NCCN Guidelines® Insights
Bladder Cancer, Version 5.2018
Featured Updates to the NCCN Guidelines

Abstract
The NCCN Clinical Practice Guidelines in Oncology for Bladder Cancer provide recommendations for the diagnosis, evaluation, treatment, and follow-up of patients with bladder cancer. These NCCN Guidelines Insights discuss important updates to the 2018 version of the guidelines, including implications of the 8th edition of the AJCC Cancer Staging Manual on treatment of muscle-invasive bladder cancer and incorporating newly approved immune checkpoint inhibitor therapies into treatment options for patients with locally advanced or metastatic disease.

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Please Note
The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel’s discussion, including the literature reviewed.

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Learning Objectives:

Upon completion of this activity, participants will be able to:

• Integrate into professional practice the updates to the NCCN Guidelines for Bladder Cancer

• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Bladder Cancer

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Overview

An estimated 81,190 new cases of urinary bladder cancer (62,380 men; 18,810 women) will be diagnosed in the United States in 2018, with approximately 17,240 deaths (12,520 men; 4,720 women) occurring during the same period. Bladder cancer, the sixth most common cancer in the United States, is rarely diagnosed in individuals aged <40 years. Given that the median age at diagnosis is 73 years, medical comorbidities are a frequent consideration in patient management.

The clinical spectrum of bladder cancer can be divided into 3 categories that differ in prognosis, management, and therapeutic aims. The first category consists of non–muscle-invasive bladder cancer (NMIBC), for which treatment is directed at reducing recurrences and preventing disease progression. The second group encompasses MIBC, for which the approach to treatment uses definitive local therapy (eg, surgery or radiotherapy [RT]) with curative intent. Systemic therapy, including neoad-
juvant chemotherapy, is frequently integrated with local therapy for these patients. The critical concern for the third group, consisting of locally advanced and metastatic lesions, is how to prolong quantity and maintain quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The goal of treatment across the clinical spectrum is to achieve the best possible outcome while maintaining quality of life.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer provide recommendations on treatment approaches based on current evidence. The panel updates the guidelines annually, with additional interim updates as needed. These NCCN Guidelines Insights summarize the panel discussion behind important updates to the 2018 version of the NCCN Guidelines, including implications of the 8th edition of the AJCC Cancer Staging Manual on treatment of MIBC and incorporating newly approved immune checkpoint inhibitor (ICI) therapies into treatment options for patients with locally advanced or metastatic disease.

### 2018 Updates to the AJCC Staging System

The most commonly used staging system is the AJCC TNM staging system. The NCCN Guidelines divide treatment recommendations for urothelial carcinoma of the bladder between NMIBC (Ta, T1, and Tis) and MIBC (≥T2 disease). Management of bladder cancer is based on findings of the biopsy specimen, with attention to histology, grade, and depth of invasion; these factors are used to estimate the probability of recurrence and disease progression. The 8th edition of the AJCC Cancer Staging Manual included changes to the staging of urinary bladder carcinoma, with the subdivision of stages III and IV disease (ie, stage III into stage IIIA and IIIB; stage IV into stage IVA and IVB). Notably, the new staging system groups regional lymph node me-
tastasis in the true pelvis and/or the common iliac nodes (N1–3) within stage III. Previously, N1–3 was grouped within stage IV, regardless of T stage. Additionally, M1 was subdivided into M1a and M1b, with M1a including distant metastases limited to lymph nodes beyond the common iliacs and M1b including non–lymph node distant metastasis. These changes were based on the results of several studies showing that patients with bladder cancer with metastases limited to the lymph nodes have better outcomes than those with visceral or bony metastases. Therefore, the current AJCC definition of stage IIIA includes T3–T4a,N0 or T1–T4a,N1; stage IIIB is defined as T1–T4a,N2–3. Stage IVA includes T4b,any N,M0 or any T,any N,M1a disease. Stage IVB is defined by M1b metastasis.

Prior to the implementation of the 8th edition of the AJCC Cancer Staging Manual, the NCCN treatment algorithms for MIBC were defined primarily by the pathologic T category (pT) of the tumor. Due to changes in the AJCC staging, the panel decided to reformat the algorithm pages to stratify patients based on the new staging criteria. This change was made partly so that patients with regional lymph node metastases would receive the most appropriate treatment options. Previous algorithms grouped treatment for all lymph node metastases with pT4b disease. Changes in treatment recommendations for stages IIIA, IIIB, and IVA—and the rationale behind them—are discussed in detail in the following sections.

**Muscle-Invasive Bladder Cancer**

**Treatment of Stage IIIA Tumors**

The 8th edition of the AJCC TNM Staging System defines stage IIIA bladder cancer as T3 (“tumor invades the perivesical tissue”) or T4a (extravesical tumor invades the prostatic stroma, seminal vesicles, uterus, and/or vagina) with no lymph node metastasis, or T1 (tumor invades the lamina propria [subepithelial connective tissue]) through T4a with a single metastasis in the true pelvis and/or the common iliac nodes (N1–3) within stage III. Previously, N1–3 was grouped within stage IV, regardless of T stage. Additionally, M1 was subdivided into M1a and M1b, with M1a including distant metastases limited to lymph nodes beyond the common iliacs and M1b including non–lymph node distant metastasis. These changes were based on the results of several studies showing that patients with bladder cancer with metastases limited to the lymph nodes have better outcomes than those with visceral or bony metastases. Therefore, the current AJCC definition of stage IIIA includes T3–T4a,N0 or T1–T4a,N1; stage IIIB is defined as T1–T4a,N2–3. Stage IVA includes T4b,any N,M0 or any T,any N,M1a disease. Stage IVB is defined by M1b metastasis.

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PRINCIPLES OF SYSTEMIC THERAPY

<table>
<thead>
<tr>
<th>First-line systemic therapy for locally advanced or metastatic disease (Stage IV)</th>
</tr>
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<tbody>
<tr>
<td><strong>Cisplatin eligible</strong></td>
</tr>
<tr>
<td>Preferred regimens</td>
</tr>
<tr>
<td>• Gemcitabine and cisplatin(^a) (category 1)</td>
</tr>
<tr>
<td>• DDMVAC with growth factor support (category 1)(^2,8)</td>
</tr>
<tr>
<td><strong>Cisplatin ineligible</strong></td>
</tr>
<tr>
<td>Preferred regimens</td>
</tr>
<tr>
<td>• Gemcitabine and carboplatin(^11)</td>
</tr>
<tr>
<td>• Atezolizumab(^12) (only for patients whose tumors express PD-L1(^a) or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
<tr>
<td>• Pembrolizumab(^13) (only for patients whose tumors express PD-L1(^b) or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression)</td>
</tr>
<tr>
<td><strong>Other recommended regimens</strong></td>
</tr>
<tr>
<td>• Gemcitabine(^14)</td>
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<tr>
<td>• Gemcitabine and paclitaxel(^15)</td>
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<tr>
<td><strong>Useful under certain circumstances</strong></td>
</tr>
<tr>
<td>• Ifosfamide, doxorubicin, and gemcitabine(^16) (for patients with good kidney function and good PS)</td>
</tr>
</tbody>
</table>

\(^a\) Atezolizumab: PD-L1 stained tumor-infiltrating immune cells covering ≥ 5% of the tumor area.

**Continued**

Regional lymph node metastasis in the true pelvis\(^3\) (perivesical, obturator, internal and external iliac, or sacral lymph node) (see BL-5, page 1043).

The decision to group N1 lymph node metastasis with T3–T4a,N0 disease was based on studies showing that patients with N1 bladder cancer tend to have a better prognosis than those with more extensive lymph node involvement and/or distant metastasis.\(^5-10\) In addition, research has shown that these patients tend to benefit from more aggressive treatment (eg, cystectomy or bladder preservation with chemoradiotherapy [CRT]), with some showing long-term survival or cure following primary treatment.\(^10-13\)

The recommended primary treatment approach for most patients with stage IIIA disease is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and pelvic lymphadenectomy.\(^14-17\) If neoadjuvant cisplatin-based chemotherapy is not given, postoperative adjuvant chemotherapy may be considered based on pathologic risk, such as positive nodes or pT3–T4 lesions.\(^18\) Adjuvant RT, alone or in combination with chemotherapy, is another option.\(^19\)

Many patients with stage IIIA disease are candidates for bladder preservation; in these patients, maximal transurethral resection of the bladder tumor (TURBT) followed by concurrent CRT may be considered.\(^20-25\) Optimal candidates for this bladder-sparing approach include patients with tumors that present without hydronephrosis and/or allow a visibly complete or a maximally debulking TURBT. RT with concurrent cisplatin-based chemotherapy or 5-FU + mitomycin as a radiosensitizer is the most common and well-studied CRT method used to treat MIBC.\(^20,21,26-31\) The following radiosensitizing regimens are recommended: cisplatin/5-FU, cisplatin/paclitaxel, 5-FU/mitomycin C, and cisplatin alone; doublet chemotherapy is generally preferred. Low-dose gemcitabine (category 2B) may be considered as an alternative regimen.
For bladder preservation, overall tumor status should be reassessed 2 to 3 months after completion of treatment. If no residual tumor is detected, observation is appropriate. If disease is present, further treatment should be pursued. The NCCN Panel added additional treatment options for tumors detected after bladder preservation, depending on the site of residual disease. Residual disease that is confined to the bladder may be surgically consolidated, or alternatively, intravesical bacillus Calmette-Guérin (BCG) may be considered for Tis, Ta, or T1 disease. For residual disease present in the lymph nodes or if new sites of metastatic disease are identified, treatment is the same as for metastatic (stage IVB) disease.

For patients with extensive comorbid disease or a poor performance status who are noncystectomy candidates, treatment options include concurrent CRT or RT alone. Based on high-level evidence showing its superiority to RT alone, the panel recommends CRT.\(^{26,28}\) Overall tumor status should be reassessed 2 to 3 months after treatment. If no tumor is evident after RT, the patient should be observed. If tumor is observed, chemotherapy, palliative TURBT, or best supportive care may be given.

### Treatment of Stage IIIIB Tumors

The 8th edition of the AJCC Cancer Staging Manual defines stage IIIIB bladder cancer as T1–T4a with multiple regional lymph node metastases in the true pelvis (perivesical, obturator, internal and external iliac, or sacral lymph node) or lymph node metastasis to the common iliac nodes.\(^3\) In discussing appropriate treatment options, panel members mentioned that treatment of stage IIIIB bladder cancer is not based on strong data, because there is a lack of prospective randomized trials defining how to best treat these patients. Some population-based studies have shown that downstaging chemotherapy or CRT can be effective for patients with node-positive bladder cancer\(^{32,33}\) (see BL-6, page 1044).
A population-based study of 659 patients with cT1–T4a, node-positive urothelial bladder cancer tested the effectiveness of induction chemotherapy for pathologic downstaging.\(^\text{33}\) For cN1 disease, pathologic downstaging was achieved in 39% of patients who received induction chemotherapy compared with 5% who did not. For cN2–3, the rate of pathologic downstaging was 27% versus 3% for these 2 groups. Overall survival (OS) was also improved in patients who received induction chemotherapy (\(P<.001\)), although the nature of the study limits interpretation of the OS results.\(^\text{33}\) Another study used the National Cancer Database to analyze outcomes of 1,783 patients with clinically node-positive bladder cancer treated with chemotherapy alone (\(n=1,388\)) or CRT (\(n=395\)).\(^\text{32}\) Study results demonstrated that patients treated with CRT had a higher median OS than those treated with chemotherapy (19.0 vs 13.8 months; \(P<.001\)). The improvement in outcome with CRT persisted on evaluation of propensity-matched populations (\(P<.001\)).\(^\text{32}\)

Based on the limited available data, as well as their experiences in clinical practice, the NCCN Panel members decided it would be appropriate to develop a new algorithm page for treatment of stage IIIB bladder cancer. Most panel members indicated that they would use either downstaging systemic therapy or concurrent CRT for primary treatment in patients able to tolerate such therapy. Panel members stressed that subsequent disease management depends on response to primary treatment and—because data to guide subsequent disease management are extremely limited—several different treatment modalities are commonly used in this setting. The panel agreed that choice of subsequent treatment would be made on a case-by-case basis and is often discussed in a multidisciplinary setting at their institutions.

Patients who showed a complete response to primary therapy may be subsequently observed or, in the case of primary downstaging systemic therapy, may undergo consolidation cystectomy or CRT. Those who achieved a partial response to primary therapy may undergo surgical consolidation of residual disease or, if eligible, treatment with CRT or other local therapy options (eg, intravesical BCG for Tis, Ta, or T1 residual disease). If metastatic residual disease is present or disease progression was noted after primary treatment, treatment should be the same as for metastatic disease, often with systemic therapy. Stable disease may be treated as either partial response or progression, depending on patient characteristics and preference of the treating physician.

### Treatment of Stage IVA Tumors

Stage IVA includes patients with an extravascular tumor invading the pelvic and/or abdominal wall but no lymph node or distant metastases (cT4b, any N, M0), or patients with distant metastasis limited to lymph nodes beyond the common iliacs (any T, any N, M1a).\(^\text{3}\) Panel members described these patients as being in a good prognostic risk category within stage IV disease. Therefore, treatment options are broader than those for patients with stage IVB disease (M1b, non–lymph node distant metastases), but narrower than those for patients with stage III disease (see BL-7, page 1045).

For patients with stage IVA disease, treatment options differ depending on the presence of lymph node metastases beyond the common iliacs (M0 vs M1a). Primary treatment recommendations for patients with stage IV M0 disease include systemic therapy or concurrent CRT followed by evaluation with cystoscopy, examination under anesthesia (EUA), TURBT, and imaging of the abdomen, pelvis, and chest. If no evidence of tumor is present after initial treatment, consolidation systemic therapy or completion of definitive RT may be considered. If a partial radiation dose of 40 to 45 Gy was given as primary treatment, completion of definitive RT is recommended. Alternatively, adjuvant treatment with CRT may be initiated if the patient did not receive prior RT.

If residual disease is noted on evaluation after primary therapy, systemic therapy or cystectomy is recommended. Systemic therapy may include an ICI, CRT (if no prior RT), or chemotherapy. Cystectomy may be an option if the tumor exhibits a favorable response to upfront systemic therapy, with an anticipated complete resection with negative surgical margins, and the bladder is the only site of residual disease.

Patients with M1a disease should receive systemic therapy, or consideration of CRT in select patients. Those select patients with metastatic disease treated with curative intent should be evaluated with cystoscopy, EUA, TURBT, and abdominal/pelvic/chest imaging. If a complete response is noted after primary treatment of metastatic disease, these
patients may receive more aggressive or completion local therapy, such as a radiation boost or a cystectomy. If the disease remains stable or progresses after primary therapy, treatment should follow recommendations for recurrent or persistent disease.

**Treatment of Metastatic (Stage IVB) Tumors**

Approximately 4% of patients have metastatic disease at the time of diagnosis. Additionally, approximately half of all patients experience disease relapse after cystectomy, depending on the pathologic stage of the tumor and nodal status. Local recurrences account for approximately 10% to 30% of relapses, whereas distant metastases are more common.

Platinum-based chemotherapy has been standard of care in patients with metastatic disease, with an OS of 9 to 15 months. However, in patients with disease that relapses after platinum-based chemotherapy, median survival is reduced to 5 to 7 months. Several new agents, notably ICIs for the treatment of metastatic urothelial carcinoma, have resulted in improved patient outcomes compared with standard therapies in the post-platinum setting. To better define optimal use of the agents recommended in the guideline, the panel assigned NCCN Categories of Preference to the systemic therapy options.

**First-Line Therapy**

First-line systemic therapy regimens recommended for patients with metastatic bladder cancer depend on the presence or absence of medical comorbidities, such as cardiac disease and renal dysfunction, and the risk classification of the patient based on disease extent. Regimens with lower toxicity profiles are recommended for patients with compromised liver or renal status or serious comorbid conditions. Gemcitabine/cisplatin (GC), doxorubicin/cisplatin (ddMVAC) with growth factor support, or dose-dense methotrexate/vinblastine/carboplatin (methotrexate/carboplatin/vinblastine. However, among patients who were unfit and had renal impairment (glomerular filtration rate, <60 mL/min), response rates decreased to 26% and 20%, respectively, with increased toxicity.

The 2017 accelerated FDA approvals of 2 ICIs—atezolizumab (a PD-L1 inhibitor) and pembrolizumab (a PD-1 inhibitor)—for first-line treatment of cisplatin-ineligible patients expanded the therapy options for these patients. The 2-cohort, multicenter, phase II IMvigor 210 trial evaluated atezolizumab in patients with metastatic disease. In cohort 1, atezolizumab was evaluated as a first-line therapy in 119 patients with locally advanced or metastatic urothelial carcinoma ineligible for cisplatin. Data from this cohort showed an objective response rate of 23%, with 9% of patients showing a complete response. Median OS was 15.9 months. Grade 3 or 4 treatment-related adverse events (AEs) occurred in 16% of patients.

The single-arm phase II KEYNOTE-052 trial evaluated pembrolizumab as a first-line therapy in 370 patients with advanced urothelial carcinoma who were ineligible for cisplatin-based therapy. Data from this study showed an overall response rate of 24%, with 5% of patients achieving a complete response. Grade ≥3 treatment-related AEs occurred in 16% of patients treated with pembrolizumab at the time of data cutoff.

In May 2018, the FDA issued a safety alert for the use of first-line atezolizumab and pembrolizumab, which warned that early reviews of data from 2 ongoing clinical trials (IMvigor 130 and KEYNOTE-361) showed decreased survival in patients with low PD-L1 expression receiving atezolizumab or pembrolizumab as first-line monotherapy compared with cisplatin- or carboplatin-based therapy. Based on these data, prescribing information for atezolizumab and pembrolizumab was amended in June 2018 to restrict first-line use to patients who are either (1) not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1, or (2) not eligible for any platinum-containing chemotherapy regardless of PD-L1 status. Measurement of PD-L1 expression is specific to the agent used, with PD-L1 expression defined as PD-L1–stained tumor-infiltrating immune cells covering at least 5% of the tumor area for atezolizumab and a combined positive score of at least 10 for pembrolizumab.
Panel members discussed the implication of the safety alert and changes to the FDA-approved indications for first-line use of these ICIs. At the time of guideline update, the primary data prompting the changes were not yet available for public review. Although the panel agreed it was difficult to fully understand the ramifications without seeing the data, most felt that the NCCN Guidelines should match the FDA-approved indications in this situation. The panel will reevaluate the guideline recommendations for the first-line setting after the data become available for review.

Based on results of the IMvigor 210 and KEY-NOTE-052 trials, and the subsequent revisions to the FDA labels, atezolizumab and pembrolizumab were added as preferred first-line systemic therapy options for patients not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1, or in those not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression. Gemcitabine/carboplatin remains another preferred option for these patients (see BL-G 2 of 5, page 1046).

**Second- and Subsequent-Line Therapy**

Based on approvals for ICIs in the first-line setting, the panel subdivided the subsequent-line setting to recommend therapies based on whether they are given after a platinum-containing regimen or an ICI. FDA approval of 5 ICIs in the post-platinum setting expanded the treatment options for these patients. These approvals for urothelial carcinoma have not required documentation of increased PD-L1 expression levels and, with the exception of post-platinum pembrolizumab, have been accelerated approvals.

The open-label, randomized, phase III KEY-NOTE-045 trial compared pembrolizumab and chemotherapy (paclitaxel, docetaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma that recurred or progressed after platinum-based chemotherapy. Data from this trial showed a longer median OS in patients treated with pembrolizumab compared with chemotherapy (10.3 vs 7.4 months; \( P = .002 \)). In addition, fewer grade ≥3 treatment-related AEs occurred in those treated with pembrolizumab compared with chemotherapy (15.0% vs 49.4%).

Results from this trial led the NCCN Panel to assign pembrolizumab a category 1 recommendation as a second-line therapy. In addition, because it was the only ICI in this setting to show an OS benefit in a randomized study at the time of the 2018 panel meeting, the panel designated pembrolizumab as the preferred post-platinum subsequent-line therapy.

Cohort 2 of the IMvigor 210 trial enrolled 310 patients with metastatic urothelial carcinoma after platinum treatment and showed a significantly improved overall response rate compared with historical controls (15% vs 10%; \( P = .0058 \)), and durable responses. Further, durable responses were noted with responses ongoing in 38 of 45 responders (84%) after a median follow-up of 11.7 months.

The multicenter, randomized, controlled, phase III IMvigor 211 study compared atezolizumab and chemotherapy (vinflunine, paclitaxel, or docetaxel) in 931 patients with locally advanced or metastatic urothelial carcinoma after progression with platinum-based chemotherapy.\(^4^4\) The primary end point of this study, median OS in patients with high (IC2/3) PD-L1 expression levels (n=234), showed no significant difference between atezolizumab and chemotherapy (11.1 vs 10.6 months; \( P = .41 \)). Likewise, confirmed objective response rates were similar between the atezolizumab and chemotherapy groups (23% vs 22%). Although atezolizumab was not associated with significantly longer OS compared with chemotherapy, its safety profile was favorable, with 20% of patients experiencing grade 3 or 4 AEs versus 43% with chemotherapy. Atezolizumab was also associated with a longer duration of response, including durable response, consistent with observations in the previous phase II study.\(^4^5\) Based on these data, the panel designated atezolizumab as an alternative preferred subsequent-line therapy option in the post-platinum setting.

In addition to pembrolizumab and atezolizumab, nivolumab (a PD-1 inhibitor), durvalumab, and avelumab (both PD-L1 inhibitors) have been approved for the treatment of locally advanced or metastatic urothelial cell carcinoma that has progressed during or after platinum-based chemotherapy, or that has progressed within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. These agents have all shown favorable efficacy and safety results in phase I and/or II trials, but do not yet have reported phase III results.\(^4^5^–^5^0\) Based on the promising phase I/II results and the lack of phase III data, the panel designated nivolumab, durvalumab, and avelumab as alterna-
Bladder Cancer, Version 5.2018

tive preferred subsequent-line therapy options in the post-platinum setting. The panel’s preference of these agents and their assigned category of evidence and consensus may be reconsidered after publication of phase III data.

The value of ICIs is reflected in the unanimous decision by the NCCN Panel to include pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab as second-line systemic therapy options after platinum-based therapy (and for atezolizumab and pembrolizumab, as first-line therapy options for patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 or in those not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) for locally advanced or metastatic disease. With the exception of pembrolizumab as a subsequent treatment option (category 1), the use of ICIs are all category 2A recommendations (see BL-G 3 of 5, page 1047).

Conclusions

Recent medical advances have brought new treatment options to patients with MIBC and/or metastatic bladder cancer, thereby increasing survival and/or improving the quality of life of these patients. Recent updates to the AJCC Cancer Staging Manual prompted the NCCN Bladder Cancer Panel to revisit treatment approaches for patients with node-positive MIBC, leading to a substantial redrawing of the algorithm pages and expanded treatment options for many patients in this category. Likewise, the recent FDA approvals of several ICIs for the treatment of advanced or metastatic urothelial carcinoma in the first-line, non–cisplatin-eligible, and post-platinum settings have expanded treatment options for patients with metastatic bladder cancer. To help guide optimal use of these new agents, the panel members assigned NCCN Categories of Preference to the systemic therapy regimens recommended in the guideline.

References


Bladder Cancer, Version 5.2018

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Posttest Questions

1. True/False: Based on the updated 8th edition of the AJCC Cancer Staging Manual, any lymph node metastases group a patient with bladder cancer within stage IV disease.

2. Which of the following systemic therapies are recommended for first-line treatment of locally advanced or metastatic bladder cancer in patients not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1, or in those not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression?
   a. Nivolumab
   b. Pembrolizumab
   c. Atezolizumab
   d. Both a and b
   e. Both b and c
   f. a, b, and c

3. Which of the following systemic therapies has phase III trial data showing an OS benefit for patients with locally advanced or metastatic bladder cancer that recurred or progressed after platinum-containing chemotherapy, leading to a category 1 preferred recommendation in the NCCN Guidelines?
   a. Atezolizumab
   b. Avelumab
   c. Durvalumab
   d. Nivolumab
   e. Pembrolizumab