Navigating Precision Medicine in Bladder Cancer – Optimizing the Identification and Selection of Patients for Immunotherapy

Overview: This text-based CME activity reviews the recent clinical developments in the immunotherapy and immunomodulatory therapeutic modalities for high-risk non-muscle-invasive bladder cancer as well as for locally advanced or metastatic disease.

CE Information

Faculty Reviewer

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Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Distinguish among new and emerging checkpoint inhibitor therapies for advanced bladder cancer in accordance with the latest data
- Differentiate tumor progression from pseudoprogression to better evaluate therapeutic response with checkpoint inhibitor therapy
- Select an appropriate course of treatment for a patient who presents with an immune-related adverse event
- Collaborate with patients to develop treatment plans that are culturally sensitive and in alignment with patients' needs and expectations
- Recognize adverse events and potential drug-drug interactions associated with newly-approved treatments

Target Audience

The target learning audience is oncologists, urologists and other healthcare providers who care for patients with bladder cancer.

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Overview

Epidemiology, Risk, and Burden

Bladder cancer is a highly prevalent malignancy and is associated with significant morbidity, mortality, and health care cost.[1,2,3,4] Indeed, bladder cancer is the most expensive malignancy to manage in the USA.[5] With 81,190 estimated new cases and 17,240 deaths in 2018, bladder cancer is the 4th most common malignancy in US men (12th in women).[1] With an expanding population, both in terms of absolute numbers and a disproportionate increase in the geriatric sector, the bladder cancer incidence and mortalities are anticipated to demonstrate a continued increase over time.[2] Cigarette smoking is the most common known risk factor for bladder cancer and is responsible for approximately half of all cases; the highly mutational characteristic of bladder cancer, especially the more aggressive variants, may also be related to other environmental exposures.[6]

Signs, Symptoms, Evaluation, and Diagnosis

The most common symptom of bladder cancer is hematuria, which may be either microscopic (not visible), detected in ~15% of patients, or macroscopic (visible), observed in ~75% of patients, the latter of which may increase the risk of a more advanced pathological stage.[7] Bladder cancer may also be suspected if the patient presents with nonspecific symptoms of the lower urinary tract: urinary urgency, frequency, and/or dysuria.[8] Despite the fact that earlier detection of disease, before development of visible hematuria, could influence survival, many patients with microscopic hematuria are inadequately evaluated and oftentimes reflexively treated with antibiotics and not adequately assessed for bladder cancer.[9] The gold-standard for evaluation of patients suspected of having bladder cancer is cystoscopy.[10,11,12]

Types, Stage, Grade, and Prognosis

Urothelial carcinoma (UC) represents the most common type of bladder cancer. However, variant histologies such as squamous cell carcinoma, small cell carcinoma, and adenocarcinoma have been described in 10%-25% of cases.[13] Approximately 75% of newly diagnosed patients have non-muscle-invasive bladder cancer (NMIBC, which is defined as papillary tumor confined to the mucosa or invading the lamina propria, stage Ta or T1, respectively, or flat high-grade tumor confined to the mucosa, classified as carcinoma *in situ* – ie, CIS or Tis – with a high malignant potential) and 25% have muscle-invasive bladder cancer (MIBC) or metastatic disease (Table 1).[11,15,16]

Table 1. TNM classification of urinary bladder cancer.[11,15]

T: Primary tumor		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Ta	Noninvasive papillary carcinoma	
Tis	Carcinoma *in situ*: ''flat tumor''	
T1	Tumor invades subepithelial connective tissue; attempt for subcategorization in TUR recommended	
T2	Tumor invades muscle; staging of diverticular cancers has no T2	
	T2a	Tumor invades superficial muscle (inner half)
	T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue	
	T3a	Microscopically
	T3b	Macroscopically (extravesical mass)
T4	Tumor invades any of the following: prostate (must be transmural from bladder; subepithelial stromal invasion staged as T2, urethral), uterus, vagina, pelvic wall, abdominal wall	
	T4a	Tumor invades prostate, uterus, or vagina
	T4b	Tumor invades pelvic wall or abdominal wall
N: Lymph nodes		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral); perivesical lymph node	
N2	Metastasis in multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)	
N3	Metastasis in common iliac lymph node(s)	
M: Distant metastasis		
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Nonregional lymph node(s) only
	M1b	Non-lymph node distant metastases

Bladder cancer prognosis, as well as management, depend on bladder cancer histopathology (ie, NMIBC vs MIBC).[10,11,12] Additionally, grading is important because well-differentiated (low-grade tumors) are less aggressive than high-grade lesions (Table 2), with an attendant decreased likelihood for both recurrence and progression .[11,17]

Table 2. 1973 and 2004/2016 WHO grading classifications.[11,17]

1973 WHO grading system
Urothelial papilloma
Grade 1: Well differentiated
Grade 2: Moderately differentiated
Grade 3: Poorly differentiated
2004/2016 WHO grading system [papillary lesions]
Urothelial papilloma (completely benign lesion)
Papillary urothelial neoplasm of low malignant potential
Low-grade papillary urothelial carcinoma
High-grade papillary urothelial carcinoma

WHO, World Health Organization

Management

Initially, all newly diagnosed patients need to undergo a transurethral resection of bladder tumor (TURBT), which is performed with a goal of detailed visualization of the bladder and resection of all visible tumor, with inclusion of muscle for accurate staging.[10,11,12] In patients with incompletely resected tumor, or with tumors invading the lamina propria (T1), a repeat TURBT is recommended within 2-6 weeks. Also, it should be considered in patients with high-grade NMIBC, except in those with Tis alone, to improve staging accuracy and potentially increase recurrence-free survival (RFS) and progression-free survival (PFS).[18,19,20,21] Of note, in addition to having a diagnostic role, TURBT has also a therapeutic one and can potentially serve as curative therapy.[20]

Typically, NMIBC is managed with endoscopic resection and risk-based intravesical therapy, whereas MIBC is managed with more aggressive treatments such as radical cystectomy with or without chemotherapy.[10,11,12]

NMIBC

Management of NMIBC is informed by the risk of disease recurrence and progression (Table 3).[22,23,24] Factors associated with recurrence and progression include high stage, high grade, large tumor size, multifocality, high number of previous recurrences, presence of concomitant Tis, lymphovascular invasion, histological variants (eg, micropapillary features), and greater depth of invasion (eg, so-called deep T1 tumor).[25,26]

Table 3. Risk-stratification based treatment options for patients with NMIBC.[23]

Risk	Treatment
Low-risk NMIBC (low-grade Ta tumor)	Postoperative (within 6 h) intravesical instillation of chemotherapeutic drug (eg, mitomycin, epirubicin, or gemcitabine)
Intermediate-risk NMIBC (multifocal or multi-recurrent low-grade Ta tumors)	
Absence of multiple tumors, tumor ≥3 cm, >1 recurrence per year, recurrence within 1 year after TURBT	Same as treatment for low-risk NMIBC
One or 2 of the following: multiple tumors, tumor ≥3 cm, >1 recurrence per year after TURBT	Postoperative (within 6 h) intravesical instillation of chemotherapeutic drug; induction + 1-year maintenance treatment with either an intravesical chemotherapeutic drug or BCG
Three or more of the following: multiple tumors, tumor ≥3 cm, >1 recurrence per year, recurrence within 1 year after TURBT	Same as treatment for high-risk NMIBC
High-risk NMIBC, eg, T1 (invasive into lamina propria), Tis, or any high-grade tumor	Restaging transurethral resection in 4-6 weeks; induction + 3-year maintenance treatment with BCG; early cystectomy if high-grade T1 tumor with any of the following: multiple tumors or large tumor, micropapillary histological variant, concomitant Tis in bladder or prostatic urethra, or presence of lymphovascular invasion

BCG, bacillus Calmette-Guérin

Intravesical Therapy

The rationale behind using intravesical therapy is to decrease recurrence rates and prevent progression of NMIBC to a higher grade or stage.[10,11,12]

For patients with low-risk NMIBC, a single immediate (within 6 h) instillation of intravesical chemotherapy (eg, mitomycin, epirubicin, or gemcitabine) after TURBT is recommended, based on the reported benefit of decreased recurrence rates.[27,28] Similarly, patients with intermediate-risk NMIBC benefit from the addition of 1-year maintenance intravesical chemotherapy after TURBT by experiencing lower 1-year recurrence rates.[29] Of note, however, no studies have shown the benefit of intravesical chemotherapy in terms of lowering progression rates.

For patients with high-risk NMIBC, the best treatment option is intravesical bacillus Calmette-Guérin (BCG) immunotherapy, which is a live attenuated strain of *Mycobacterium bovis* used for vaccination against tuberculosis.[30] Several randomized studies that compared intravesical BCG with various intravesical chemotherapies have shown that BCG was superior in terms of reducing recurrences, and, moreover, preventing disease progression; the latter, however, only when BCG maintenance was used.[31] Recently, a randomized trial showed that in high-risk disease, RFS was best when BCG maintenance was delivered at full dose for 3 years (ie, with 3

weekly intravesical instillations at 3, 6, 12, 18, 24, 30, and 36 months), unlike in patients with intermediate-risk NMIBC for whom 1 year of maintenance treatment was sufficient.[32]

However, despite BCG efficaciousness, recurrence rates range from ~33% to ~42% and progression rates from ~10% to ~13%.[25,33] Cases of so-called BCG failure can be grouped into BCG-refractory disease (ie, persistent high-grade disease at 6 months after adequate BCG induction), relapsed disease after BCG (ie, recurrence of high-grade disease after a disease-free interval of ≥6 months), and failure due to BCG intolerance (ie, disease persistence due to the patient's inability to receive adequate BCG owing to its toxicity).[22,34] Recently, a new category, BCG-unresponsive disease, which includes BCG-refractory disease and a subset of the patients with relapsed disease who have recurrence within 6 months of last exposure to BCG (ie, patients on maintenance treatment), has been adopted by the US Food and Drug Administration, the International Bladder Cancer Group, and the American Society of Clinical Oncology GU Cancers Group, to facilitate patient selection for clinical trial enrollment (Table 4).[22] The lack of established and effective treatment options for patients whose tumors recur after BCG immunotherapy clearly represents an important unmet clinical need.

Table 4. Classification of BCG Failures.[22,23]

Disease Category	Description
Refractory	Persistent high-grade disease at 6 months after adequate* BCG induction and maintenance treatment or any progression in stage at 3-month assessment (ie, after induction BCG cycle)
Relapsing	Recurrence of high-grade disease after a disease-free interval of ≥6 months after adequate* BCG induction and maintenance treatment. Although this category has previously been subdivided based on time to recurrence after stopping BCG into early (<12 months), intermediate (1-2 years), or late (>24 months), for the purpose of being included in the BCG-unresponsive category, patients should be within 6 months of the last BCG exposure (eg, patient receiving maintenance therapy)
Unresponsive (developed for clinical trial design)	This category includes patients with BCG-refractory and BCG-relapsing disease as already defined (the patients with BCG-relapsing disease should have recurrence within 6 months of last BCG exposure, eg, patients on maintenance treatment); patients in the BCG unresponsive subgroup are at highest risk of recurrence and progression
Intolerant	Disease persistence due to patient's inability to receive adequate* BCG owing to BCG toxicity

*At least 5 of 6 instillations of induction therapy and at least 2 of 3 instillations of maintenance therapy over 6 months.

Post-BCG Salvage Setting – Immunotherapy and Immunomodulatory Therapeutic Modalities

Tumors that recur after intravesical BCG treatment are typically associated with high risk of progression and the optimal salvage therapy is radical cystectomy.[10,11,12] However, due to the morbidity and mortality associated with the radical cystectomy, many patients are unable or unwilling to undergo this procedure, and alternative, less-invasive salvage treatment options, are being increasingly explored.[35,36] Particular interest in 1 category of potential salvage treatment options, ie, immunotherapy and immunomodulatory therapeutic modalities, stems from the immunobiologic effect of BCG which results in its ability to induce a durable and effective antitumor immune responses (Table 5).[36,37]

Table 5. Clinical trials of immunotherapy and immunomodulatory therapeutic modalities.[36]

Study agent(s)	Disease Status	Route	Phase; ID
ALT-801 + gemcitabine	BCG intolerant or failed 1 course of BCG	IV	1b/2, single arm; NCT01625260
BCG alone vs BCG + PANVAC	Failed at least 1 course of BCG induction	Intravesical	2; NCT02015104
CG-0700	BCG unresponsive	Intravesical	2, single arm; NCT02365818
rAD-IFN/Syn3	BCG unresponsive	Intravesical	2, parallel-arm; NCT01687244 and 3, single arm; NCT02773849
VPM 1002BC	Recurrence after at least 1 cycle of BCG within 5 years	Intravesical	1/2, single arm; NCT02371447
BCG alone vs BCG + lenalidomide	Recurrence after prior BCG treatment within 2 years	PO	2; NCT01373294
Atezolizumab	BCG unresponsive, BCG relapsing	IV	1b/2, single arm; NCT02792192 and 2, single arm; NCT02844816
BCG alone vs BCG + ALT-803	BCG unresponsive	Intravesical	2/3; NCT03022825
Pembrolizumab	BCG unresponsive	IV	2, single arm; NCT02625961
Pembrolizumab + BCG	BCG refractory	Intravesical	1, single arm; NCT02808143

One type of immunotherapy/immunomodulatory treatment strategies is combining BCG with other therapies that may augment its antitumor effect and/or synergize with it (Table 5). Early studies of BCG and interferon alfa (IFNα)

combination therapy showed no significant improvement in outcome in patients receiving combination therapy vs those receiving only BCG.[38,39]

However, a recent phase 2 study of recombinant adenovirus IFNα with Syn3 (rAd–IFNα/Syn3), a replication-deficient recombinant adenovirus gene transfer vector with a polyamide surfactant, in patients with high-grade BCG-refractory or relapsed NMIBC, showed a promising efficacy and tolerability.[40] In this study, of 40 patients who received rAd–IFNα/Syn3, either 1 x 10^{11} viral particles (vp)/mL (n = 21) or 3 x 10^{11} vp/mL (n = 19), 14 (35.0%) remained free of high-grade recurrence 12 months after initial treatment, while both doses resulted in comparable 12-month high-grade RFS (33.3% of patients in the low-dose group and 36.8% in the high-dose group were alive and free of HG disease at 12 months). The median time to high-grade recurrence or death was 6.5 months (the median time to high-grade recurrence was 3.52 months for the low-dose group and was 11.73 months for the high-dose group). Of 14 patients who remained free of high-grade recurrence 12 months after initial treatment, 2 experienced recurrence at 21 and 28 months after treatment initiation, and 1 died at 17 months from an upper tract tumor without a recurrence. Overall, rAd–IFNα/ Syn3 was well tolerated with no grade 4 or 5 adverse events (AEs), and no treatment discontinuations because of AEs. The most frequently reported drug-related AEs include micturition urgency (n = 16; 40%), dysuria (n = 16; 40%), fatigue (n = 13; 32.5%), pollakiuria (n = 11; 28%), and hematuria and nocturia (n = 10 each; 25%).[40] Based on these promising results, a phase 3 trial with high-dose rAd–IFNα/Syn3, which provided longer median high-grade RFS and equivalent biosafety, has been initiated [NCT02773849].

Another adenovirus-based therapy, CG0070, showed promising efficacy and tolerability in a recent phase 2 trial.[41] Of 45 patients in this study, 24 had Tis, 8 Tis + Ta, 4 Tis + T1, 6 Ta, and 3 had T1 NMIBC. Overall 6-month complete response (CR, defined as absence of disease on cytology, cystoscopy, and random biopsies) was 47%. With regard to pathologic subsets, 6-month CR for Tis was 58%, Tis ± Ta/T1 50%, and Ta/T1 33%. However, no patients with T1 had CR at 6-month. At 6 months, the single patient that progressed to MIBC had Ta and T1 tumors at baseline. The most common treatment-related AEs (TRAEs) at 6 months were urinary bladder spasms (36%), hematuria (28%), dysuria (25%), and urgency (22%), and immune-related AEs included flu-like symptoms (12%) and fatigue (6%). Grade III TRAEs were dysuria (3%) and hypotension (1.5%), and there were no Grade IV/V TRAEs.[41]

Vicinium, a fusion protein consisting of an epithelial cell adhesion molecule (EpCAM)-specific antibody fragment fused to Pseudomonas exotoxin A, which is a potent inhibitor of protein synthesis, showed noteworthy efficacy and tolerability in a phase 2 trial of patients with BCG-refractory Tis.[42] In this trial, patients (N=46) received 1 induction cycle of either 6 (cohort 1) or 12 (cohort 2) weekly intravesical vicinium instillations of 30 mg, followed by up to 3 maintenance cycles of 3 weekly administrations every 3 months. At the 3-month evaluation, 44% of patients achieved a CR (41% in cohort 1, 39% in cohort 2). Median time to recurrence in patients who achieved a CR was 274 (cohort 1) and 408 days (cohort 2). Overall, 16% of patients remained disease-free at the time of the last follow-up (18 to 25 months). As for the AEs, the most common were mild to moderate reversible bladder symptoms.[42]

Recently presented interim data from a phase 3 VISTA trial of vicinium in patients (N=129) with BCG-unresponsive NMIBC (high grade Ta, any T1 and Tis with or without papillary disease),

confirmed prior proof-of-concept phase 2 data.[43] At the 3-month evaluation, 42% (Tis only) and 68% (papillary only) of patients achieved a CR. Again, the safety profile of vicinium was shown to be tolerable and manageable. Any grade ≥3 treatment-related AEs (TRAEs) were reported in in 4% of patients, with no grade 5 TRAEs and <1% of treatment discontinuations due to AEs or progressive disease.[43]

With regard to the immune checkpoint blockade—particularly with anti-programmed cell death 1 (PD-1), and anti-programmed cell death 1 ligand 1 (PD-L1) antibodies—atezolizumab (anti-PD-L1), pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), avelumab (anti-PD-L1), and durvalumab (anti-PD-L1) have shown durable objective response rates in patients with locally advanced or metastatic UC (mUC) and have been approved for frontline or second-line use in patients with mUC.[44,45,46,47,48,49,50]

Currently, several anti-PD-1/PD-L1 immune checkpoint inhibitors (ICIs) are being tested in patients with BCG-refractory NMIBC or patients with very high-risk BCG-naive NIMBC (NCT02451423, NCT02625961, and NCT02792192). Additionally, 2 trials are testing the efficacy of BCG/ICI combination in patients with NMIBC and the effect of locally instilled ICI in combination with BCG (NCT02324582 and NCT02808143, respectively).

Some of the additional immunotherapy/ immunomodulatory treatment strategies that are being explored in patients with NMIBC include intradermal BCG vaccination (PRIME trial, NCT02326168), and cancer vaccines such as vesigenurtacel-L (NCT02010203) and PANVAC, which is a poxviral vaccine that expresses trans-genes for tumor antigens mucin-1 and carcinoembryonic antigen, as well as a set of co-stimulatory molecules (eg, B7.1, LFA-3, and ICAM-1) to enhance the antitumor T cell responses (NCT02015104).

MIBC and Advanced Bladder Cancer

The current gold-standard approach in patients with MIBC is radical cystectomy with neoadjuvant cisplatin-based chemotherapy.[12,51] Selected patients with MIBC can be offered bladder-sparing trimodal treatment consisting of TURBT with chemoradiation. Advanced disease is treated with systemic cisplatin-based chemotherapy, and, in patients who are not eligible for any platinum-containing chemotherapy, with anti-PD-1/PD-L1 immunotherapy (ie, atezolizumab and pembrolizumab).[52,53] Anti-PD-1/PD-L1mmunotherapy (ie, atezolizumab, pembrolizumab, nivolumab, avelumab, and durvalumab) is also used as a second-line therapy in metastatic disease, based on durable therapeutic response and manageable safety profiles observed in the relevant clinical trials.[44,45,46,47,48,49,50] The rationale for using ICIs in bladder cancer is its wide mutational range that translates into a broad spectrum of neo-antigens being recognized as “non-self” by the circulating T cells, which then results in activated immune responses.[54] Moreover, a recent study demonstrated that bladder cancer is only behind melanoma and non-small cell lung cancer when it comes to the mutational burden, providing a further rationale for the use of immune checkpoint blockade.[55] To date, the published trial literature with ICIs in bladder cancer has mainly focused on the platinum-refractory mUC. However, a number of trials are ongoing with ICIs in the neoadjuvant setting as well as the first-line metastatic setting, being evaluated as monotherapy or numerous combinatorial strategies.

Platinum-Refractory Setting – Immune Checkpoint Blockade

Atezolizumab, a monoclonal immunoglobulin G1 (IgG1) anti-PD-L1 antibody, received accelerated approval by the US Food and Drug Administration (FDA) in 2016 for treatment of patients with locally advanced or mUC in the post-platinum setting.[52] The approval was based on the results of a phase 2 IMvigor 210 trial (cohort 2) that included patients (N=310, who received atezolizumab 1200 mg every 3 weeks) with locally advanced or mUC refractory to platinum-based chemotherapy.[44] Based on the PD-L1 expression in archival tumor tissue, both for tumor cells (TCs) and immune-infiltrating immune cells (ICs), tumors were classified as immunohistochemistry (IHC): 0 (<1%), 1 (≥1% but <5%), 2 (≥5 but <10%), or 3 (≥10%). At a median follow-up of 11.7 months, the overall response rate (ORR) was 16% (CR, 6%), and for patients with IC IHC 2/3 the ORR was 27%. The median PFS for the entire population was 2.1 and 2.7 months by central review and by investigator assessment, respectively. The overall survival (OS) for the entire population was 7.9 months, and 11.4 months for patients with IC 2/3. Grade 3-4 TRAEs, of which fatigue was the most common (2%), occurred in 16% of patients. Grade 3-4 immune-related AEs (irAEs) occurred in 5% of patients, with pneumonitis, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), rash, and dyspnea being the most common. Of note, no treatment-related deaths occurred during the study.[44] Updated efficacy data showed that median duration of response (DOR) was not reached in most subgroups and that median OS was 9.6 months.[56]

However, recently reported findings from the phase 3 IMvigor 211 trial (N=931) comparing atezolizumab with physician's choice chemotherapy (eg, docetaxel, paclitaxel or vinflunine) failed to demonstrate an improvement in OS for patients with high PD-L1 expression (25% of the total were IHC 2/3), which was the primary endpoint of the trial.[57] In the PD-L1-high group, median OS was 11.1 months (atezolizumab) vs 10.6 months (chemotherapy; P = 0.41). In the overall study population of the IMvigor 211 trial, however, there was a small improvement in OS with atezolizumab vs chemotherapy (8.6 vs 8.0 months; P = 0.038). Of note, however, there was a significant prolongation in the median DOR with atezolizumab vs chemotherapy (21.7 vs 7.4 months), which was consistent with the phase 2 findings, and the safety profile for atezolizumab was favorable compared with chemotherapy.[57]

Pembrolizumab, an IgG4k anti-PD-1 monoclonal antibody, was FDA approved in the post-platinum setting in 2017.[53] The approval was based on the phase 3 KEYNOTE-045 trial in which patients (N=542) were randomly assigned to either pembrolizumab 200 mg every 3 weeks for 2 years or chemotherapy.[47] PD-L1 status was defined by the combined positive score (CPS), which was the sum of the percentage of PD-L1-expressing TCs and ICs as a fraction of the total number of TCs. Although the median PFS was longer in patients receiving chemotherapy compared with those receiving pembrolizumab (3.3 vs 2.1 months), the median OS was superior for patients receiving pembrolizumab compared with those receiving chemotherapy (10.3 vs 7.4 months, P < 0.01). Also, for patients with PD-L1 CPS score ≥10%, there was a median OS advantage with pembrolizumab (8.0 vs 5.2 months, P = 0.005). Additionally, the ORR in the pembrolizumab cohort was nearly double that for chemotherapy (21.1% vs 11.4%, P = 0.001). Finally, fewer TRAEs of any grade were reported in the pembrolizumab group than in the chemotherapy group (60.9% vs 90.2%), and there were also fewer events of grade 3, 4, or 5 severity in the pembrolizumab group than in the chemotherapy group (15.0% vs 49.4%).[47]

Nivolumab, an IgG4k anti-PD-1 monoclonal antibody, received accelerated approval by FDA in 2017 in the platinum-refractory second-line setting.[58] A phase 2 CheckMate 275 trial, which was the basis for the FDA approval, evaluated nivolumab monotherapy in patients (N=265) with nonresectable, platinum-resistant, or mUC.[59] PD-L1 expression was determined in TC initially as ≥5% or ≤5%, and after the protocol amendment as ≥1% or ≤1%. Reported ORR was 19.6%; ORR in PD-L1 TC ≥1% was 23.8% and for PD-L1 ≥5% was 28.4%. In the overall population, median PFS was 2 months and median OS was 8.7 months. Grade 3-4 TRAEs occurred in 18% of patients (most commonly grade 3 fatigue and diarrhea). Moreover, 3 deaths were attributed to treatment (pneumonitis, acute respiratory failure, and cardiovascular failure).[59]

Durvalumab, an IgG1k anti-PD-L1 monoclonal antibody, received accelerated FDA approval in 2017 in the platinum-refractory setting.[60] The approval was based on a single-arm phase 1/2 trial of patients (N=191) with locally advanced or mUC who were receiving durvalumab 10 mg/kg every 2 weeks for up to 1 year.[61] Tumor testing was required, and PD-L1 expression ≥25% in either ICs or TCs was deemed as high. The study population was enriched for PD-L1-high patients as part of protocol amendments enacted during the trial. The ORR was 17.8% in the entire population (CR, 3.6%), with an ORR of 27.6% in PD-L1 high and 5.1% in PD-L1 low/negative. Median PFS and OS were 1.5 months and 18.2 months, respectively, for the overall population. Grade 3/4 TRAEs occurred in 6.8% of patients, whereas grade 3/4 irAEs occurred in 2.1% of patients. Three patients (1.6%) discontinued treatment due to TRAEs, 2 of whom had irAEs that led to death (autoimmune hepatitis and pneumonitis).[61]

Avelumab, an IgG1 anti-PD-L1 antibody, also received accelerated approval in 2017 in the post-platinum setting.[62] The approval was based on the results of a large phase 1b study (JAVELIN) that included a pooled cohort analysis of 249 patients with mUC who had either progressed after platinum-based therapy or were cisplatin-ineligible.[50,63] In an updated analysis, ORR was 17.3% CR (4.4%) and median DOR was 20.1 months; ORR in PD-L1+ and PD-L1- subgroups (≥5% tumor cell cut-off) was 25.6% and 13.7%, respectively. The median PFS was 1.6 months and median OS was 8.2 months. Grades ≥3 TRAEs occurred in 10.4% of patients, most commonly fatigue (1.6%), elevated lipase (1.6%), and pneumonitis (1.2%). irAEs occurred in 17.3% of patients (grade ≥3 in 3.6%). Eight patients (3.2%) discontinued avelumab due to a TRAEs, and there was 1 treatment-related death (pneumonitis).[63]

Platinum-Ineligible Setting – Immune Checkpoint Blockade

In 2017, atezolizumab also received first-line accelerated FDA approval for patients who are cisplatin-ineligible, based on the results of cohort 1 of the phase 2 IMvigor 210 trial.[45,52] At a median follow up of 17.2 months, in patients (N=119) with locally advanced or mUC who were cisplatin-ineligible and treatment naive, the ORR was 23% (IC 2/3, 28%; IC 0, 21%) with 9% of CR. Median DOR was not reached, with 70% of patients continuing to respond after a median follow-up of almost 1.5 years. The median PFS was 2.7 months for the entire population (IC 2/3, 4.1 months; IC 0 2.6 months). The median OS for the entire population was 15.9 months (IC 2/3, 12.3 months; IC 0/1, 19.1 months, not statistically different). TRAEs that occurred in 10% or more of patients were fatigue (30%), diarrhea (12%), and pruritus (11%). One treatment-related death (sepsis) occurred, 9 (8%) patients had an AE leading to treatment discontinuation, and irAEs occurred in 14 (12%) patients.[45]

In 2017, pembrolizumab received first-line accelerated FDA approval for patients with locally advanced or mUC who are ineligible for cisplatin-containing therapy, based on the results of the phase 2 KEYNOTE-052 trial.[53,64] At a median follow-up of 11.5 months, ORR was 28.9% (CR, 8.1%), and median DOR was not reached. Median OS was 11.5 months (6- and 12-month OS was 67.2% and 47.5%, respectively). In patients with a PD-L1 expression CPS of ≥10 (n=110), ORR was 47.3% and median OS was 18.5 months. Median OS was not reached in patients with lymph node-only disease (n=51) and was 13.1 months in patients with ECOG PS 0/1 (n=214) and 9.7 months in patients with ECOG PS 2 (n=156). TRAEs occurred in 67.6% of patients, with most common (≥15%) being fatigue (18.1%) and pruritus (17.8%). Grade ≥3 TRAEs occurred in 20.3% of patients, and irAEs occurred in 24.6% of patients.[64]

Of note, due to the decreased survival rates associated with the use of pembrolizumab or atezolizumab compared to platinum-based chemotherapy, in clinical trials of treatment-naïve patients with locally advanced or mUC who have low expression of PD-L1, in July 2018, the FDA imposed limits on the use of these 2 ICIs.[65] The labels of both ICIs have been revised to specify that pembrolizumab is indicated for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing therapy and whose tumors express PD-L1 (CPS ≥ 10), or in patients who are not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status; and atezolizumab is indicated for the treatment of patients with locally advanced or mUC who are not eligible for cisplatin-containing therapy, and whose tumors express PD-L1 (PD-L1 stained IC covering ≥5% of the tumor area), as determined by an FDA-approved test (SP142), or are not eligible for any platinum-containing therapy, regardless of PD-L1 status.[52,53] In patients already receiving atezolizumab or pembrolizumab who are cisplatin-ineligible and responding to treatment, staying on therapy could be considered, regardless of PD-L1 status. Also, the FDA has not changed the indications of atezolizumab and pembrolizumab for the treatment of patients with locally advanced or mUC who have disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment.[65]

<u>Advanced Bladder Cancer – Novel Approaches and Emerging Strategies</u>

The clinical successes of ICIs used as monotherapy have prompted further investigation into the potential benefits of combining different types of ICIs, or combining ICIs with other immunomodulatory agents, chemotherapy, antibody-drug conjugates, and targeted therapies. Some of these novel approaches may further impact the future treatment paradigm of patients with advanced bladder cancer (Table 6).

Table 6. Select clinical trials of combination immunotherapy.

Study agent(s)	Target	Setting	Phase; ID
Nivolumab + ipilimumab	PD-1 and CTLA-4	First-line	3 (CheckMate 901); NCT03036098
Durvalumab ± tremelimumab	PD-1 and CTLA-4	First-line	3 (DANUBE); NCT02516241
Durvalumab + MEDI0680	PD-L1 and PD-1	Second-line	1; NCT02118337
Pembrolizumab ± Epacadostat	PD-1 and IDO1	First-line	3 (KEYNOTE-672/ECHO-307); NCT03361865
Nivolumab + NKTR-214	PD1 and CD122	First-line/third-line	1/2 (PIVOT-02); NCT02983045
Durvalumab ± tremelimumab vs SoC chemotherapy	PD-1 and CTLA-4	First-line	3; NCT02516241
Atezolizumab ± platinum-based chemotherapy	PD-L1	First-line	3; NCT02807636
Pembrolizumab ± platinum-based chemotherapy vs chemotherapy alone	PD-1	First-line	3 (KEYNOTE-361); NCT02853305
Nivolumab + ipilimumab or SoC chemotherapy vs SoC chemotherapy alone	PD-1 and CTLA-4	First-line	3 (CheckMate901); NCT03036098
Avelumab + best supportive care (BSC) with BSC alone	PD-L1	Maintenance	3 (JAVELIN Bladder 100); NCT02500121
Pembrolizumab after initial chemotherapy	PD-1	Maintenance	2; NCT02500121
Atezolizumab ± bevacizumab	PD-L1 and VEGF-A	First-line	2; NCT03133390
JNJ-63723283 ± erdafitinib	PD-1 and FGFR	Second-/later-line	1/2; NCT03473743
Pembrolizumab or atezolizumab ± enfortumab vedotin	PD-1/PD-L1 and Nectin-4	First-/second-line	I (EV-103); NCT03288545

CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; FGFR, fibroblast growth factor receptor; IDO1, indoleamine-2,3-dioxygenase; VEGFR, vascular endothelial growth factor A

ICI Response Assessment and Its Impact on the Treatment Decision-Making Process

Many patients treated with ICIs demonstrate a relatively rapid response, characterized by tumor shrinkage or stable disease, thereby meeting traditional RECIST criteria. However, some patients demonstrate tumor response kinetics that are not in line with RECIST criteria, eg, responses may occur as late as 6-12 months after treatment initiation, or sometimes even later than that.[66] Also, responses that

eventually result in tumor regression or long-term disease stability may be preceded by tumor flare—which is caused by transient immune cell infiltration and priming of the immune system—and would traditionally categorized as tumor progression, or in some cases even as hyperprogression.[67,68,69] These unique mechanisms of ICI-associated responses prompted the development of specific immune-related response criteria (irRC) to help clinicians better capture the benefits of the ICI therapy.[70]

Management of irAEs

As previously mentioned, ICIs are associated with a unique spectrum of irAEs such as diarrhea and/or colitis, skin rash, pneumonitis, hepatitis, interstitial nephritis, and endocrinopathies that are typically transient and tend to occur within the first 6 months of treatment, but some, however, can be severe or life-threatening.[44,45,46,47,48,49,50,71]

Although the overall management of irAEs depends on the organ system affected, typically, in case of grade 1 toxicities, ICI therapy should be continued with close monitoring (except for some neurologic, hematologic, and cardiac grade 1 toxicities).[71] For most grade 2 toxicities, ICI therapy may be suspended, with optional use of corticosteroids and consideration of resuming when symptoms revert to grade 1 or less. Generally, grade 3 toxicities warrant suspension of ICI therapy and the initiation of high-dose corticosteroids (prednisone 1-2 mg/kg/d or methylprednisolone 1-2 mg/kg/d), which should be tapered over the course of at least 4 to 6 weeks. Refractory irAEs, however, may require infliximab or other immunosuppressive therapy. In case of grade 4 toxicities, permanent discontinuation of ICI therapy is generally recommended, except for endocrinopathies that may be controlled by hormone replacement.[71]

Strategies to Improve Health Care in Patients with Bladder Cancer

Health and survival disparities in patients with advanced bladder cancer are longstanding and have not improved over the past 2 decades.[72] A recently published study on discrepancies in staging, treatment, and outcomes in patients with bladder cancer, which was based on the National Cancer Database 2004-2013 data, demonstrated that female sex, black race, Hispanic ethnicity, and living in a region of lower income and education were all associated with increased odds of advanced disease and likely worse OS.[73] Although ICIs offer new hope to patients with advanced cancer, access to care and the associated abovementioned disparities will persist without a concerted effort to engage patients within marginalized groups.[74] Improving physicians' ability to communicate with their patients to develop treatment plans that are culturally sensitive and align with patient needs and expectations will be key to advancing health care progress.[75,76] Strategies for effective communication within the multidisciplinary health team are also essential, as shared decision making must be coordinated, and the resulting treatment plans executed, across providers.[77,78]

Conclusion

Best practices for bladder cancer are changing rapidly as the new data on NMIBC, MIBC and advanced disease emerge. Ongoing clinical developments of immunotherapy and immunomodulatory therapeutic modalities, their combinations with various chemotherapy and targeted therapeutic modalities, as well as predictive biomarkers, are likely to broaden the role of these agents across the spectrum of disease, and significantly improve patient outcomes.

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