Exhibit 248

NCCN Continuing Education

Target Audience: This journal article is designed to meet the educational needs of oncologists, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

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Release date: May 10, 2024; Expiration date: May 10, 2025

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

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

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Tyler Stewart, MD, Panel Member, has disclosed serving as a scientific advisor to Astellas Pharma US, Inc., AstraZeneca Pharmaceuticals LP, Pfizer Inc., and SeaGen; and receiving grant/research support from GRAIL.

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Bladder Cancer, Version 3.2024
Featured Updates to the NCCN Guidelines

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Abstract

Bladder cancer, the sixth most common cancer in the United States, is most commonly of the urothelial carcinoma histologic subtype. The clinical spectrum of bladder cancer is divided into 3 categories that differ in prognosis, management, and therapeutic aims: (1) non–muscle-invasive bladder cancer (NMIBC); (2) muscle invasive, nonmetastatic disease; and (3) metastatic bladder cancer. These NCCN Guidelines Insights detail recent updates to the NCCN Guidelines for Bladder Cancer, including changes in the fifth edition of the *WHO Classification of Tumours: Urinary and Male Genital Tumours* and how the NCCN Guidelines aligned with these updates; new and emerging treatment options for bacillus Calmette-Guérin (BCG)–unresponsive NMIBC; and updates to systemic therapy recommendations for advanced or metastatic disease.

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Overview

An estimated 83,190 new cases of urinary bladder cancer (63,070 males and 20,120 females) will be diagnosed in the United States in 2024, with approximately 16,840 deaths (12,290 males and 4,550 females) occurring during this same period.[1] 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[2] and the associated risk factors, comorbid medical conditions are a frequent consideration in patient management.

Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain medications, chronic infection or irritation of the urinary tract, and certain medical conditions, including obesity and diabetes.[3–6] Although diabetes mellitus appears to be associated with an elevated risk of developing bladder cancer,[4] treatment with metformin may be associated with improved prognosis in patients with bladder cancer and diabetes.[7] Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma.[8]

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), comprising approximately 75% of newly detected cases,[9] for which treatment is directed at reducing recurrences and preventing progression to a more advanced stage, while minimizing adverse events (AEs) related to treatment. The second group encompasses muscle-invasive, nonmetastatic disease. Unlike NMIBC, muscle-invasive disease poses a much greater risk for progression and requires more aggressive therapy, often a multidisciplinary approach including a combination of systemic therapy, surgery, and/or radiation. The critical concern for the third group, consisting of metastatic lesions, is how to prolong survival and maintain quality of life. Numerous agents with different mechanisms of action have antitumor effects on this disease. The goal is to use these agents to increase survival and quality of life.

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The full and most current version of these NCCN Guidelines is available at NCCN.org.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

NCCN CATEGORIES OF PREFERENCE

Preferred intervention: Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention: Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances: Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Guidelines® are a statement of evidence and 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.

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

Updates to Bladder Cancer Histology and Principles of Pathology

Urothelial (transitional cell) carcinoma is the most common histologic subtype of bladder cancer in the United States and Europe and may develop anywhere urothelium is present, from the renal pelvis to the ureter, bladder, and proximal two-thirds of the urethra.[10] Anatomically, >90% of urothelial tumors originate in the urinary bladder, 8% originate in the renal pelvis, and the remaining 2% originate in the ureter and urethra. Urothelial carcinomas are classified as low-grade or high-grade as defined by the extent of cytologic and architectural atypia. Non–muscle-invasive urothelial tumors may have flat and/or papillary histology. Flat urothelial lesions may be classified as urothelial carcinoma in situ (CIS), a type of high-grade noninvasive urothelial carcinoma. The term *urothelial dysplasia* may be used in rare circumstances in which the morphologic features fall short for a diagnosis of CIS. Papillary lesions may be benign (ie, urothelial papilloma, inverted papilloma) or malignant. The latter group includes papillary urothelial neoplasms of low malignant potential (PUNLMP) and papillary urothelial carcinoma (low- and high-grade). In some cases, a Ta or T1 NMIBC will have an associated urothelial CIS component.

The fifth edition of the *WHO Classification of Tumours: Urinary and Male Genital Tumours* was published in November 2022, and included several changes to the classification of urinary tract tumors.[11,12] One major change was the adoption of a modified terminology where the designation of "subtype" was adopted to replace "variant" histology when referring to distinct morphologic categories within a given tumor type. The reasoning behind this change is that the term "variant" has increasingly been used to describe genomic rather than morphologic alterations, and therefore the WHO Classification system reserves "variant" for this purpose to avoid confusion. The presence of histologic subtypes of urothelial carcinoma are important to document, because data suggest that the subtype may help define the natural history and inherent risk of progression, reflect different genetic etiology, and subsequently determine whether a more aggressive treatment approach should be considered (see section on "Bladder Cancer: Non-Urothelial and Urothelial With Subtype Histology" in the full version of these NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines], available at NCCN.org).[13–15] In addition, the 2022 WHO Classification update provided new information on the grading of invasive urothelial carcinomas, as well as noninvasive urothelial neoplasms, and the definition of precursor lesions.[16]

In response to the revisions in the 2022 WHO Classification of Tumours of the Urothelial Tract, the change from "variant" to "subtype" histology when describing morphologic categories within a tumor type has been adopted throughout the NCCN Guidelines for Bladder Cancer. The NCCN Guidelines also updated the list of invasive urothelial carcinoma and noninvasive urothelial neoplasm subtypes according to the 2022 WHO Classification (see Figure 1). In addition, the Principles of Pathology Management have been updated to better detail items that should be included in a pathology report for biopsy, TURBT, or cystectomy specimens (see BL-C 2 of 2 in the full version of these guidelines, available online at NCCN.org).

Treatment of BCG-Unresponsive or BCG-Intolerant NMIBC

Following transurethral resection of the bladder tumor (TURBT), treatment of nonmuscle invasive disease is stratified based on the American Urological Association (AUA) risk group[17] and often includes intravesical therapy or, for those at particularly high risk, cystectomy (for information on AUA risk stratification, see BL-2 in the full version of these guidelines at NCCN.org). Intravesical therapy is implemented to reduce recurrence or delay progression of bladder cancer to a higher grade or stage. Although intravesical chemotherapy, often using mitomycin C or gemcitabine, is an option for intermediate-risk disease, intravesical treatment with BCG is recommended as first-line treatment of high-risk NMIBC.

Induction BCG has been shown to decrease the risk of bladder cancer recurrence following TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full reevaluation at week 12 (ie, 3 months) after the start of therapy.[18] Several meta-analyses demonstrate that BCG after TURBT is superior to TURBT alone or TURBT and chemotherapy in preventing recurrences of high-grade Ta and T1 tumors.[19–22] A meta-analysis including 9 trials of 2,820

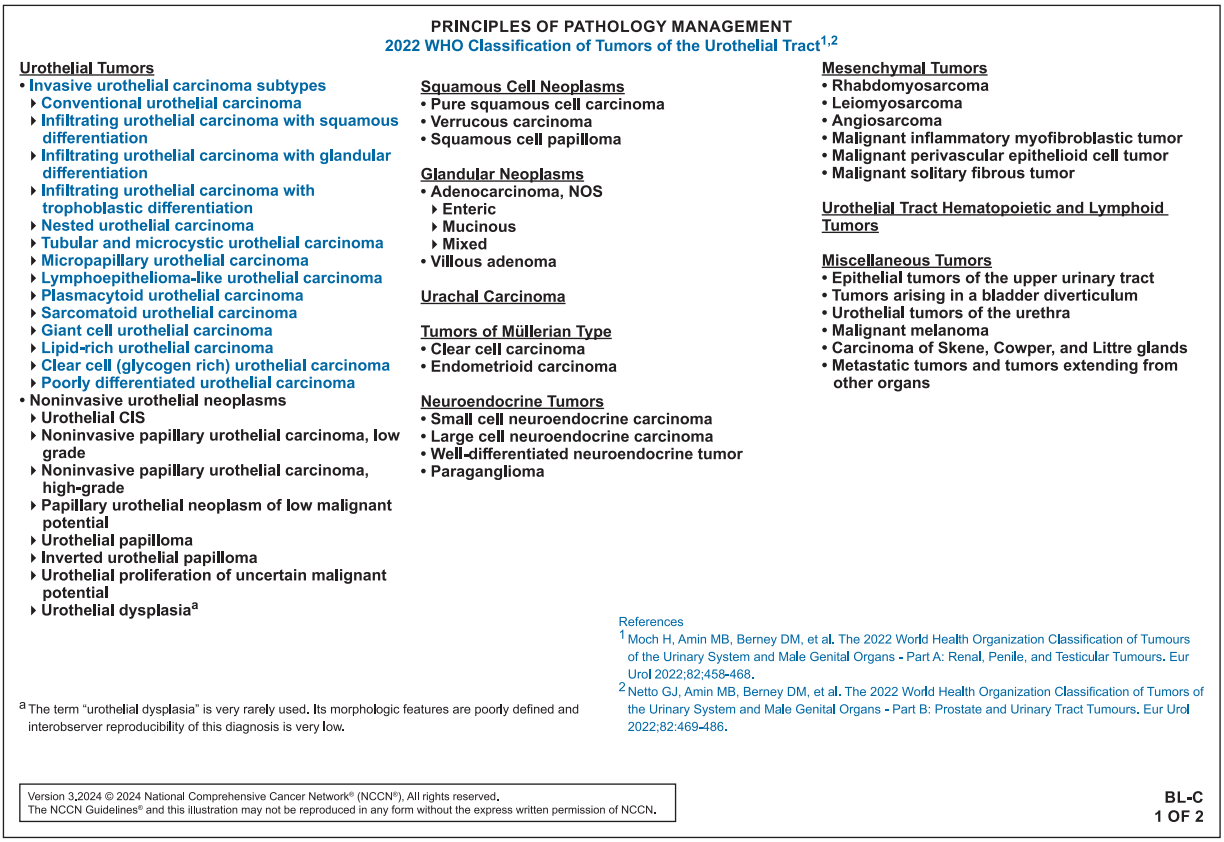


Figure 1. BL-C 1 of 2. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 3.2024.

patients with NMIBC reported that mitomycin C was superior to BCG without maintenance in preventing recurrence, but inferior to BCG in trials using BCG maintenance.[23] Using the SEER database, a reduction in mortality of 23% was reported in patients receiving BCG therapy.[24] Other studies have also reported that BCG was better at reducing recurrence in intermediate- and high-risk NMIBC when compared with mitomycin C.[25,26] An ongoing shortage of BCG has existed in the United States, necessitating development of strategies to prioritize use of intravesical BCG and identify alternative treatment approaches for some patients with NMIBC.[27] See the full guidelines at NCCN.org for strategies to help alleviate problems associated with this shortage.

For some patients, BCG is not an option due to side effects or a BCG-resistant tumor. BCG induces a systemic, nonspecific, immunostimulatory response leading to secretion of proinflammatory cytokines. This causes patients to experience flu-like symptoms that may last 48 to 72 hours.[28] Installation of BCG into the bladder also can mimic a urinary tract infection and may produce intense local discomfort. Dysuria has been reported in 60% of patients in clinical trials.[28] The side effects of treatment have translated to discontinuation of BCG therapy. However, the side effects are treatable in almost all cases[29] and no increase in toxicity has been reported with cumulative doses. For patients in whom BCG is not effective due to intolerance or resistance, cystectomy is preferred, although other intravesical chemotherapy (eg, sequential gemcitabine and docetaxel), nadofaragene firadenovec, or systemic pembrolizumab are other options. Although pembrolizumab and nadofaragene firadenovec are newer options in this setting, several panel members noted that use of these agents is limited in their own clinical practice based on a lack of enthusiasm for the efficacy data that are available and the perception that cystectomy or a change in intravesical therapy are better options for these patients. There have also been notable issues with availability and affordability for nadofaragene firadenovec that have limited use of this agent among panel members. In addition, this setting is an active area of investigation, and multiple experimental agents for treatment of BCG-unresponsive, high-risk NMIBC are currently in clinical trials that may change the treatment landscape in the coming years.

Pembrolizumab for NMIBC

Pembrolizumab is a PD-1 inhibitor that has been evaluated as systemic therapy for BCG-unresponsive, NMIBC with CIS in the single-arm, phase II KEYNOTE-057 study (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma, as detailed in the full guidelines at NCCN.org). In the KEYNOTE-057 study, 101 patients with high-risk CIS, with or without papillary tumor, who received previous BCG therapy and were either unable or unwilling to undergo cystectomy were treated with pembrolizumab[30]; 96 patients were eligible for inclusion in the efficacy analysis. The 12-month complete response (CR) rate was 19% (18 of 96 total patients on the study), and the median duration of response (DoR) from time of onset was 16.2 months (95% CI, 6.7–36.2). Grade ≥3 treatment-related AEs (trAEs) were reported in 13% of patients, with arthralgia and hyponatremia being the most common. Serious trAEs occurred in 8% of patients.

The NCCN panel considers pembrolizumab as an option for select patients with BCG-unresponsive or -intolerant, high-risk NMIBC (see Figure 2). Specifically, pembrolizumab may be considered for patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors as a category 2A recommendation. In addition, pembrolizumab may also be considered for patients with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS as a category 2B recommendation. Although this second recommendation does not fall within the FDA-approved indication for pembrolizumab, it is supported by clinical trial evidence. Cohort B of the KEYNOTE-057 study included 132 patients with high-risk, BCG-unresponsive NMIBC with high-grade Ta or any-grade T1 papillary tumors (without CIS). An abstract presented at the 2023 ASCO Genitourinary Cancers Symposium reported efficacy data after a median follow-up of 45.4 months.[31] Median high-risk disease-free survival (DFS) was 7.7 months and progression-free survival (PFS) to worsening of grade, stage, or death was 44.5 months. Thirty-one patients (23.5%) underwent radical cystectomy after discontinuation of pembrolizumab. Twelve-month overall survival (OS) was 96.2%. However, the more limited data for this setting is reflected in the category 2B designation given by the panel.

Nadofaragene Firadenovec-vncg

Nadofaragene firadenovec is a nonreplicating adenoviral vector-based gene therapy that is indicated for the treatment of patients with high-risk, BCG-unresponsive NMIBC with CIS, with or without papillary tumors. A phase III open-label, multicenter study evaluated nadofaragene firadenovec in 157 patients with BCG-unresponsive NMIBC.[32] Of the 103 patients on the study with CIS, with or without a high-grade Ta or T1 tumor, 25 remained free of high-grade recurrence at 12 months (24.3% 12-month CR rate; 95% CI, 16.4–33.7). Urinary urgency was the most common grade ≥3 trAE (1% of patients). A longer-term follow-up from this same cohort of patients was reported in an abstract presented at the 2021 AUA Annual Meeting, with a mean follow-up of 23.5 months.[33] Twenty-four months after the first dose, 19.4% of patients remained free of high-grade recurrence, with a median duration of high-grade recurrence-free survival of 12.2 months. Of the 55 patients who achieved a CR, 20 (36.4%) remained free of high-grade recurrence at 24 months. By 24 months, cystectomy-free survival was 64.6% and OS was 94.4%. The most common drug-related AEs were instillation site discharge (24.3%), fatigue (23.4%), bladder spasm (17.8%), and urinary urgency (16.8%), with most AEs being grades 1 to 2. Two patients discontinued treatment due to drug-related AEs.

The same phase III trial included a second cohort of 48 patients with BCG-unresponsive NMIBC with high-grade Ta/T1 tumors only. Another abstract presented at the 2021 AUA Annual Meeting reported on 2-year follow-up results from this cohort.[34] Of the 48 patients in this cohort, 72.9%, 43.8%, and 33.3% were high-grade recurrence-free at 3, 12, and 24 months, respectively. Of those who were free of high-grade recurrence at 3 months, 45.7% were high-grade recurrence-free at 24 months, with a median duration of high-grade recurrence-free survival of

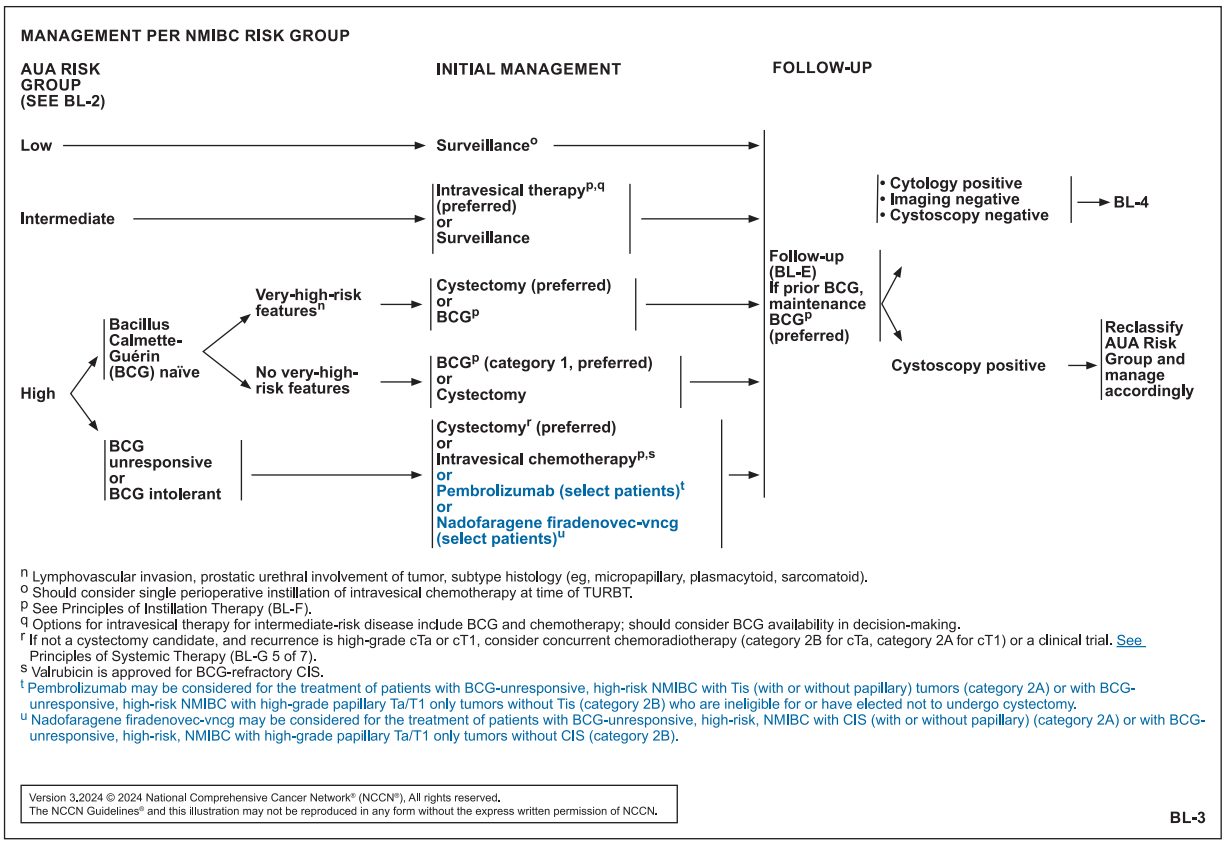


Figure 2. BL-3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 3.2024.

19.8 months. As estimated at 24 months, cystectomy-free survival was 69.8% and OS was 93.2%.

The NCCN panel considers nadofaragene firadenovec as an option for select patients with BCG-unresponsive or -intolerant, high-risk NMIBC (see Figure 2). Specifically, this agent may be considered for patients with BCG-unresponsive, high-risk NMIBC with CIS (with or without papillary) tumors as a category 2A recommendation or those with BCG-unresponsive, high-risk NMIBC with high-grade papillary Ta/T1 only tumors without CIS as a category 2B recommendation. Although this second recommendation does not fall within the FDA-approved indication for nadofaragene firadenovec, it is supported by clinical trial evidence, as detailed earlier. The NCCN panel intentionally mirrored the recommendations for nadofaragene firadenovec and pembrolizumab because they felt that the 2 agents would be considered under similar circumstances and the data for the agents was similar in this setting.

Investigational Agents for BCG-Unresponsive NMIBC

Several investigational agents are currently in clinical trials for treatment of BCG-unresponsive NMIBC. TAR-200 is an intravesical drug delivery system that is designed to provide sustained local release of gemcitabine to the bladder. It is currently being investigated for treatment of BCG-unresponsive NMIBC in the phase IIb SunRISe-1[35] and the phase III SunRISe-3 trials. TAR-200 received a breakthrough therapy designation from the FDA in December 2023 for patients with BCG-unresponsive high-risk NMIBC who are ineligible for or elected not to undergo radical cystectomy. Cretostimogene grenadenorepvec (CG0700) is a selective oncolytic adenovirus that has been studied both alone and in combination with pembrolizumab for treatment of BCG-unresponsive NMIBC. CG0700 is being studied as a monotherapy in the phase II BOND2 trial[36] and in combination with pembrolizumab in the phase II CORE1 study.[37] N-803 is an immune cell-activating IL-15 superagonist that is being studied in combination with BCG in the phase II/III QUILT-3.032 study.[38] Although the FDA previously declined to approve N-803 in combination with BCG in May 2023, it has since accepted the resubmission of a biologics license application for the combination, which was still under review at the time of writing.

While the panel eagerly awaits further data on these agents as well as others that are actively being investigated in this setting, these agents are not recommended in the NCCN Guidelines at this time.

Systemic Therapies for Locally Advanced or Metastatic Urothelial Carcinoma

Approximately 5% of patients with bladder cancer have metastatic disease at the time of diagnosis.[2] Additionally, approximately half of all patients experience 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. The NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted early, ideally at diagnosis of advanced bladder cancer, to facilitate treatment decision-making and to prevent delays in administering later lines of therapy. In addition to determining eligibility for FDA-approved therapies, molecular/genomic testing may be used to screen for clinical trial eligibility.

The mainstay of treatment for metastatic urothelial bladder cancer is systemic therapy, although palliative radiotherapy may be an option for some patients.

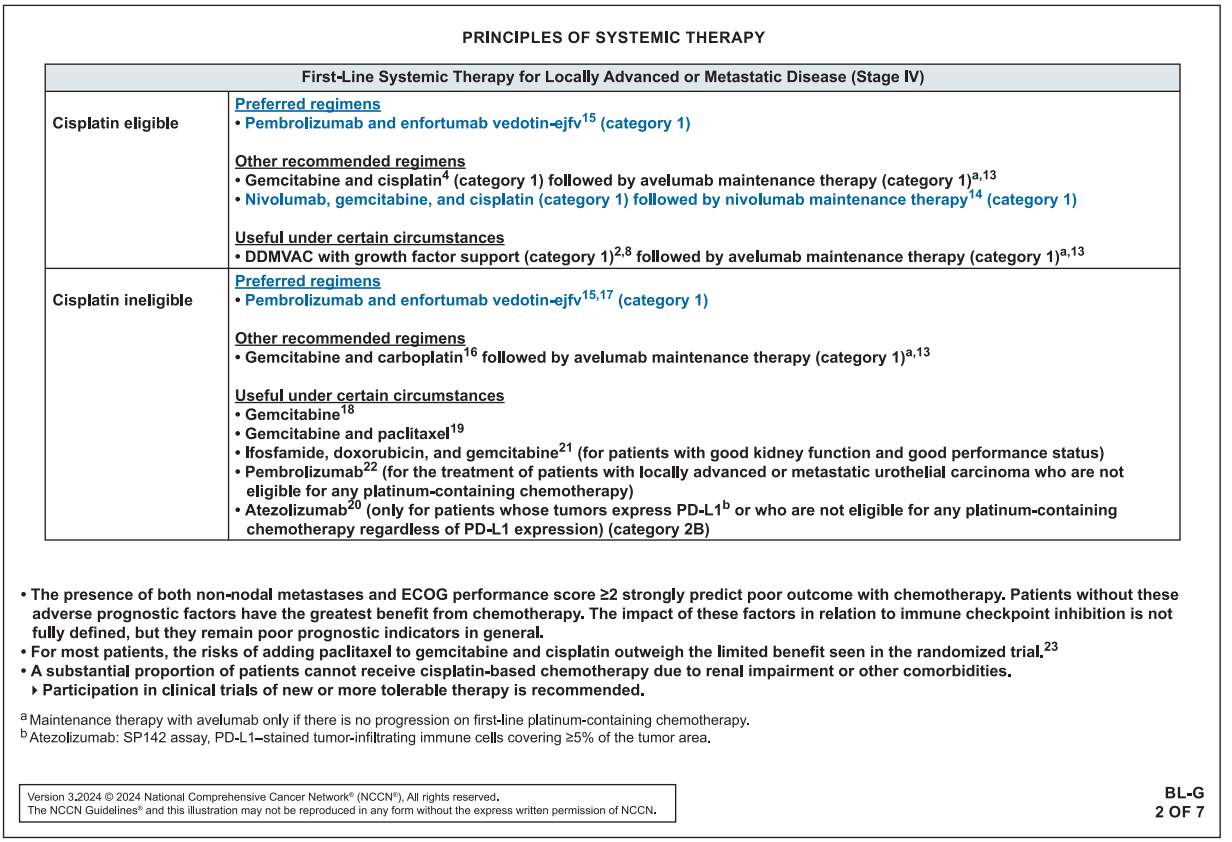
The specific systemic therapy regimen recommended partially depends on the presence or absence of medical comorbidities, such as cardiac disease, autoimmune disease, peripheral neuropathy, diabetes, and renal dysfunction, along with the risk classification of the patient based on disease extent. In general, long-term survival with combination platinum-based chemotherapy has been reported only in patients with lower-risk disease, defined as those with good performance status, no visceral (ie, liver, lung) nor bone disease, and normal alkaline phosphatase or lactic dehydrogenase levels. Patients with higher-risk disease, defined as those with poor performance status or visceral disease, have consistently shown higher discontinuation rates with multiagent platinum-based combination chemotherapy regimens and few complete remissions, which are prerequisites for cure. An assessment of clinical application is currently underway to better determine how "platinum-ineligible" may be defined.[39,40] Newer agents with generally improved toxicity profiles, such as the immune checkpoint inhibitors (ICIs), antibody–drug conjugates, and targeted therapies, provide other treatment options for these patients who are not candidates for cisplatin-based chemotherapy. This section will detail some of the recent systemic therapy updates for metastatic urothelial cancer in the NCCN Guidelines for Bladder Cancer.

Updates in First-Line Systemic Therapy for Metastatic Disease

Pembrolizumab + Enfortumab Vedotin-ejfv

A combination of the ICI pembrolizumab with the antibody–drug conjugate enfortumab vedotin was investigated in the phase III EV-302 trial, which randomized 886 patients with previously untreated locally advanced or metastatic urothelial carcinoma to either enfortumab vedotin + pembrolizumab or gemcitabine in combination with either cisplatin or carboplatin.[41] After a median follow-up of 17.2 months, median PFS was significantly longer with enfortumab vedotin + pembrolizumab compared with chemotherapy (12.5 vs 6.3 months; hazard ratio [HR], 0.45; 95% CI, 0.38–0.54; $P<.001$). Median OS was also significantly longer with enfortumab vedotin + pembrolizumab (31.5 vs 16.1 months; HR, 0.47; 95% CI, 0.38–0.58; $P<.001$). Confirmed overall response rate (ORR) was 67.7% and 44.4% for enfortumab vedotin plus pembrolizumab and chemotherapy, respectively ($P<.001$), with CRs observed in 29.1% of patients in the enfortumab vedotin + pembrolizumab group and 12.5% of those in the chemotherapy group. Grade ≥3 trAEs occurred in 55.9% of patients receiving enfortumab vedotin + pembrolizumab and 69.5% of those receiving chemotherapy. These results have led to the FDA approval of enfortumab vedotin in combination with pembrolizumab for the treatment of adult patients with locally advanced or metastatic urothelial cancer, regardless of cisplatin eligibility.

Based on these results, the combination of pembrolizumab and enfortumab vedotin was added to the NCCN Guidelines as a preferred regimen for patients, both eligible and ineligible for cisplatin (see Figure 3). The NCCN panel was particularly enthusiastic about the noteworthy results from the phase III EV-302 trial, with some panel members stating that these results entirely change the way that clinicians should be thinking about first-line decision-making. Upon publication of data from the EV-302 trial,



PRINCIPLES OF SYSTEMIC THERAPY

First-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)	
Cisplatin eligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-ejfv[15] (category 1) Other recommended regimens • Gemcitabine and cisplatin[4] (category 1) followed by avelumab maintenance therapy (category 1)[a,13] • Nivolumab, gemcitabine, and cisplatin (category 1) followed by nivolumab maintenance therapy[14] (category 1) Useful under certain circumstances • DDMVAC with growth factor support (category 1)[2,8] followed by avelumab maintenance therapy (category 1)[a,13]
Cisplatin ineligible	Preferred regimens • Pembrolizumab and enfortumab vedotin-ejfv[15,17] (category 1) Other recommended regimens • Gemcitabine and carboplatin[16] followed by avelumab maintenance therapy (category 1)[a,13] Useful under certain circumstances • Gemcitabine[18] • Gemcitabine and paclitaxel[19] • Ifosfamide, doxorubicin, and gemcitabine[21] (for patients with good kidney function and good performance status) • Pembrolizumab[22] (for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for any platinum-containing chemotherapy) • Atezolizumab[20] (only for patients whose tumors express PD-L1[b] or who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 expression) (category 2B)

- The presence of both non-nodal metastases and ECOG performance score ≥2 strongly predict poor outcome with chemotherapy. Patients without these adverse prognostic factors have the greatest benefit from chemotherapy. The impact of these factors in relation to immune checkpoint inhibition is not fully defined, but they remain poor prognostic indicators in general.
- For most patients, the risks of adding paclitaxel to gemcitabine and cisplatin outweigh the limited benefit seen in the randomized trial.[23]
- A substantial proportion of patients cannot receive cisplatin-based chemotherapy due to renal impairment or other comorbidities.
  - Participation in clinical trials of new or more tolerable therapy is recommended.

[a] Maintenance therapy with avelumab only if there is no progression on first-line platinum-containing chemotherapy.
[b] Atezolizumab: SP142 assay, PD-L1–stained tumor-infiltrating immune cells covering ≥5% of the tumor area.

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Figure 3. BL-G 2 of 7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 3.2024.

the panel voted to assign the combination a category 1 designation in both the cisplatin-eligible and cisplatin-ineligible settings, reflecting the high level of evidence and consensus on which this recommendation is based. A panel vote was also held to reevaluate all NCCN Categories of Preference for the first-line regimens, resulting in enfortumab vedotin + pembrolizumab being listed as the only preferred first-line regimen in both the cisplatin-eligible and cisplatin-ineligible settings.

It is important to note that, although enfortumab vedotin + pembrolizumab is the preferred first-line regimen for most patients with advanced or metastatic urothelial cancer, there are circumstances where a patient may not be eligible for this combination, due to comorbidities or other factors. Other systemic therapy options are available for these patients, including cisplatin- or carboplatin-containing regimens (followed by avelumab maintenance therapy when appropriate), other chemotherapy regimens, or checkpoint inhibitor monotherapy options.

Gemcitabine, Cisplatin, and Nivolumab

The multinational, phase III CheckMate901 study compared nivolumab + gemcitabine/cisplatin to gemcitabine/cisplatin alone in 608 patients with previously untreated unresectable or metastatic urothelial carcinoma.[42] Patients who received the nivolumab combination also received maintenance nivolumab for up to 2 years. After a median follow-up of 33.6 months, nivolumab + gemcitabine/cisplatin showed longer median OS compared with gemcitabine/cisplatin alone (21.7 vs 18.9 months; HR, 0.78; 95% CI, 0.63–0.96; P=.02). Median PFS was similar in the 2 arms (7.9 vs 7.6 months; P=.001), but the PFS curves separated over time. At 12 months, the PFS was 34.2% with the nivolumab combination compared with 21.8% with chemotherapy alone. The ORR was 57.6% with the nivolumab combination compared with 43.1% with chemotherapy alone; 21.7% of those in the nivolumab + gemcitabine/cisplatin group had CRs. Grade ≥3 AEs occurred in 61.8% of those in the nivolumab combination group and 51.7% of those who received chemotherapy alone.

Based on these data, the NCCN panel added nivolumab, gemcitabine, and cisplatin followed by nivolumab maintenance therapy as a category 1 first-line therapy option for patients who are eligible to receive cisplatin for locally advanced or metastatic disease (see Figure 3). Based on a panel vote to reevaluate all NCCN Categories of Preference for the first-line regimens, this combination was categorized as an 'other recommended regimen'.

Second-Line and Subsequent Therapy for Metastatic Disease

With the recent changes to first-line treatment options for metastatic disease, many providers are moving toward ICI combinations, such as enfortumab vedotin + pembrolizumab, as a first-line treatment option. In this evolving paradigm, there is limited evidence to guide optimal selection of second- and subsequent-line therapies following these new first-line regimens. The panel anticipates further discussions on this topic as new evidence and information become available. This section details some of the recent changes to the NCCN

recommendations for second-line and subsequent therapy for metastatic urothelial carcinoma based on current data.

Erdafitinib

Erdafitinib is a pan-FGFR inhibitor that was evaluated in a global, open-label phase II trial of 99 patients with a prespecified *FGFR* alteration who had either previously received chemotherapy or who were cisplatin-ineligible, chemotherapy-naïve. Of these patients, 12% were chemotherapy-naïve and 43% had received ≥2 prior lines of therapy. The confirmed ORR was 40% (95% CI, 31%–50%), consisting of 3% CRs and 37% partial responses. Among patients who had previously received immunotherapy, the confirmed ORR was 59%. Median PFS was 5.5 months and the median OS was 13.8 months. Grade ≥3 trAEs were reported in 46% of patients, and 13% of patients discontinued treatment due to AEs.[43] Upon long-term follow-up (median, 24.0 months) of the aforementioned study, the investigator-assessed ORR was 40% (95% CI, 30%–49%) and the safety profile remained similar to the primary analysis.[44]

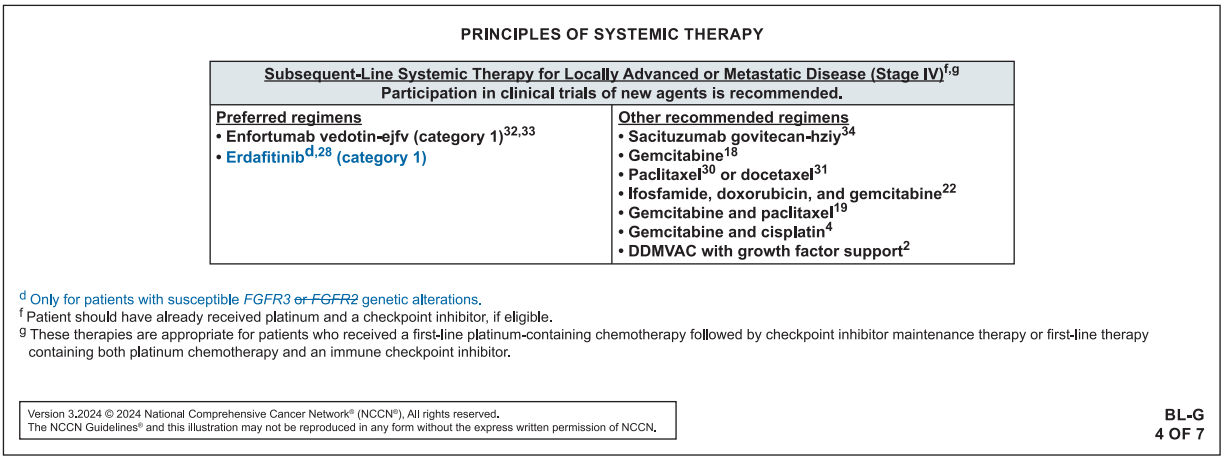
The phase III THOR trial compared erdafitinib to chemotherapy (docetaxel or vinflunine) or pembrolizumab in patients with metastatic urothelial carcinoma with susceptible *FGFR3* or *FGFR2* alterations who had disease progression on or after prior treatment. THOR had 2 cohorts: cohort 1 required 1 or 2 prior treatments, at least one of which included a checkpoint inhibitor; cohort 2 required one prior treatment that did not include a checkpoint inhibitor. For the 266 patients in cohort 1, after a median follow-up of 15.9 months, the median OS was longer with erdafitinib compared with chemotherapy (12.1 vs 7.8 months; HR, 0.64; 95% CI, 0.47–0.88; $P=.005$).[45] Median PFS was also longer with erdafitinib than with chemotherapy (5.6 vs 2.7 months; $P<.001$). The incidence of grade ≥3 trAEs was similar between the 2 groups, with 45.9% reporting in the erdafitinib group compared with 46.4% in the chemotherapy group. trAEs that lead to death occurred in 0.7% of those treated with erdafitinib and 5.4% of those treated with chemotherapy. In the intention-to-treat population of 351 patients in cohort 2, there was no significant difference between the treatment arms for median OS (10.9 months for erdafitinib vs 11.1 months for pembrolizumab; HR, 1.18; 95% CI, 0.92–1.51; $P=.18$).[46] The ORR was 40.0% for erdafitinib compared with 21.6% for pembrolizumab, although pembrolizumab had a longer DoR at 14.4 months, compared with 4.3 months for erdafitinib. Grade 3 to 4 AEs were reported in 64.7% of patients treated with erdafitinib versus 50.9% treated with pembrolizumab; 2.9% of patients treated with erdafitinib and 6.9% of those treated with pembrolizumab had AEs that led to death.

Based on the phase III THOR trial results, where all patients had previously received an ICI, and 89.1% had also received at least one line of chemotherapy (cisplatin in 50.8% and carboplatin in 29.3%),[45] erdafitinib was given a category 1 designation by the panel in the subsequent-line, postplatinum and post-ICI setting (see Figure 4). Also, because around 11% of patients on the THOR trial had not previously received platinum-based chemotherapy, the NCCN panel voted to move erdafitinib to a preferred regimen in the second-line, post-ICI setting (see Figure 5). The panel did not feel that the data supported a category 1 designation in this setting, however, so the recommendation remains category 2A in the second-line, post-ICI setting.

On January 19, 2024, the FDA amended the indication for erdafitinib that was previously granted under accelerated approval to provide full approval for adult patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* genetic alterations, whose disease has progressed on or after at least one prior line of systemic therapy.[47] Furthermore, the FDA indication notes that erdafitinib is not recommended for the treatment of patients who are eligible for and have not received prior PD-1 or PD-L1 inhibitor therapy. In response to the amended FDA indication, the NCCN panel made the decision to match the biomarker requirements and specify susceptible *FGFR3* genetic alterations, when the FDA indication and NCCN recommendation previously supported erdafitinib for susceptible *FGFR3* or *FGFR2* genetic alterations. Although the NCCN panel noted the FDA's decision to limit erdafitinib eligibility to only those who had previously received, or were unable to receive, an ICI, the panel decided to retain the erdafitinib recommendation for second-line therapy, postplatinum or other chemotherapy without an ICI, at this time (see the top table on Figure 5). The NCCN panel will continue to monitor and review the data to make appropriate changes in the future.

Summary

Urothelial tumors represent a spectrum of diseases with a range of prognoses. After a tumor is diagnosed anywhere within the urothelial tract, the patient remains at risk for developing a new


PRINCIPLES OF SYSTEMIC THERAPY

Subsequent-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV)[f,g]
Participation in clinical trials of new agents is recommended.

Preferred regimens	Other recommended regimens
• Enfortumab vedotin-ejfv (category 1)[32,33]	• Sacituzumab govitecan-hziy[34]
• Erdafitinib[d,28] (category 1)	• Gemcitabine[18]
	• Paclitaxel[30] or docetaxel[31]
	• Ifosfamide, doxorubicin, and gemcitabine[22]
	• Gemcitabine and paclitaxel[19]
	• Gemcitabine and cisplatin[4]
	• DDMVAC with growth factor support[2]

[d] Only for patients with susceptible *FGFR3* ~~or *FGFR2*~~ genetic alterations.
[f] Patient should have already received platinum and a checkpoint inhibitor, if eligible.
[g] These therapies are appropriate for patients who received a first-line platinum-containing chemotherapy followed by checkpoint inhibitor maintenance therapy or first-line therapy containing both platinum chemotherapy and an immune checkpoint inhibitor.

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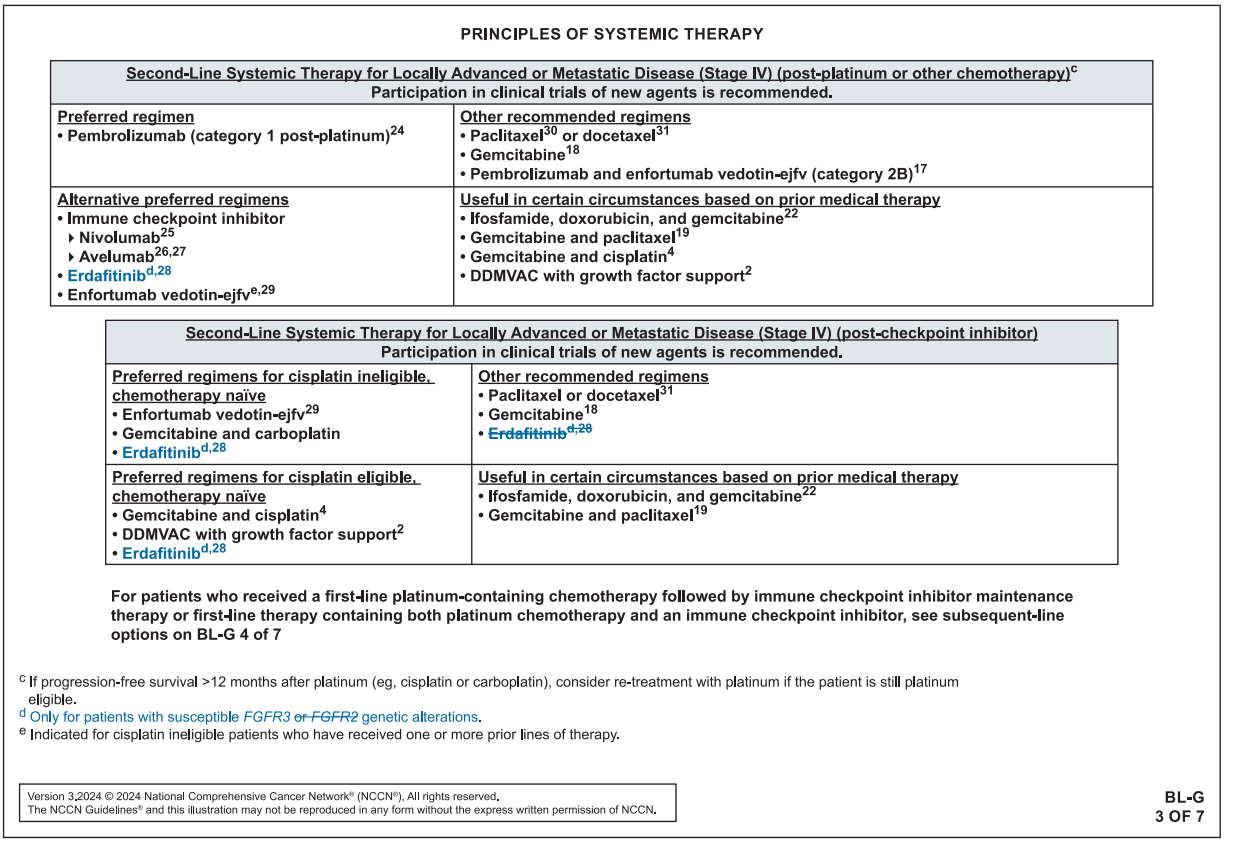
Figure 4. BL-G 4 of 7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 3.2024.



PRINCIPLES OF SYSTEMIC THERAPY

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-platinum or other chemotherapy)[c]
Participation in clinical trials of new agents is recommended.

Preferred regimen	Other recommended regimens
• Pembrolizumab (category 1 post-platinum)[24]	• Paclitaxel[30] or docetaxel[31] • Gemcitabine[18] • Pembrolizumab and enfortumab vedotin-ejfv (category 2B)[17]
Alternative preferred regimens • Immune checkpoint inhibitor ▸ Nivolumab[25] ▸ Avelumab[26,27] • Erdafitinib[d,28] • Enfortumab vedotin-ejfv[e,29]	**Useful in certain circumstances based on prior medical therapy** • Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19] • Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2]

Second-Line Systemic Therapy for Locally Advanced or Metastatic Disease (Stage IV) (post-checkpoint inhibitor)
Participation in clinical trials of new agents is recommended.

Preferred regimens for cisplatin ineligible, chemotherapy naïve	Other recommended regimens
• Enfortumab vedotin-ejfv[29] • Gemcitabine and carboplatin • Erdafitinib[d,28]	• Paclitaxel or docetaxel[31] • Gemcitabine[18] • ~~Erdafitinib~~[d,28]
Preferred regimens for cisplatin eligible, chemotherapy naïve	**Useful in certain circumstances based on prior medical therapy**
• Gemcitabine and cisplatin[4] • DDMVAC with growth factor support[2] • Erdafitinib[d,28]	• Ifosfamide, doxorubicin, and gemcitabine[22] • Gemcitabine and paclitaxel[19]

For patients who received a first-line platinum-containing chemotherapy followed by immune checkpoint inhibitor maintenance therapy or first-line therapy containing both platinum chemotherapy and an immune checkpoint inhibitor, see subsequent-line options on BL-G 4 of 7

[c] If progression-free survival >12 months after platinum (eg, cisplatin or carboplatin), consider re-treatment with platinum if the patient is still platinum eligible.
[d] Only for patients with susceptible *FGFR3* ~~or *FGFR2*~~ genetic alterations.
[e] Indicated for cisplatin ineligible patients who have received one or more prior lines of therapy.

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Figure 5. BL-G 3 of 7. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 3.2024.

lesion at the same or a different location and with a similar or more advanced stage. For patients with nonmuscle invasive disease, continued monitoring for recurrence is an essential part of management, because most recurrences are NMIBC and can be treated endoscopically. Within each category of disease, more refined methods to determine prognosis and guide management, based on molecular staging, are under development with the goal of optimizing each patient's likelihood of cure and chance for organ preservation.

Within the category of metastatic disease, several new agents and combination regimens have been studied and seem to be superior to those that were previously considered standard therapies. In particular, ICIs, antibody–drug conjugates, and targeted therapies have emerged as new options for the treatment of metastatic bladder cancer. Experts surmise that the treatment of urothelial tumors will evolve rapidly over the next few years, with improved outcomes across all disease stages.

To participate in this journal CE activity, go to https://education.nccn.org/node/94843

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