcitabine	IDO1 inhibitor, ICI, chemotherapy	
Neoadjuvant/adjuvant, cisplatin-ineligible			
KEYNOTE-905 (NCT03924895)	Pembrolizumab	ICI	pCR rate, EFS
	Surgery alone	None	
	Pembrolizumab+EV	ICI, ADC	
PIVOT IO 009 (NCT04209114)	Nivolumab+bempegaldesleukin	ICI, CD122-biased agonist	pCR rate, EFS
	Nivolumab	ICI	
	Surgery alone	None	
Adjuvant			
IMvigor010 (NCT02450331)	Atezolizumab	ICI	DFS
	Observation	None	
CheckMate 274 (NCT02632409)	Nivolumab	ICI	DFS
	Placebo	None	
AMBASSADOR (NCT03244384)	Pembrolizumab	ICI	OS, DFS
	Observation	None	

ADC, antibody-drug conjugate; DFS, disease-free survival; EFS, event-free survival; EV, enfortumab vedotin; ICI, immune checkpoint inhibitor; MIBC, muscle-invasive bladder cancer; OS, overall survival; pCR, pathologic complete response.

1 year or observation. There were no differences in DFS between the arms, which was the primary endpoint. The trial continues to be followed for OS.[44]

Nivolumab has also been evaluated in the adjuvant setting in the randomized placebo-controlled phase III CheckMate 274 trial, which met its co-primary DFS endpoints in the ITT population and the group with tumors with elevated PD-L1 expression in patients who had undergone radical surgery for muscle-invasive (including node-positive) urothelial carcinoma. Initial results from 709 patients (353 randomized to nivolumab including 140 with tumors PD-L1 ≥1% and 356 randomized to placebo including 142 with tumors PD-L1 ≥1%) demonstrated a statistically significant and clinically meaningful improvement in median DFS with adjuvant nivolumab after radical surgery compared with placebo, at 21.0 months (range 17.1–33.4) vs 10.9 months (range 8.3–13.9) in the ITT population (HR 0.70; 98.31% CI 0.54 to 0.89; p=0.0006) and median DFS not yet reached (range 22.0 to not estimable) vs 10.8 months (range 5.7 to 21.2) in the tumor PD-L1 ≥1% group (HR 0.53; 98.87% CI 0.34 to 0.84; p=0.0004). Significant improvement was also seen for the secondary endpoint of non-urothelial tract RFS for adjuvant nivolumab in both the ITT group (HR 0.72; 95% CI 0.58 to 0.89) and in patients with tumors with PD-L ≥1% (HR 0.54; 95% CI 0.38 to 0.77).[45] The FDA granted priority review status to the Biologics License Application for nivolumab for adjuvant treatment of patients with surgically resected, high-risk MIBC in April 2021.

Pembrolizumab is also being tested in a randomized phase III trial as adjuvant therapy after radical surgery in patients with muscle-invasive (node-positive) urothelial carcinoma. This trial, AMBASSADOR, is enrolling patients with ≥ypT2 disease and/or nodal involvement at radical surgery after neoadjuvant chemotherapy, or ≥ypT3 disease after no neoadjuvant chemotherapy and

Table 4 Phase II clinical trials of immunotherapy for MIBC

Trial	Interventions	Agent description	Rate of downstaging at time of surgery	Rate of ypT0 at time of surgery
ABACUS (NCT02662309)[41]	Atezolizumab	ICI	NR	31%
PURE-01 (NCT02736266)[151]	Pembrolizumab	ICI	54% (to non-invasive disease)	42%
NABUCCO (NCT03387761)[152]	Nivolumab+ipilimumab	ICI	58% (to non-invasive disease)	45%
NCT02812420[153]	Durvalumab+tremelimumab	ICI	58% (to ypT1 or less)	38%
BLASST-1 (NCT03294304)[90]	Nivolumab+gemcitabine+cisplatin	ICI+chemotherapy	66%	34%
HCRN GU14-188 (NCT02365766)[154 155]	Pembrolizumab+gemcitabine+cisplatin (eligible cohort) Pembrolizumab+gemcitabine (cisplatin-ineligible cohort)	ICI+chemotherapy	Cisplatin-eligible cohort I: 53% (to ypT0/Tis) Cisplatin-ineligible cohort II: 52% (to ypT0/Tis)	Cisplatin-eligible cohort I: 44% Cisplatin-ineligible cohort II: 45%
DUTRENEO (NCT03472274)[91]	Durvalumab+tremelimumab	ICI	NR	35%

ICI, immune checkpoint inhibitor; MIBC, muscle-invasive bladder cancer; NR, not reported.

will randomize patients to 1 year of pembrolizumab or observation. Accrual is still ongoing.

Early phase trials of ICI neoadjuvant therapy for MIBC

Immunotherapy in the neoadjuvant setting has been tested in phase I and II trials, some of which have completed accrual and have reported results (see table 4). Approaches include ICI as monotherapy before surgery as well as ICI in combination with another ICI or platinum-based chemotherapy. These trials have reported pathologic complete responses (pCRs), also referred to as ypT0, in a subset of patients at the time of surgical intervention, a finding that has correlated with better long-term survival in prior studies of neoadjuvant chemotherapy. Neoadjuvant ICI therapy has been examined in the cisplatin-ineligible (NABUCCO, HCRN GU14-188 Cohort II, NCT02812420) and cisplatin-eligible (BLASST-1, HCRN GU14-188 Cohort I, DUTRENEO) patient populations.

PD-L1 positivity of the tumor by CPS (IHC 22C3 assay) correlated with pembrolizumab responses in the PURE-01 study and ipilimumab and nivolumab in the NABUCCO study. Additionally, in the DUTRENEO trial, for patients in the PD-L1-high group (as measured by the E1L3N XP antibody) the ypT0 rate was 57.1%, while it was 14.3% for patients in the PD-L1-low group.[91] However, all other monotherapy and combination studies in table 4 did not identify a significant response correlation with tumor or IC PD-L1 status.

Overall, ICI monotherapy or combination therapy has been reported to have manageable toxicity and has not been associated with delay of cystectomy. These promising data support ongoing phase III trials, but are not yet practice-changing. Comparisons across these small-moderate sized single-arm phase II trials, however, should be approached cautiously. Significant differences in initial staging techniques, type and length of treatment, biomarker assays, and eligible patient populations exist across these studies. Additionally, the potential correlation between pathologic assessment after neoadjuvant immunotherapy regimens and OS (and/or RFS) remains unclear.

Immunotherapy with chemoradiation as bladder-sparing therapy

Radiation and chemotherapy cause immunogenic cell death,[92 93] which may synergize with ICI therapy to potentiate antitumor responses. Two randomized phase III trials are investigating concurrent anti-PD-(L)1 therapy in combination with external beam radiation and radiosensitizing chemotherapy. The randomized, phase III trial NCT03775265 (SWOG/NRG 1806) is testing atezolizumab and the randomized, phase III KEYNOTE-992 (NCT04241185) is testing pembrolizumab in this setting. In addition, the phase II, randomized NCT03768570 is examining durvalumab following trimodal therapy (surgery, chemotherapy, and radiotherapy).

Panel recommendation

- The full results of CheckMate 274 are eagerly awaited to guide the potential use of immunotherapy in the adjuvant setting. Active investigation is ongoing into various neoadjuvant and adjuvant strategies, either as single agents or in combination with chemotherapy, radiotherapy, or novel agents.

ADVANCED/METASTATIC UROTHELIAL CARCINOMA

The treatment of mUC typically involves platinum-based chemotherapy as the first-line, SOC modality.[94] Chemotherapy may also play a role in relapsed/refractory (R/R) disease settings. The introduction of immunotherapy, however, has expanded the available options and a number of ICIs have now been approved by the FDA for the treatment of mUC. A treatment algorithm

Table 5 mUC treatment algorithm

Patient population		Management		
Cisplatin-eligible		Platinum-based chemotherapy	If no disease progression	Avelumab maintenance
			If disease progression	Pembrolizumab Avelumab Nivolumab*
Cisplatin-ineligible	PD-L1-positive tumors†	Atezolizumab* Pembrolizumab*		
	PD-L1-negative tumors†	Carboplatin-based chemotherapy		
Cisplatin- and carboplatin-ineligible		Atezolizumab‡* Pembrolizumab‡*		

Individual rows represent treatment decision options that can be followed from left to right horizontally in adjacent columns.
*Accelerated approvals contingent on confirmatory trials at the time of guideline publication.
†As determined by the appropriate FDA-approved companion diagnostic (ie, PD-L1 staining immune cells (IC) ≥5% of the tumor area by SP142 assay for atezolizumab and combined positive score (CPS) ≥10 by IHC 22C3 assay for pembrolizumab).
‡Recommendation based on US-only indication.
mUC, advanced/metastatic urothelial cancer; PD-L1, programmed death-ligand 1.

summarizing expert panel recommendations for immunotherapy management of mUC in various patient populations is provided in table 5.

Data from large phase II and III clinical trials evaluating ICIs for mUC are summarized in table 6 and further described in the narrative text below. Another agent, EV, is an ADC that is FDA-approved for the treatment of mUC that has progressed following both platinum-based chemotherapy and ICI treatment.[95]

Immunotherapies for first-line treatment of mUC

The phase II, single-group assignment clinical trial IMvigor210 examined the efficacy of atezolizumab for the treatment of mUC. In cohort I of the trial (NCT02951767), 119 cisplatin-based chemotherapy-ineligible patients received first-line atezolizumab.[96] The ORR was 24% (95% CI 16% to 32%), and the median DOR was not reached at 2-year follow-up.[31 97] On the basis of ORR and DOR data from both cohorts of the IMvigor210 trial, the FDA approved atezolizumab for the first-line treatment of PD-L1-positive mUC in patients who are ineligible for cisplatin-containing chemotherapy or those who are not eligible for any platinum-based chemotherapy, regardless of PD-L1 status, in April 2017.[5]

In the KEYNOTE-052 (NCT02335424) phase II trial, 374 patients with mUC who were ineligible for cisplatin-based chemotherapy received pembrolizumab as first-line treatment, irrespective of PD-L1 status.[98] At the most recent updated analysis, the ORR was 29% and the median DOR was 30.1 months.[30] Subgroup analysis of the PD-L1-negative (CPS<10) and PD-L1-positive (CPS≥10) groups showed higher DOR and OS in the PD-L1-positive group. A follow-up report of long-term outcomes found that 2-year OS was 31.2%.[30] Based on OS and ORR data from KEYNOTE-045 (described in the **Immunotherapies for R/R mUC** section) and ORR and DOR data from KEYNOTE-052, in May 2017, the FDA approved pembrolizumab for use as a first-line treatment of mUC (in patients who are ineligible for cisplatin-based chemotherapy and PD-L1-positive, or any patient ineligible for platinum-based chemotherapy) and for the treatment of R/R mUC (in patients who have experienced disease progression following platinum-based chemotherapy) regardless of PD-L1 status.[3]

The activity of PD-(L)1 inhibitors for the first-line treatment of cisplatin-ineligible patients with mUC raised the hypothesis of whether PD-(L)1 blockade as single-agent therapy should be extended to cisplatin-eligible patients as well and whether regimens combining platinum-based chemotherapy and PD-(L)1 blockade might further improve outcomes. IMvigor130 was a placebo-controlled phase III trial randomized 1:1:1 to test whether atezolizumab monotherapy or atezolizumab with gemcitabine and platinum (cisplatin or carboplatin) improved survival compared with placebo plus gemcitabine and platinum. The study enrolled 1,213 patients and demonstrated longer PFS for atezolizumab plus chemotherapy compared with chemotherapy alone (8.2 months vs 6.3 months; stratified HR 0.82; 95% CI 0.70 to 0.96; one-sided p=0.007). The interim analysis for OS showed a trend toward longer OS with the atezolizumab plus chemotherapy combination, which was not statistically significant (HR 0.83; 95% CI 0.69 to 1.00; one-sided p=0.027). The median OS for atezolizumab monotherapy was 15.7 months compared with 13.1 months for chemotherapy. In patients with high levels of PD-L1 expression in tumor-infiltrating ICs (IC2/3 by SP142 assay), atezolizumab monotherapy median OS was not estimable at interim analysis (95% CI 17.7 to not estimable) vs 17.8 months (95% CI 10.0 to not estimable) in the chemotherapy-alone group (stratified HR 0.68; 95% CI 0.43 to 1.08). As atezolizumab versus chemotherapy could not be formally compared at this interim analysis due to the hierarchical

Table 6 Large phase II and III clinical trials investigating ICIs for mUC

			Results for immunotherapy treatment			
Trial	**Design**	**Interventions (n patients)**	**ORR**	**Median DOR**	**OS**	**Median PFS**
IMvigor210, cohort I (NCT02951767)[31 97]	Phase II, single-arm, open-label	Atezolizumab (first-line) (n=119)	24% (95% CI 16% to 32%)	Median not reached (2-year follow-up)	2-year OS 41% (95% CI 32% to 50%)	2.7 months (95% CI 2.1 to 4.2)
IMvigor210, cohort II (NCT02108652)[17 97]	Phase II, single-arm, open-label	Atezolizumab (R/R) (n=310)	16% (95% CI 13% to 21%)	27.7 months (95% CI 2.1 to 33.4)	2-year OS 23% (95% CI 19% to 28%)	2.1 months (95% CI 2.1 to 2.1)
IMvigor211 (NCT02302807)[28]	Phase III, randomized, open-label	Atezolizumab vs chemotherapy (R/R) (n=931)	PD-L1 IC2/3: 23% ITT: 13.4%	PD-L1 IC2/3: 15.9 months (95% CI 10.4 to NE) ITT: 12.7 months (95% CI 13.0 to 21.7)	Median OS PD-L1 IC2/3: 11.1 months (95% CI 8.6 to 15.5) ITT: 8.6 months (95% CI 7.8 to 9.6) Stratified HR 0.87 (95% CI 0.63 to 1.21; p=0.41)	PD-L1 IC2/3: 2.4 months (95% CI 2.1 to 4.2) ITT: 2.1 months (95% CI 2.1 to 2.2)
IMvigor130 (NCT02807636)[32]	Phase III, randomized, double-blind	Atezolizumab vs chemotherapy (first-line) (n=451)	23% (95% CI 19% to 28%)	NE (95% CI 15.9 months to NE)	Median OS 15.7 months (95% CI 13.1 to 17.8) Stratified HR 0.83, (95% CI 0.69 to 1.00; one-sided p=0.027)	NR
IMvigor130 (NCT02807636)[32]	Phase III, randomized, double-blind	Atezolizumab+gemcitabine/platinum (first-line) vs chemotherapy (n=362)	47% (95% CI 43% to 52%)	8.5 months (95% CI 7.2 to 10.4)	Median OS 16.0 months (95% CI 13.9 to 18.9) HR (1.02 95% CI 0.83 to 1.24)	8.2 months (95% CI 6.5 to 8.3) Stratified HR 0.82 (95% CI 0.70 to 0.96; one-sided p=0.007)
JAVELIN Bladder100 (NCT02603432)[37]	Phase III, randomized, open-label	Avelumab maintenance vs best supportive care (n=700)	9.7% (95% CI 6.8% to 13.3%)	NR	Median OS 21.4 months (95% CI 18.9 to 26.1) HR 0.69 (95% CI 0.56 to 0.86; p=0.001)	3.7 months (95% CI 3.5 to 5.5) HR 0.62 (95% CI 0.52 to 0.75)
DANUBE (NCT02516241)[100]	Phase III, randomized, open-label	Durvalumab+tremelimumab vs chemotherapy (first-line) (n=1,126)	36%	11.1 months (95% CI 7.9 to 18.5)	Median OS 15.1 months (95% CI 13.1 to 18.0) Durvalumab monotherapy HR 0.89 (95% CI 0.71 to 1.11; p=0.30) Durvalumab+tremilumab HR 0.85 (95% CI 0.72 to 1.02; p=0.075)	NR
CheckMate 275 (NCT02387996)[113]	Phase II, single-arm, open-label	Nivolumab (R/R) (n=386)	20.7% (95% CI 16.1% to 26.1%)	20.3 months (95% CI 11.5 to 31.3)	3-year OS 22%; Median OS 8.6 months (95% CI 6.1 to 11.3)	1.9 months (95% CI 1.9 to 2.3)
KEYNOTE-052 (NCT02335424)[156 157]	Phase II, single-arm, open-label	Pembrolizumab (first-line) (n=374)	24% (95% CI 20% to 29%)	Median not reached (1-year follow-up)	1-year OS 47.5%	2 months (95% CI 2 to 3)
KEYNOTE-045 (NCT02256436)[116]	Phase III, randomized, open-label	Pembrolizumab (R/R) (n=542)	21.1% (95% CI 16.4% to 26.5%)	Median not reached (2-year follow-up)	2-year OS 26.9% HR 0.70 (95% CI 0.57 to 0.85; p<0.001)	2.1 months (95% CI 2.0 to 2.2) HR 0.96 (p=0.32)
KEYNOTE-361 (NCT02853305)[99]	Phase III, randomized, open-label	Pembrolizumab+gemcitabine/platinum vs chemotherapy (first-line) (n=542)	54.7%	8.5 months	1-year OS 61.8% HR 0.86	8.3 months (95% CI 7.5 to 8.5) HR 0.78 (p=0.0033)
HCRN GU14-182 (NCT02500121)[106]	Phase II, randomized, double-blind	Pembrolizumab maintenance vs placebo (n=108)	23%	NR	NR	5.4 months (95% CI 3.1 to 7.3)

CI, confidence interval; DOR, duration of response; HR, hazard ratio; ICI, immune checkpoint inhibitor; ITT, intent-to-treat; mUC, metastatic urothelial cancer; NE, not estimable; NR, not reported; ORR, overall response rate; OS, overall survival; PD-L1, programmed death-ligand 1; PD-L1 IC2/3, PD-L1 expression in ≥5% of tumor-infiltrating immune cells; PFS, progression-free survival; R/R, relapsed/refractory.

statistical analysis plan, these arms will be further evaluated at future analyses. In patients with tumors harboring low PD-L1 expression levels (IC0/1), the median OS was 13.5 months (95% CI 11.1 to 16.4) in the atezolizumab monotherapy group vs 12.9 months (95% CI 11.3 to 15.0) for patients treated with chemotherapy (unstratified HR 1.07; 95% CI 0.86 to 1.33).[32] As noted in the **Diagnostic tests and biomarkers for urothelial cancer immunotherapy** section, however, an unplanned analysis prompted by the Data and Safety Monitoring Committee revealed increased early deaths in patients with low PD-L1 expressing tumors treated with atezolizumab compared with platinum-based chemotherapy—a result that became apparent even before the trial completed accrual and results were publically available.[22 32] This led the FDA and EMA to restrict the label for atezolizumab monotherapy for cisplatin-ineligible patients to only those having tumors with high levels of PD-L1 expression (IC2/3 by Ventana SP142 assay) or, in the US only, patients considered platinum-ineligible (unable to receive even carboplatin) regardless of PD-L1 expression status.

The KEYNOTE-361 trial (NCT02853305) was a phase III randomized trial that assigned 1,010 patients to receive pembrolizumab monotherapy, pembrolizumab with chemotherapy, or SOC chemotherapy. The final results of KEYNOTE-361 revealed no significant improvement in PFS or OS with pembrolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy or with single-agent pembrolizumab versus platinum-based chemotherapy.[33 99] In parallel with events unfolding in the IMvigor130 trial, as described above and in the **Diagnostic tests and biomarkers for urothelial cancer immunotherapy** section, the FDA restricted the prescribing label for pembrolizumab when used in the cisplatin-ineligible frontline setting to patients with PD-L1 expression ≥10 by CPS or to those who were considered platinum-ineligible (unable to receive carboplatin) regardless of PD-L1 expression. Importantly, neither IMvigor130 nor KEYNOTE-361 were designed to specifically compare single-agent PD-(L)1 blockade versus carboplatin-based chemotherapy in patients ineligible for cisplatin, the current labeled indication for front-line treatment of mUC.

DANUBE (NCT02516241) was a phase III trial that randomized 1,126 patients to receive first-line durvalumab with tremelimumab, durvalumab monotherapy, or SOC chemotherapy. DANUBE did not reach its co-primary endpoints of an improvement in OS for durvalumab versus chemotherapy in patients with PD-L1-high tumors or with tremelimumab plus duravlumab versus chemotherapy in the ITT population.[100]

Maintenance approaches in MUC

First-line platinum-based chemotherapy results in disease control in mUC in 65%–75% of patients, but PFS and OS are relatively short, with median PFS less than 9 months.[94 101] While significant progress has been made with five anti-PD-(L)1 inhibitors being approved by the FDA for mUC patients who progress after platinum-based chemotherapy, response rates with second-line anti-PD-(L)1 inhibitors are modest and only a minority of patients obtain durable clinical benefit. Moreover, there is a substantial patient drop off from first-line to second-line therapy in mUC, with only approximately 40% of patients with mUC receiving second-line therapy as seen from patterns of care and outcomes in real-world settings.[102 103] The current 'watch-and-wait' approach for patients with mUC following response or stable disease after first-line platinum-based chemotherapy and prior to initiation of second-line treatment is suboptimal as almost all patients progress within 9 months of active therapy.[94] Maintenance therapy with anti-PD-(L)1 inhibitors after cessation of first-line platinum-based chemotherapy is an attractive treatment strategy in mUC to improve patient outcomes. Historically, maintenance therapy approaches with targeted therapies have not been successful in mUC.[104 105] However, the antitumor activity and relatively favorable safety profile of PD-(L)1 antagonists in mUC make them a potentially attractive option for maintenance therapy.

Two recent trials have evaluated the efficacy of single-agent checkpoint inhibition after completion of first-line systemic platinum-based chemotherapy (HCRN GU14-182 and JAVELIN Bladder 100).[37 106] In the HCRN GU14-182 trial, a phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy, 108 patients with mUC achieving at least stable disease after up to 8 cycles of first-line platinum-based chemotherapy were enrolled and treated with pembrolizumab or placebo for up to 24 months. The primary endpoint was PFS. Significantly longer PFS was achieved with maintenance pembrolizumab (5.4 months; 95% CI 3.1 to 7.3) compared with placebo (3.0 months; 95% CI 2.7 to 5.5). Median OS was 22 months (95% CI 12.9 to not reached) with pembrolizumab and 18.7 months (95% CI 11.4 to not reached) with placebo, a secondary endpoint for which the trial was not adequately powered and did not reach statistical significance.[106]

The JAVELIN Bladder 100 trial was a phase III, multicenter, multinational, randomized, open-label, parallel-arm study investigating first-line maintenance treatment with avelumab plus best supportive care (BSC) versus BSC alone in patients with mUC who did not have disease progression after first-line platinum-containing chemotherapy. A total of 700 patients were randomly assigned to receive either avelumab plus BSC or BSC alone, and the primary endpoint was OS. Median OS with avelumab and BSC was significantly longer compared with BSC alone (21.4 vs 14.3 months, respectively; HR 0.69; 95% CI 0.56 to 0.86; p=0.001). Median PFS was 3.7 months with avelumab and BSC (95% CI 3.5 to 5.5) compared with 2 months with BSC alone (95% CI 1.9 to 2.7; HR 0.56; 95% CI 0.40 to 0.79; p<0.001).[38] Based on the results of this trial, the FDA approved avelumab as maintenance therapy for patients with locally advanced or mUC that has not progressed with first-line platinum-containing chemotherapy. It is

important to note that the upfront chemotherapy and maintenance avelumab was approved based a randomized phase III trial, representing a higher LE than the approvals for pembrolizumab and atezolizumab, which were based on phase II data.

Immunotherapies for R/R mUC

Cohort II of the IMvigor210 trial (NCT02108652) enrolled 310 patients with mUC who had experienced disease progression following platinum-based chemotherapy and explored the activity of atezolizumab.[107] The ORR was 16% (95% CI 13% to 21%), and the median DOR was 27.7 months (95% CI 2.1 to 33.4).[17 97] On the basis of ORR and DOR data from both cohorts of the IMvigor210 trial, the FDA granted accelerated approval to atezolizumab for the treatment of R/R mUC in May 2016.[5]

A randomized open-label phase III trial, IMvigor211, randomized patients with disease progression following platinum-based chemotherapy to either atezolizumab or investigator's choice of chemotherapy (single-agent paclitaxel, docetaxel, or vinflunine (European Union only)). The primary endpoint of this trial was OS in patients with PD-L1-high expression on tumor infiltrating ICs (IC 2/3 by SP142 assay). Of the 931 patients randomized, 234 were PD-L1-high. In that group, there was no significant difference in OS (stratified HR 0.87; 95% CI 0.63 to 1.21; p=0.41). Based on the study design, no additional formal analyses were performed, though an OS benefit was observed with atezolizumab versus chemotherapy (regardless of PD-L1 status) in the ITT population in an exploratory analysis. Atezolizumab therapy was associated with fewer grade 3 or 4 AEs and numerically longer DOR than chemotherapy. These results were comparable to those of IMvigor210 cohort II.[28] Because IMvigor211 failed to meet its primary OS endpoint, however, the indication for atezolizumab in patients with mUC who have previously received platinum-based chemotherapy was voluntarily withdrawn in March 2021.

Avelumab received accelerated approval from the FDA in May 2017, for the treatment of R/R mUC based on the JAVELIN Solid Tumor (NCT01772004) phase I expansion trial, which enrolled 242 patients.[4 108] The FDA based its decision on an ORR of 17% (95% CI 11% to 24%) and DOR data (median not reached at 6 months).[26] In an updated safety and efficacy analysis with more than 2 years of follow-up, ORR was 16.5% (95% CI 12.1% to 21.8%), median DOR was 20.5 months (95% CI 9.7 to not reached), and the 24-month OS was 20.1% (95% CI 15.2% to 25.4%) with avelumab.[109]

Study 1108 (NCT01693562), a phase II trial, examined the efficacy of durvalumab in 191 patients with R/R mUC (182 of which had previously received platinum-based chemotherapy).[25 110] The ORR was 20.4% (95% CI 13.1% to 29.5%) and DOR (median not reached at 1 year) data from this trial formed the basis of FDA-accelerated approval for the use of durvalumab to treat R/R mUC (that had progressed following platinum-based chemotherapy) in May 2017.[111 112] In November 2020, however, the FDA indication for durvalumab for use in previously treated patients with locally advanced or metastatic bladder cancer was voluntarily withdrawn because the phase III DANUBE trial did not meet its primary end points.

Nivolumab was granted accelerated approved by the FDA for the treatment of R/R mUC for patients with disease progression following platinum-based chemotherapy in February 2017.[6] This approval was based on ORR (20.7%; 95% CI 16.1% to 26.1%) and DOR (median 20.3 months; 95% CI 11.5 to 31.3) data from the phase II CheckMate 275 (NCT02387996) trial, which evaluated nivolumab monotherapy in 386 patients with R/R mUC (270 of these patients had experienced disease progression after platinum-based chemotherapy).[113 114] Extended follow-up of this trial confirmed the safety and efficacy data previously reported.[21]

The KEYNOTE-045 (NCT02256436) phase III trial compared pembrolizumab to chemotherapy for 542 patients with mUC who had experienced disease progression after prior platinum-based chemotherapy.[115] At updated long-term follow-up (median 28 months), patients treated with pembrolizumab exhibited a statistically significant advantage compared with chemotherapy in 2-year OS rates (26.9% vs 14.3%; HR 0.70; 95% CI 0.5 to 0.85; p=0.00015) and ORR (21.1% vs 11.0%; p=0.002). However, there was no significant difference in PFS at the 1-year or 2-year landmarks.[3 116] Median DOR was not reached with pembrolizumab at this updated analysis, but was 4.4 months for chemotherapy.

Panel recommendations

- The first-line SOC for mUC is platinum-based chemotherapy. Atezolizumab or pembrolizumab can also be considered as first-line therapy for cisplatin-ineligible patients harboring PD-L1-positive tumors based on a companion assay, or for patients who cannot receive carboplatin (the latter in US only) (LE: 2). Combination ICI and chemotherapy treatment are not currently recommended for this setting.
- In patients with with locally advanced or mUC that has not progressed with first-line platinum-containing chemotherapy, avelumab maintenance therapy improves OS (LE: 2).
- Pembrolizumab is recommended for the treatment of patients with platinum-refractory mUC based on a significant OS benefit in a randomized phase III trial (LE: 2). Avelumab and nivolumab also have approvals in this setting.

IMMUNOTHERAPIES IN DEVELOPMENT FOR UROTHELIAL CANCER

Numerous immunotherapeutic options are currently in advanced stages of development, either alone or

in combination with other agents. Table 7 summarizes information on select novel immunotherapies and immunotherapeutic combinations currently in late phase clinical trials. This table is not intended to be a comprehensive exhaustive list of all trials across therapy settings.

EV is an ADC currently approved as monotherapy for patients with mUC whose cancer has progressed after previous platinum chemotherapy and ICI therapy. EV delivers a payload of monomethyl auristatin E, a tubulin-disrupting agent, to mUC, which overexpresses the nectin-4 surface receptor target of the monoclonal antibody. Although not considered a classical immunotherapy, induction of the innate immune system is emerging as an important mechanism contributing to the antitumor action for EV. Nectin-4 has been found to be a negative regulator of NK cell activity through binding of the inhibitory receptor T cell immunoreceptor with Ig and ITIM domains (TIGIT) and blocking the nectin-4–TIGIT interaction, which enhances NK cell antitumor activity in vitro and in vivo.[117] Additionally, EV induces an endoplasmic reticulum stress response, which triggers an immunogenic cell death pathway.[118] Several trials are currently studying the potential for enhanced antitumor activity when ADCs are combined with agents that target adaptive antitumor immunity, such as ICIs.[93 119–122] EV103 (cohort A) is a biomarker-agnostic phase Ib trial of first-line EV and pembrolizumab in patients who are cisplatin-ineligible with mUC. Among 43 patients, 93% had a tumor reduction and the ORR was 73%, with a 15% CR rate and a median time to response of 2 months.[122] Responses in this trial were durable; per interim data at median follow-up of 11 months, the median DOR has not been reached.[122] The phase III randomized trial, EV302 (NCT04223856), which randomizes patients to one of three arms of EV and pembrolizumab; EV, pembrolizumab, and platinum-based chemotherapy; or SOC gemcitabine and platinum-based chemotherapy, is currently enrolling.

Panel recommendation

- Participation in clinical trials should be discussed with all patients at any stage of bladder cancer.

RECOGNITION AND MANAGEMENT OF irAEs

ICIs are associated with a spectrum of irAEs, which may occur in a variety of organ systems, most commonly in the gastrointestinal tract or the skin.[123] While irAEs can generally be managed by temporarily withdrawing ICI treatment and/or with immunosuppressives, such as corticosteroids, severe irAEs may carry significant risks of morbidity or mortality. Given the potential risks associated with ICI treatment, several groups have developed suggested guidelines for the work up and management of suspected irAEs, including the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), and SITC.[124–128] While the incidence and severity of irAEs may vary depending on the specific ICI used[129] or on the tumor type being treated, the treatment of urothelial cancer with ICIs has not been shown to carry any risks above baseline for the incidence or severity of irAEs.[130]

Panel recommendation

- SITC's guidelines for the management of ICI-related AEs should be consulted for the treatment of irAEs in patients with bladder cancer.

PATIENT SUPPORT AND QOL

While immunotherapy for urothelial cancer has well-described benefits for patient outcomes, therapeutic selection and administration also have potential impacts on patient QOL, as well as a unique AE profile. It is important to assess QOL in patients receiving immunotherapy as well as to provide adequate education and support for promptly recognizing and managing any AEs that may occur during or as a result of treatment.

Tools to assess health-related QOL (HRQOL) have been developed that are specific to patients with bladder cancer. Two validated methods of assessment, the Functional Assessment of Cancer Therapy-Vanderbilt Cystectomy Index (FACT-VCI) and the Bladder Cancer Index (BCI), are currently used.[131 132] The FACT-VCI and BCI correlate moderately well, although the BCI is more specifically focused on the effects of bladder cancer treatments.[133] An additional tool to assess outcomes from a patient-focused perspective is the patient-reported outcomes (PRO) version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE). In a study of bladder cancer patients, the PRO-CTCAE showed significant correlation with the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30, especially for psychological measures.[134]

Despite BCG's long-standing historical efficacy for patients with NMIBC, its administration may negatively affect QOL by causing discomfort and functional impairment. While the majority of patients complete the 6-cycle induction course, a substantial number of patients discontinue maintenance due to symptoms negatively affecting their QOL. In a study of 411 patients with NMIBC treated with BCG, 74.9% were able to complete induction and begin maintenance, but only 52.3% completed 1 year of maintenance treatments. Of the patients who discontinued maintenance, the majority (59.6%) discontinued due to physical discomfort leading to reduced QOL, despite experiencing only grade 1 toxicities.[135] The dose of BCG may also impact QOL—in an analysis of 166 patients, those who received low-dose BCG induction reported significantly improved QOL, with less functional impairment and significantly less occurrence of fever and micturition pain.[136] Nonetheless, further studies are still needed to validate efficacy outcomes of

Table 7 Immunotherapies in development for the treatment of bladder cancer

Trial	Disease state	Interventions	Agent description	Primary outcome(s) for assessment
S1602 (NCT03091660)	NMIBC (first-line)	TICE-BCG (I/M)	BCG strain	Time to high-grade recurrence
		Tokyo-172 BCG (I/M)	BCG strain	
		Tokyo-172 BCG (I/M) with priming	BCG strain	
ALBAN (NCT03799835)	NMIBC (first-line)	BCG (I/M)	BCG	RFS
		Atezolizumab+BCG (I/M)	ICI, BCG	
POTOMAC (NCT03528694)	NMIBC (high-risk, first-line)	BCG (I/M)	BCG	DFS
		Durvalumab+BCG (I/M)	ICI, BCG	
		Durvalumab+BCG (I)	ICI, BCG	
B8011006 (NCT04165317)	NMIBC (high-risk, first-line)	BCG (I/M)	BCG	EFS
		PF-06801591+BCG (I/M)	ICI, BCG	
		PF-06801591+BCG (I)	ICI, BCG	
CheckMate 7G8 (NCT04149574)	NMIBC (high-risk, R/R to BCG)	BCG (I/M)+nivolumab	ICI, BCG	EFS
		BCG (I/M)+placebo	BCG	
CheckMate 9UT (NCT03519256)	NMIBC (high-risk, R/R to BCG)	Nivolumab	ICI	CR rate, duration of CR
		Nivolumab+BCG	ICI, BCG	
		Nivolumab+BMS-986205	ICI, IDO1 inhibitor	
		Nivolumab+BMS-986205+BCG	ICI, IDO1 inhibitor, BCG	
QUILT-3.032 (NCT03022825)	NMIBC (high-risk, R/R to BCG)	BCG+ALT-803	BCG, IL-15 superagonist	CR rate, disease-free rate
		ALT-803	IL-15 superagonist	
MK-3475–676/ KEYNOTE-676 (NCT03711032)	NMIBC (high-risk, R/R to BCG)	BCG (I/M)+pembrolizumab	ICI, BCG	CR rate
		BCG (I/M)	BCG	
S1605 (NCT02844816)	NMIBC (BCG-unresponsive)	Atezolizumab	ICI	CR rate, EFS
NCT03661320	MIBC (NA, A)	Gemcitabine/cisplatin (NA)	Chemotherapy	CR rate, EFS
		Gemcitabine/cisplatin (NA)+nivolumab (NA, A)+placebo (NA, A)	ICI, chemotherapy	
		Gemcitabine/cisplatin (NA)+nivolumab (NA, A)+BMS-986205 (NA, A)	ICI, IDO1 inhibitor, chemotherapy	
NIAGARA (NCT03732677)	MIBC (NA, A)	Gemcitabine/cisplatin (NA)+durvalumab (NA, A)	ICI, chemotherapy	CR rate, EFS
		Gemcitabine/cisplatin (NA)	Chemotherapy	
MK-3475–905/ KEYNOTE-905 (NCT03924895)	MIBC (NA, A)	Pembrolizumab (NA, A)	ICI	CR rate, EFS
		Surgery alone	None	
MK-3475–866/ KEYNOTE-866 (NCT03924856)	MIBC (NA, A)	Pembrolizumab (NA, A)+gemcitabine/cisplatin (NA)	ICI, chemotherapy	CR rate, EFS
		Gemcitabine/cisplatin (NA)+placebo (NA, A)	Chemotherapy	
PIVOT IO 009 (NCT04209114)	MIBC (NA, A)	Nivolumab (NA, A)+NKTR-214 (NA, A)	ICI, CD122-biased agonist	CR rate, EFS
		Nivolumab (NA, A)	ICI	
		Surgery alone	None	
INTACT SWOG/NRG 1806 NCT03775265	MIBC (bladder preservation)	Radiotherapy+chemotherapy	Chemotherapy	Bladder-intact EFS
		Radiotherapy+chemotherapy+atezolizumab	ICI, chemotherapy	
MK-3475–992/ KEYNOTE-992 (NCT04241185)	MIBC (bladder preservation)	Pembrolizumab+chemotherapy+radiotherapy	ICI, chemotherapy	Bladder-intact EFS
		Placebo+chemotherapy+radiotherapy	Chemotherapy	

Continued

Table 7 Continued

Trial	Disease state	Interventions	Agent description	Primary outcome(s) for assessment
AMBASSADOR (NCT03244384)	MIBC (A)	Pembrolizumab	ICI	OS, DFS
		Observation	None	
CheckMate 274 (NCT02632409)	MIBC (A)	Nivolumab	ICI	DFS
		Placebo	None	
NILE (NCT03682068)	Metastatic (first-line)	Durvalumab+platinum/gemcitabine	ICI, chemotherapy	OS
		Durvalumab+tremelimumab+platinum/gemcitabine	ICI, chemotherapy	
		Platinum/gemcitabine	Chemotherapy	
Checkmate 901 (NCT03036098)	Metastatic (first-line)	Ipilimumab+nivolumab	ICI	OS, PFS
		Ipilimumab+nivolumab+chemotherapy	ICI, chemotherapy	
		Chemotherapy	Chemotherapy	
EV 302 (NCT04223856)	Metastatic (first-line)	EV+pembrolizumab	ICI, ADC	PFS, OS
		Gemcitabine+platinum	Chemotherapy	
		EV+pembrolizumab+platinum	ICI, ADC, chemotherapy	
LEAP-011 (NCT03898180)	Metastatic (first-line)	Pembrolizumab+lenvatinib	ICI, tyrosine kinase inhibitor	PFS, OS
		Pembrolizumab+placebo	ICI	
THOR (NCT03390504)	Metastatic (second- or third-line)	Erdafitinib	FGFR kinase inhibitor	OS
		Pembrolizumab	ICI	

A, adjuvant; ADC, antibody-drug conjugate; AE, adverse event; BCG, Bacillus Calmette-Guérin; CR, complete response; DFS, disease-free survival; EFS, event-free survival; FGFR, fibroblast growth factor receptor; I, induction; ICI, immune checkpoint inhibitor; IL-15, interleukin-15; I/M, induction and maintenance; M, maintenance; MIBC, muscle-invasive bladder cancer; NA, neoadjuvant; NMIBC, non-muscle-invasive bladder cancer; OS, overall survival; PFS, progression-free survival; RFS, recurrence-free survival; R/R, relapsed/refractory.

BCG dose reductions in comparison to full-dose BCG regimens.

While ICIs often exhibit better AE and QOL profiles in comparison to platinum-based chemotherapy, there is a paucity of direct comparisons specifically in patients with bladder cancer. An analysis of participants in the KEYNOTE-045 trial, however, demonstrated that pembrolizumab prolonged time to deterioration in HRQOL score when compared with investigator's choice chemotherapy (median time to deterioration 3.5 months vs 2.3 months, respectively; HR 0.72; p=0.004). The change in HRQOL scores from baseline to week 15 of treatment was also significantly different, at 0.69 (95% CI −2.40 to 3.77) in the pembrolizumab arm and −8.36 (95% CI −11.84 to −4.89) in the chemotherapy arm (mean difference 9.05; 95% CI 4.61 to 13.50; p<0.001).[137]

Another key consideration for patient QOL is access to treatment and financial limitations. Patients with bladder cancer who report experiencing financial toxicity (defined as 'paying more for medical care than you can afford') may delay treatment due to issues concerning expense management and work productivity. Patients who experience financial toxicity report significantly lower HRQOL.[138] The possibility of financial toxicity presents a major barrier to equitable healthcare access and contributes to disparities in medical care, including in the context of clinical trial participation.[139 140]

In the context of the SARS-CoV-2 pandemic, cancer care and many aspects of patient QOL may also be impacted. Patients with cancer appear to be more prone to death and to severe outcomes requiring hospitalization from COVID-19.[141–144] Additionally, treatment with ICIs has been associated with increased risk of severe COVID-19 respiratory disease in some analyses, but this association was not confirmed in other analyses.[145–148] The data with regard to BCG treatment is less clear; while some studies indicate that vaccination with BCG (common in regions where tuberculosis infection is a high risk) may be associated with reduced risk of COVID-19,[149 150] further study is still required. Beyond possible impact on outcomes, additional important considerations during the pandemic for patients with cancer include attempts to reduce in-person appointments when possible, use of telemedicine, potential disruptions in public transportation, interruption of clinical trials, and potentially delayed or altered treatment schedules, screening, diagnostic work up, and surveillance. These changes to treatment schedules could create complications in a patient's ability to attend appointments or increase the financial hardship of doing so, potentially negatively impacting cancer care.

Panel recommendations

- Patient navigation and PRO tools can help eliminate barriers to oncologic care, enhance patient decision-making, and improve the patient experience during their cancer care. This has been demonstrated in screening outcomes for a variety of malignancies and confirmed in recent studies of NMIBC and MIBC. Combining patient-focused information and educational resources with comprehensive patient-provider conversations can contribute to improved QOL both during treatment and surveillance.
- Comprehensive conversations with patients about all aspects of medical treatment, including financial obligations, could involve multiple clinical and institutional providers. Conversations should continue throughout patient-provider relationships that reflect the evolving nature of treatment timing, options, and patient concerns.
- Urothelial cancer-specific outcome measures for BCG and ICI treatments should be developed, validated, and utilized as tools for patient navigation.
- ICI-specific measures should address a range of treatment protocols and QOL, including ICI alone, combinations with chemotherapy and/or radiation, or any other combination of therapies. Such measures should recognize the often-lengthy nature of bladder cancer treatment and surveillance, along with the potential for adverse effects to occur after the period of initial treatment.
- Practical patient information and education resources are needed for both BCG and ICI treatment. As more patients are treated with ICIs, written and digital educational materials are needed. Patient information resources in written and digital formats are available from bladder cancer and medical education organizations, in addition to materials provided by the providing clinic.
- There is now an opportunity to develop, study, and deploy digital/mobile technologies to increase patient awareness and reporting of BCG- and ICI-related AEs. Innovation in patient-provider communication and application of technology to PRO/QOL communication could affect patient care for initial and follow-up of patients with urothelial cancer.

CONCLUSION

The introduction of ICI therapies has expanded options for patients with urothelial cancer, both in the NMIBC and mUC settings. ICIs, and other immunotherapies, are likely to continue to function as a cornerstone of urothelial cancer treatment, especially as emerging data from ongoing clinical trials provide evidence for their benefits in additional settings. Ongoing clinical trials hold promise for the development of new immunotherapies for the treatment of urothelial cancer, including a gene therapy (nadofaragene firadenovec), a CD122-biased agonist, an IL-15 agonist, an IDO1 inhibitor, and new strains of BCG. The recommendations in this manuscript were based on available evidence at the time of manuscript preparation and the consensus of the SITC Urothelial Cancer Immunotherapy Guideline Expert Panel. As the field progresses, this guideline will be updated as needed.

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