ABSTRACT

The past decade has seen a host of advancements in the management of metastatic urothelial carcinoma. Although efforts to identify novel systemic therapies are still ongoing, immune checkpoint inhibitors have become the preferred treatment option in this patient population. Recommendations for optimal treatment strategies—based on a patient’s eligibility for cisplatin—have been outlined in the NCCN Guidelines for Bladder Cancer in both the first-line and subsequent-line settings.

“What a difference 10 years have made in this field, as there are now several significant advancements that have altered the way we treat metastatic urothelial carcinoma,” asserted Thomas W. Flaig, MD, a medical oncologist practicing at the University of Colorado Cancer Center; Professor of Medicine and Vice Chancellor, University of Colorado Anschutz Medical Campus; and Chair of the NCCN Guidelines Panel for Bladder Cancer. During the NCCN 2024 Annual Conference, Dr. Flaig discussed the emerging therapeutic approaches recommended for patients with this type of genitourinary cancer and thoroughly reviewed current clinical trials, exploring the benefits of various drug classes in this patient population and how they have been incorporated into the updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer.

Antibody–Drug Conjugates

“There is growing familiarity with this [antibody–drug conjugates] class of drugs,” stated Dr. Flaig, as he discussed the 2 key components that interact to regulate the efficacy of antibody–drug conjugates. The specific therapeutic payload represents the drug being delivered to the patient.1 The target dictates where the antibody will guide the payload. According to Dr. Flaig, understanding the distribution of the target is critical to determining the potential treatment-related toxicities.

“In the past, therapeutic strategies effective in other diseases have been utilized for the management of bladder cancer,” Dr. Flaig remarked. Enfortumab vedotin-ejfv and sacituzumab govitecan-hziy are novel antibody–drug conjugates that have demonstrated improved clinical outcomes for patients with bladder cancer. Enfortumab vedotin was initially approved for the treatment of urothelial carcinoma, whereas sacituzumab govitecan was first approved for the management of breast cancer.

Enfortumab vedotin targets nectin-4, a cell-adhesion molecule with an increased expression in urothelial carcinoma. Dr. Flaig discussed an open-label phase III trial that randomly assigned patients with previously treated, locally advanced, or metastatic urothelial carcinoma to receive treatment with enfortumab vedotin or an investigator-selected chemotherapy agent (docetaxel, paclitaxel, or vinflunine).2 Key findings from the study included an improved overall response rate (ORR) with enfortumab vedotin (40.6%) compared with standard chemotherapy (17.9%). Complete response rates were also increased with enfortumab vedotin (4.9% vs 2.7%). Similarly, treatment with enfortumab vedotin significantly improved the median progression-free survival (PFS; 5.6 vs 3.7 months; hazard ratio [HR], 0.62; 95% CI, 0.51–0.75; P < .001) and median overall survival (OS; 12.9 vs 9.0 months; HR, 0.70; 95% CI, 0.56–0.89; P = .001).

“We have a new class of drugs for bladder cancer with good efficacy, which have shown clear improvement over our standard of care,” commented Dr. Flaig. He then continued to discuss the treatment-related adverse effects associated with enfortumab vedotin, which include neuropathy, skin reactions, and hyperglycemia. He emphasized the importance of closely monitoring these patients, because cases of diabetic ketoacidosis have been documented as a result of treatment. According to Dr. Flaig, enfortumab vedotin should be held if the blood glucose level is >250 mg/dL.

The TROPHY-U-01 trial evaluated the efficacy of sacituzumab govitecan, whose specific payload SN-38 targets the protein TROP-2.3 This phase II, single-arm study included patients with locally advanced or metastatic urothelial carcinoma who experienced disease progression.
after treatment with platinum-based chemotherapy and immune checkpoint inhibitors (ICIs). Patients demonstrated a median PFS of 5.4 months (95% CI, 3.5–7.2 months), a median OS of 10.9 months (95% CI, 9.0–13.8 months), and a response rate of 27%.

Treatment-related side effects included hypersensitivity reactions, nausea, vomiting, diarrhea, and bone marrow suppression. Of note, Dr. Flaig discussed that the risk of bone marrow suppression is increased in patients who are homozygous for the UGT1A1*28 allele. “The current recommendation is to closely monitor patients with this particular finding if it is known at the time of treatment,” he suggested.

### ICI Combinations

“There has been a history of using immunotherapy for bladder cancer that goes back a very long time,” explained Dr. Flaig, as he discussed the role of bacillus Calmette-Guérin (BCG) in the immune response. For decades, BCG has been used as a standard of care for bladder cancer, but its limited availability has made it difficult to obtain for patients.

The long-standing success of BCG immunotherapy in the management of localized bladder cancer has prompted researchers to evaluate ICIs in advanced urothelial carcinoma. An open-label, phase III trial conducted by Bellmunt et al investigated the clinical efficacy of the PD-1 inhibitor pembrolizumab compared with investigator-selected chemotherapy (docetaxel, paclitaxel, or vinflunine) in 542 patients with advanced urothelial carcinoma. These patients were previously treated with platinum-based chemotherapy and now demonstrated evidence of disease progression. This study showed a significant improvement in OS for patients treated with pembrolizumab (HR, 0.73; 95% CI, 0.59–0.91; P = .002). Although PFS was also increased for these patients, it did not significantly differ from those treated with standard chemotherapy (HR, 0.98; 95% CI, 0.81–1.19; P = .42). ORRs were higher in patients treated with pembrolizumab (21%), with evidence suggesting ongoing responses to therapy compared with standard chemotherapy (11%).

Dr. Flaig emphasized that although “pembrolizumab has a modest ORR, many of those responses are durable. This has been one of the primary goals in oncology for a long time.”

According to Dr. Flaig, one of the most important advancements in the management of urothelial carcinoma is the combination of the antibody–drug conjugate enfortumab vedotin and the PD-1 inhibitor pembrolizumab. In the EV-302 study, 886 patients with untreated advanced or metastatic urothelial carcinoma were randomly assigned to either the combination of enfortumab vedotin + pembrolizumab or platinum-based combination chemotherapy.

Key findings from the EV-302 trial, which Dr. Flaig called “a truly remarkable study in the field of bladder cancer,” include (1) the ORR was increased with enfortumab vedotin + pembrolizumab (67.7%) compared with platinum-based combination chemotherapy (44.4%); (2) the complete response rate was significantly increased with the enfortumab vedotin + pembrolizumab (29.1% vs 12.5%); (3) PFS was significantly improved at 12.5 versus 6.3 months (HR, 0.45); and (4) OS was significantly improved (31.5 vs 16.1 months; HR, 0.47) (Figure 1).

“If this next study was developed and the previous study hadn’t been, it would have been frontline news, because it went against the standard therapy of gemcitabine +

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**Figure 1.** First-line systemic therapy for locally advanced or metastatic disease (stage IV). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Bladder Cancer, Version 2 2024 [BL-G 2 of 7]. ©2024 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines and this illustration may not be reproduced in any form without the express written permission of NCCN. To view the recent and complete version of these NCCN Guidelines, go to NCCN.org.
cisplatin for bladder cancer, which has been the standard for decades,” Dr. Flaig stated. In light of the data supporting enfortumab vedotin + pembrolizumab, this regimen is listed as an ‘other recommended regimen’ for first-line patients who are cisplatin-eligible (Figure 1). In the phase III CheckMate 901 trial,^{9} the clinical benefits arising from the addition of nivolumab to gemcitabine + cisplatin combination therapy were investigated. Patients who received nivolumab demonstrated an improved ORR (57.6% vs 43.1%) and complete response rate (21.7% vs 11.8%). Similarly, the addition of nivolumab resulted in longer PFS (7.9 vs 7.6 months; HR, 0.72; 95% CI, 0.59–0.88; P = .001) and OS (21.7 vs 18.9 months; HR, 0.78; 95% CI, 0.63–0.96; P = .02) compared with gemcitabine + cisplatin alone. Despite the observed clinical benefits, the addition of nivolumab led to an increased number of grade 3 adverse events (61.8%).

**Targeted Therapy**

“Approximately 1 in 5 patients with advanced urothelial carcinoma develops mutations in FGFR,” reported Dr. Flaig. The tyrosine kinase inhibitor erdafitinib specifically targets FGFR1–4 and inhibits its functioning. Treatment with erdafitinib in patients with previously treated unresectable or metastatic urothelial carcinoma demonstrated a confirmed response to therapy in approximately 40% of patients; median OS was 13.8 months.

Of note, adverse events associated with the use of erdafitinib include hyperphosphatemia, which may require dose reductions or dietary modifications or result in stomatitis or ocular disorders. “It is recommended that patients have monthly eye examinations during the first 4 months of therapy, followed by every 3 months to assess for visual changes,” Dr. Flaig advised.

In January 2024, the FDA approved erdafitinib for the treatment of advanced or metastatic urothelial carcinoma with susceptible FGFR3 genetic mutations. According to Dr. Flaig, this modification was made from the original NCCN Guidelines, which enabled the use of erdafitinib in patients with mutations in FGFR2 or FGFR3.

### Featured Updates in NCCN Guidelines

In 2015, the NCCN Guidelines for Bladder Cancer featured platinum-based therapies as the preferred first-line option, with no recommended second-line treatments available. In contrast, the 2024 NCCN Guidelines outline new first-line therapeutic options, integrating ICIs, and also multiple options for second and subsequent lines of therapy, including targeted agents.

“We continue to say cisplatin-eligible and cisplatin-ineligible, and I think as a field, we will give more thought to this to determine whether it is the correct starting point,” remarked Dr. Flaig. Regardless of eligibility status, the 2024 NCCN Guidelines recommend the combination of enfortumab vedotin + pembrolizumab as the preferred management strategy in this patient population (Figure 1)^9^. "This demonstrates just how quickly NCCN can adapt to changes in this regard,” Dr. Flaig commented. “What I think is notable here is that all of the preferred or recommended regimens [consist of] a combination that includes an ICI.”

Although recommendations have been outlined for second-line and subsequent-line therapies, studies to identify the best therapeutic option are ongoing, noted Dr. Flaig. The current NCCN Guidelines recommend pembrolizumab as second-line therapy in patients previously treated with chemotherapy regimens. However, in patients who were previously treated with ICIs, treatment recommendations are based on a patient’s eligibility for cisplatin. Cisplatin-ineligible patients should receive enfortumab vedotin, whereas cisplatin-eligible patients should receive gemcitabine + cisplatin. Subsequent-line therapy recommendations include enfortumab vedotin and erdafitinib.

### Disclosures

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