Abstract: Bladder cancer accounts for nearly 170,000 deaths worldwide annually. For over 4 decades, the systemic management of muscle-invasive and advanced bladder cancer has primarily consisted of platinum-based chemotherapy. Over the past 10 years, innovations in sequencing technologies have led to rapid genomic characterization of bladder cancer, deepening our understanding of bladder cancer pathogenesis and exposing potential therapeutic vulnerabilities. On the basis of its high mutational burden, immune checkpoint inhibitors were investigated in advanced bladder cancer, revealing durable responses in a subset of patients. These agents are now approved for several indications and highlight the changing treatment landscape of advanced bladder cancer. In addition, commonly expressed molecular targets were leveraged to develop targeted therapies, such as fibroblast growth factor receptor inhibitors and antibody-drug conjugates. The molecular characterization of bladder cancer and the development of novel therapies also have stimulated investigations into optimizing treatment approaches for muscle-invasive bladder cancer. Herein, the authors review the history of muscle-invasive and advanced bladder cancer management, highlight the important molecular characteristics of bladder cancer, describe the major advances in treatment, and offer future directions for therapeutic development.

Keywords: antibody-drug conjugates, bladder cancer, fibroblast growth factor receptor (FGFR), genitourinary, immunotherapy, neoadjuvant, urothelial carcinoma

Introduction

Bladder cancer carries a large societal burden, with over 430,000 men and women diagnosed worldwide every year.¹ The disease disproportionately affects men (3:1 ratio) and the elderly, with median age at diagnosis of 69 years in men and 71 years in women.² Bladder cancer has many associated risk factors, although many patients are diagnosed without any apparent exposures.³ Cigarette smoking is the most common exposure contributing to the increased incidence of bladder cancer in Western countries. In addition, the extent of smoking may relate to the aggressiveness of bladder cancer, with heavy smokers more likely to have high-grade tumors and muscle-invasive disease.⁴ Occupational exposures to paint components such as polyaromatic hydrocarbons, diesel exhausts, fire-related carcinogens such as benzene, and aromatic amines exposures in the automobile, metal, paper, rubber, and hairdressing industries, among others, account for approximately 20% of new cases of bladder cancer.⁵,⁶

In the early 2000s, bladder cancer was the most underfunded among the most common cancers in terms of National Institutes of Health funding.⁷ This disproportionate funding was attributed, at least in part, to a lack of public awareness.⁷ Long periods of limited funding stifled research, contributed to a limited understanding of bladder tumor biology, and ultimately led to insufficient progress in treatment (Fig. 1). Despite major therapeutic advances in other cancers, systemic therapy for bladder cancer remained largely unchanged for more than 30 years. However, in the last decade, a better understanding of the pathogenesis of bladder cancer, coupled with an increased interest in clinical drug development in bladder
cancer, has rapidly expanded the treatment armamentarium. Ongoing activities have focused on improved application of therapies through the development of predictive biomarkers and rational combination regimens. In this review, we describe the evolution of the therapeutic landscape in muscle-invasive and advanced bladder cancer and its future directions.

Bladder cancer is a heterogeneous disease associated with various clinical outcomes. Urothelial cancer (UC), previously often referred to as transitional cell cancer, is the predominant histologic type in the United States and Europe. UC originates less commonly from the upper urinary tract (ie, renal pelvis, ureter, and urethra). Tumors that invade the detrusor muscle are referred to as muscle-invasive bladder cancers (MIBCs) and have a higher propensity to spread to lymph nodes and other organs. Nonmuscle-invasive bladder cancers (NMIBCs) comprise distinct entities, including carcinoma in situ (CIS), papillary noninvasive tumors, and papillary tumors invading the lamina propria. NMIBCs account for approximately 70% of new bladder cancer diagnoses and, given the common need for repeated endoscopic assessments and resections, is among the most expensive malignancies to care for on a per-patient basis. NMIBC is a heterogeneous entity that requires careful risk stratification for enhancing clinical decision making and counseling of patients. The most widely used and validated tools include those developed in 2006 by the European Organization for Research and Treatment of Cancer (EORTC), the European Association of Urology, and the Club Urologico Espanol de Tratamiento Oncologico. Most NMIBCs can be managed with curative intent, and the 5-year overall survival (OS) rate for patients with NMIBC is approximately 90%. Approximately 15% to 20% of NMIBCs progress to MIBC, and CIS and high-grade papillary tumors have a higher likelihood of progressing to MIBC compared with low-grade papillary tumors. The 5-year OS rate for patients with MIBC is approximately 60% to 70%. Approximately 10% of patients with UC present with disease beyond the bladder, with an associated 5-year OS rate of 5% to 30%.

Muscle-Invasive Bladder Cancer

MIBC represents approximately 20% of newly diagnosed cases of bladder cancer. Despite radical cystectomy (RC) and pelvic lymph node dissection, approximately 50% of patients ultimately develop disease at distant sites because of disseminated micrometastases. Therefore, systemic therapy plays a key role in conjunction with local therapy to reduce rates of recurrence (Table 1).

TABLE 1. Key Clinical Trials of Neoadjuvant Cisplatin-Based Chemotherapy for Muscle-Invasive Bladder Cancer

| STUDY                        | YEAR       | ELIGIBILITY   | NO.   | PHASE | INTERVENTION                      | PATHOLOGIC CR RATE* | OS         |
|------------------------------|------------|---------------|-------|-------|-----------------------------------|---------------------|------------|
| Malmstrom 199617 (Nordic Trial I) | 1996       | cT2-cT4aNx    | 325   | 3     | CA + RT + surgery vs RT + surgery | —                   | 5-y OS: 59% vs 51% (P = .1) |
| Sherif 200218 (Nordic Trial II) | 2002       | cT2-cT4aNx    | 317   | 3     | CM + surgery vs surgery           | 26.4% vs 11.5% (P = .001) | 5-y OS: 53% vs 46% (P = .24) |
| BA06 30894 trial: International Collaboration of Trialists 1999, 201119,20 | 1999, 2011 | cT2-cT4aN0    | 976   | 3     | CMV + surgery vs surgery          | 32.5% vs 12.3% (P = .037) | 10-y OS: 36% vs 30% (P = .037) |
| Grossman 200321 (SWOG-8710)  | 2003       | cT2-cT4aN0    | 317   | 3     | MVAC + surgery vs surgery         | 38% vs 15% (P < .001) | 5-y OS: 57% vs 43% (P = .06) |
| Choueiri 201422              | 2014       | cT2-cT4aN0-N1 | 39    | 2     | ddMVAC + surgery                  | 26%                 | 2-y OS: 79% |
| Plimack 201423              | 2014       | cT2-cT4aN0-N1 | 40    | 22    | ddMVAC + surgery                  | 38%                 | 1.8-y OS: 83% |

Abbreviations: BA06 30894 trial, European Organization for Research and Treatment of Cancer-Medical Research trial 30894/BA06; CA, cisplatin and doxorubicin; CMV, cisplatin, methotrexate, vinblastine; CR, complete response; cT, clinical tumor classification; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, cisplatin; MAVC, methotrexate, vinblastine, doxorubicin, cisplatin; Nordic Trial I, Nordic Cystectomy Trial I; Nordic Trial II, Nordic Cystectomy Trial II; RT, radiation therapy; SWOG-8710, Southwest Oncology Group/Intergroup trial 8710 (Neoadjuvant Chemotherapy Plus Cystectomy Compared With Cystectomy Alone for Locally Advanced Bladder Cancer); OS, overall survival.

*Pathologic complete response was defined as pT0N0.
Neoadjuvant Chemotherapy Becomes the Standard of Care

Initial testing of cisplatin in the perioperative setting was based on the pioneering work in the 1970s and 1980s that established its activity in metastatic UC (mUC).24-28 Neoadjuvant cisplatin-based chemotherapy was first tested in the 1980s as a potential treatment strategy for MIBC. Scher et al treated 50 patients with MIBC using 1 to 5 cycles of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), and 30 subsequently underwent RC. Among the patients who underwent RC, 33% achieved a pathologic complete response (pCR), and an additional 17% had downstaging of disease to less than a pathologic T2 (pT2) tumor classification with negative lymph node status (<pT2N0).29 Downstaging of MIBC with neoadjuvant chemotherapy (NAC) has been correlated with improved survival in multiple analyses.30,31

The Nordic Cooperative Bladder Cancer Study Group performed the first randomized phase 3 study of cisplatin-based chemotherapy in MIBC. In Nordic Cystectomy Trial I, patients were randomized to receive either neoadjuvant cisplatin plus doxorubicin or no NAC before short-term radiotherapy (RT) and RC.17 In Nordic Cystectomy Trial II, neoadjuvant cisplatin plus methotrexate was compared with no NAC before RC. Both trials established the tolerability and feasibility of giving NAC before surgery; however, neither showed an improvement in OS, although both trials were small and underpowered.17,18

The BA06 30894 trial (Phase III Study of Primary Chemotherapy [CMV] in T2G3, T3 and T4a, N0-X, M0 Transitional Cell Carcinoma of the Bladder [MRC/EORTC Collaborative Study]) is the largest study of NAC completed to date.32 In that trial, 976 patients received either neoadjuvant cisplatin, methotrexate, and vinblastine (CMV) or no NAC before RC and/or RT. With a median follow-up of 8 years, the use of neoadjuvant CMV improved 10-year survival from 30% to 36% (hazard ratio [HR], 0.84; 95% CI, 0.72-0.99; P = .037).19 The Southwest Oncology Group (SWOG)/Intergroup 8710 (SWOG-8710) study (Trial of Cystectomy Alone Versus Neoadjuvant M-VAC + Cystectomy in Patients With Locally Advanced Bladder Cancer) randomly assigned 317 patients to receive 3 cycles of MVAC followed by RC versus RC alone.21 Disease-specific survival was improved with the use of NAC compared with no NAC before surgery (HR, 0.60; 95% CI, 0.41-0.82; P = .002), and there was a trend toward an improvement in 5-year OS (57% vs 45%; HR, 0.75; 95% CI, 0.57-1.00; P = .06).21 Of note, the study design called for one-sided statistical testing because the standard of medical practice would be changed only if combination therapy proved to be superior to cystectomy alone. However, in accordance with the policy of The New England Journal of Medicine, only 2-sided P values were reported, with borderline significance. However, the pCR rate was improved with the addition of NAC (38% vs 15%; P < .0001), and achieving a pCR was correlated with a 5-year OS rate of 85%, similar to prior reports.31 An updated meta-analysis of 11 clinical trials including >3000 patients demonstrated a 5-year OS benefit of 5% and a 14% reduction in the risk of death (HR, 0.86; 95% CI, 0.77-0.95; P = .003) with the addition of NAC.32 This clinical benefit is similar to that of adjuvant chemotherapy reported in patients with breast cancer13 and colon cancer.34 Hence, the use of neoadjuvant cisplatin-based chemotherapy has become the standard of care for eligible patients with MIBC.

A potential concern with standard-dose MVAC is the risk for adverse events (AEs), such as myelosuppression and mucositis. Consequently, the improved tolerability of gemcitabine plus cisplatin (GC), with similar efficacy demonstrated in the metastatic setting, led to early substitution of GC in the neoadjuvant setting even in the absence of prospective trials.35,36 Most, but not all, retrospective studies comparing GC versus MVAC NAC have demonstrated similar pCR rates and survival outcomes with these regimens.37,38

Another strategy to overcome toxicities related to standard-dose MVAC is administration in a dose-dense fashion (ddMVAC). Compared with 4-week cycles of standard-dose MVAC, ddMVAC consists of the delivery of MVAC plus granulocyte-colony-stimulating factor in 2-week cycles. ddMVAC has demonstrated similar clinical efficacy and less toxicity compared with classical MVAC in mUC trials.39,40 Consequently, in 2014, 2 single-arm prospective clinical studies investigated ddMVAC NAC with granulocyte-colony-stimulating factor support in patients with MIBC.22,23 Choueiri et al enrolled 39 patients on a phase 2 trial exploring 4 cycles of ddMVAC and reported <pT2N0 and pCR rates of 49% and 26%, respectively.22 Plimack et al enrolled 40 patients on a phase 2 trial exploring 3 cycles of ddMVAC and reported <pT2N0 and pCR rates of 53% and 38%, respectively.23 In the latter study, the median time from the initiation of chemotherapy to surgery was 9.7 weeks,23 compared with 16 to 19 weeks for standard-dose MVAC.21 Over time, ddMVAC has become the preferred dosing strategy over classical MVAC.

Similar to neoadjuvant MVAC, the combination of neoadjuvant GC has also been tested in a dose-dense fashion. The rationale was based on improved safety and similar efficacy of dose-dense GC (ddGC), compared with standard-dose GC, in the metastatic setting.41,42 In a phase 2 study of 49 patients with clinical T2 (cT2) to cT4aN0M0 UC, 57% of patients were downstaged to <pT2N0, which
correlated with improved recurrence-free survival and OS.\(^{43}\) Importantly, no patients failed to undergo RC as a result of treatment-related toxicities. Although this regimen demonstrated efficacy similar to that of ddMVAC and was well tolerated, ddMVAC and GC have been widely adopted in clinical practice.

Only recently have randomized trials comparing ddMVAC versus standard-dose GC been reported. The SWOG-1314 trial (A Randomized Phase II Study of Co-Expression Extrapolation [COXEN]-Directed Neoadjuvant Chemotherapy for Localized, Muscle-Invasive Bladder Cancer) was the first to report this comparison in 167 patients who had cT2-cT4N0M0 UC to receive either ddMVAC or GC. Preliminary data showed that the pCR rates were 32% for ddMVAC and 35% for GC, whereas the ≤pT1 rates were 55% and 49%, respectively.\(^{44}\) Of note, this study was designed to explore the utility of gene expression-based biomarkers for pCR prediction in patients receiving NAC and did not directly compare these 2 regimens. In a more recent report, the Genitourinary Group/French Association of Urology V05 VESPER (Perioperative Chemotherapy for Patients With Locally Advanced Bladder Cancer; ClinicalTrials.gov identifier NCT01812369) investigators randomized 500 patients with cT2-cT4N0M0 UC to receive either ddMVAC or GC. Preliminary data showed that the pCR rates were higher in patients receiving ddMVAC compared with those receiving GC (42% vs 36%; \(P = .02\)).\(^{45}\) In addition, the rates of nonmuscle-invasive disease (≤pT1N0) and organ-confined disease (≤pT2N0) were also improved with ddMVAC compared with GC. The following grade ≥3 toxicities were more common in the ddMVAC arm than in the GC arm: anemia (22% vs 8%; \(P = .00002\)), febrile neutropenia (7% vs 2%; \(P = .05\)), nausea/vomiting (10% vs 3%; \(P = .03\)), and asthenia (14% vs 4%; \(P = .0002\)). The primary endpoint of 3-year progression-free survival (PFS) will be reported in 2021.

**Biomarkers of Response to Cisplatin-Based NAC**

The benefit of NAC is limited to only a subset of patients, and the inability to predict responsiveness remains a major challenge. Over the last decade, next-generation sequencing technologies have facilitated several large-scale analyses to uncover the genomic complexity of UC and understand its responsiveness to current therapies. Notably, cisplatin forms DNA crosslinks that interfere with DNA replication and gene transcription, and tumors with impairment in DNA repair mechanisms may be more vulnerable to cisplatin.\(^{46,47}\) Van Allen et al studied 50 MIBC specimens pretreatment and found that \(ERCC2\), a nucleotide excision repair gene, was enriched in cisplatin responders compared with nonresponders (\(P < .001\)).\(^{48}\) Plimack et al found that the presence of alterations in at least one of three DNA repair genes, \(ATM, RB1,\) and \(FANCC\), was enriched in responders compared with nonresponders to either ddMVAC or GC (training cohort: 87% vs 0%; \(P < .001\), validation cohort: 64% vs 15%; \(P = .033\)).\(^{49}\) Of note, that analysis did not include \(ERCC2\) in the gene sequencing panel and, on repeat analysis with \(ERCC2\) included, responders were more likely to harbor alterations in this gene compared with nonresponders (40% vs 7%; \(P = .01\)).\(^{50}\) In addition to genes implicated in DNA repair mechanisms, Groenendijk et al reported that recurrent \(ERBB2\) mutations were present more commonly in cisplatin responders compared with nonresponders (23% vs 0%; \(P = .003\)).\(^{51}\) Of note, although Van Allen et al and Plimack et al also found recurrent \(ERBB2\) mutations, they were not associated with a complete response (CR).\(^{48,49}\)

Therefore, further studies are needed to elucidate the predictive value of \(ERBB2\).

In addition to the discovery of specific gene alterations associated with NAC responsiveness, RNA sequencing of UC from The Cancer Genomic Atlas (TCGA) and other groups has identified distinct molecular subtypes and associated clinical behavior and treatment response.\(^{52-56}\) In the initial TCGA analysis of 131 MIBC samples, UC, similar to breast cancer, clustered under 2 major subtypes: basal and luminal.\(^{54-56}\) Basal tumors expressed patterns of less differentiated stem-like and mesenchymal cells and often had squamous and/or sarcomatoid features.\(^{54,57-59}\) Generally, basal tumors were more aggressive and invasive at presentation. Luminal tumors harbored genes similar to those in luminal-differentiated breast cancer, such as \(FOXA1, GATA3\), and \(PPARY\), and possessed papillary-like morphology.\(^{60}\) Interestingly, in a separate study of 73 MIBC samples, a subset of luminal tumors that share a \(p53\)-driven expression signature was associated with chemoresistance; in contrast, the basal subtype was associated with chemosensitivity.\(^{54,57}\)

In a separate cohort of 49 patients for external validation, no correlation between intrinsic subtype and pathologic downstaging was found.\(^{54}\) A single-sample genomic classifier was developed by Seiler et al and applied to a cohort of transurethral resection of bladder tumor (TURBT) samples from patients who subsequently received NAC and a cohort of samples from patients with MIBC who did not receive NAC.\(^{61}\) Notably, patients with luminal tumors had the best OS regardless of whether they received NAC, whereas those with claudin-low tumors were associated with poor OS irrespective of whether they received NAC. Patients who had basal tumors, conversely, exhibited the largest improvement in OS with NAC versus surgery alone. However, given the retrospective nature of the analysis and the lack of randomization between NAC and cystectomy alone in the studied data sets, the clinical validity and utility of intrinsic subtypes of MIBC in informing NAC decisions remain unclear.
Is There a Clear Role for Adjuvant Cisplatin-Based Chemotherapy?

In theory, the use of chemotherapy in an adjuvant setting may be optimal because of the ability to assess the risk of recurrence based on the pathologic extent of disease after surgery. Therefore, this approach affords the opportunity to refine patient selection and mitigate inappropriate use of chemotherapy. In practice, however, this strategy is difficult to implement. First, RC is an extensive operation, and approximately 30% of patients experience complications within 3 months of surgery, potentially delaying or preventing the receipt of adjuvant chemotherapy. Second, bladder cancer is predominantly a disease of elderly patients, who often have comorbidities that impair postoperative recovery. In fact, multiple randomized trials exploring adjuvant chemotherapy have closed early because of poor accrual.

In the largest study, EORTC 30994 (Randomized Phase III Trial Comparing Immediate Versus Deferred Chemotherapy After Radical Cystectomy in Patients With pT3-pT4, and/or N+M0 Transitional Cell Carcinoma [TCC] of the Bladder; ClinicalTrials.gov identifier NCT00028756), 284 patients with pT3-pT4 and/or lymph node-positive (N+) disease received chemotherapy either in the adjuvant setting or at the time of disease relapse. Chemotherapy regimens included GC, MVAC, or ddMVAC. At a median follow-up of 7 years, patients who received adjuvant chemotherapy had longer PFS (HR, 0.45; 95% CI, 0.40-0.73; P < .0001) compared with those who received deferred chemotherapy; however, there was no difference in OS (HR, 0.78; 95% CI, 0.56-1.08; P = .13).

To investigate further whether adjuvant chemotherapy might be associated with benefit in patients with pT3-pT4 and/or lymph node-positive disease in a real-world setting, Galsky et al retrospectively evaluated 5653 patients who were treated between 2003 and 2006 in the American College of Surgeons and American Cancer Society National Cancer Database. In this cohort, 23% of patients received adjuvant chemotherapy. After using approaches to adjust for observed (and potentially observed) confounders, the authors found an improvement in OS with the receipt of adjuvant chemotherapy compared with no chemotherapy (HR, 0.70; 95% CI, 0.64-0.76). Notwithstanding the limitations of retrospective analyses, these data do provide additional support for prospective randomized trials exploring adjuvant chemotherapy, which collectively suggest a survival benefit with this approach.

Neoadjuvant Strategies for Cisplatin-Ineligible Patients

Although cisplatin-based NAC is the established perioperative approach, approximately 50% of patients with MIBC are ineligible because of age-related and/or disease-related risk comorbidities. Galsky et al established a consensus definition of cisplatin-ineligibility as meeting one of the following criteria: an Eastern Cooperative Oncology Group performance status ≥2, impaired renal function with creatinine clearance (CrCl) ≤60 mg per minute per 1.73 m², New York Heart Association class III heart failure, Common Terminology Criteria for Adverse Events (version 4) grade ≥2 hearing loss, and Common Terminology Criteria for Adverse Events (version 4) grade ≥2 neuropathy. Carboplatin plus gemcitabine (GCa), a less effective alternative to GC in mUC, has been studied in several retrospective analyses of patients with MIBC who had pCR rates of 20% to 30%. Single-arm, phase 2 trials of paclitaxel, carboplatin, and gemcitabine or nanoparticle-bound paclitaxel, carboplatin, and gemcitabine led to lower rates of pCR and higher rates of hematologic toxicities compared with cisplatin-based regimens.

The use of immune checkpoint inhibitors (ICIs) is a key emerging treatment strategy to address the difficulties of delivering effective neoadjuvant or adjuvant systemic therapy to a large subset of patients with UC. PD-1/PD-L1 inhibitors are already approved in select first-line and second-line settings for advanced UC. On the basis of the safety and activity of these therapies in patients with advanced disease, there is an expanded investigation into their use in the neoadjuvant, adjuvant, and bladder-sparing settings (Fig. 2).

PURE-01 (Neoadjuvant Pembrolizumab for Muscle-Invasive Urothelial Bladder Carcinoma; ClinicalTrials.gov identifier NCT02736266), a single-arm phase 2 trial, was among the first studies of single-agent ICI in the neoadjuvant setting in which 50 patients with MIBC received pembrolizumab. In this novel study design, which included patients regardless of cisplatin eligibility, 3 cycles of pembrolizumab were given before RC, and the option of ddMVAC before surgery was included for those experiencing early disease progression. Forty-six patients (92%) were deemed cisplatin-eligible, and 4 patients received sequential MVAC chemotherapy as a result of early disease progression on pembrolizumab. In the entire patient cohort, 21 patients (42%) achieved a pCR, and downstaging to <pT2N0 occurred in 27 patients (54%). Of note, the pCR rate in patients who had a combined positive score (CPS) ≥10, as measured by the percentage of PD-L1–positive tumor and tumor-infiltrating immune cells, was higher compared with those who had a CPS <10.
In the neoadjuvant setting, there are ongoing trials of single-agent immune checkpoint inhibitors (ICIs), dual ICIs, and ICIs with chemotherapy. In the bladder-sparing setting, there are ongoing trials of ICIs with radiation therapy (RT). ICIs with concurrent chemoradiation therapy (CCRT), and ICIs after CCRT. (C) ICI trials in the adjuvant setting are listed. Asterisks indicate phase 3 studies, and all other trials are phase 1/2. The study name (if available) or the national clinical trial (NCT) number is indicated in parentheses. ± indicates with or without; AMBASSADOR, Testing MK-3475 (Pembrolizumab) After Surgery for Localized Muscle-Invasive Bladder Cancer and Locally Advanced Urothelial Cancer (ClinicalTrials.gov identifier NCT03244384); AURA, Avelumab as Neoadjuvant Therapy in Subjects With Urothelial Muscle Invasive Bladder Cancers (ClinicalTrials.gov identifier NCT03674424); BLASt-2, A Feasibility Study of Durvalumab ± Oleclumab as Neoadjuvant Therapy for Muscle-Invasive Bladder Cancer (ClinicalTrials.gov identifier NCT03773666); CheckMate 274, An Investigational Immuno-Therapy Study of Nivolumab, Compared to Placebo, in Patients With Bladder Cancer (MEDI4736) and Tremelimumab in Neoadjuvant Bladder Cancer Patients (ClinicalTrials.gov identifier NCT03472274); ENERGIZE, A Study of Chemo Only Versus Chemo Plus Nivo With or Without BMS-986205, Followed by Post-Surgery Therapy With Nivo or Nivo and BMS-986205 in Patients With MIBC (ClinicalTrials.gov identifier NCT03361320); IMMUNOPRESERVE, Durvalumab Plus Tremelimumab With Concurrent Radiotherapy for Localized Muscle Invasive Bladder Cancer Treated With a Selective Bladder Preservation Approach (ClinicalTrials.gov identifier NCT03702179); KEYNOTE-866, Perioperative Pembrolizumab (MK-3475) Plus Neoadjuvant Chemotherapy Versus Perioperative Placebo Plus Neoadjuvant Chemotherapy for Cisplatin-Eligible Muscle-Invasive Bladder Cancer (MIBC) (ClinicalTrials.gov identifier NCT03924856); NABUCCO, Neo-Adjuvant Bladder Urothelial Carcinoma Combination-Immunotherapy (ClinicalTrials.gov identifier NCT03387761); NaCCT, neoadjuvant cisplatin-based chemotherapy; NCT02451423, Neoadjuvant Atezolizumab in Localized Bladder Cancer (ClinicalTrials.gov identifier NCT02451423); NCT02621151, Pembrolizumab (MK-3475), Gemcitabine, and Concurrent Hypofractionated Radiation Therapy for Muscle-Invasive Urothelial Cancer of the Bladder (ClinicalTrials.gov identifier NCT02621151); NCT03577132, The Efficacy of Neoadjuvant Atezolizumab Treatment in Patients With Advanced Urothelial Bladder Cancer (ClinicalTrials.gov identifier NCT03577132); NCT03617913, Avelumab in Combination With Fluorouracil and Mitomycin or Cisplatin and Radiation Therapy in Treating Participants With Muscle-Invasive Bladder Cancer (ClinicalTrials.gov identifier NCT03617913); NCT03697850, Atezolizumab After Chemoradiotherapy for MIBC Patients Not Eligible for Radical Cystectomy (ClinicalTrials.gov identifier NCT03697850); NCT03747419, Avelumab and Radiation in Muscle-Invasive Bladder Cancer (ClinicalTrials.gov identifier NCT03747419); NCT02775265, Chemoradiotherapy With or Without Atezolizumab in Treating Patients With Localized Muscle Invasive Bladder Cancer (ClinicalTrials.gov identifier NCT03775265); NCT02845323, Neoadjuvant Nivolumab With and Without Ureteral Cell Ineligibility or Chemotherapy Refusing Patients With Muscle-Invasive Urothelial Carcinoma of the Bladder (ClinicalTrials.gov identifier NCT02845323); NCT03520491, A Study to Test the Safety of Immunotherapy With Nivolumab Alone or With Ipilimumab Before Surgery for Bladder Cancer Patients Who Are Not Suitable for Chemotherapy (ClinicalTrials.gov identifier NCT03520491); NEMIO, Neoadjuvant Dose-Dense MVAC in Combination With Durvalumab and Tremelimumab in Muscle-Invasive Urothelial Carcinoma (ClinicalTrials.gov identifier NCT03549715); NEODURVARIB, Durvalumab Plus Olaparib Administered Prior to Surgery of Resectable Urothelial Bladder Cancer (ClinicalTrials.gov identifier NCT03534492); NIAGARA, Durvalumab + Gemcitabine/Cisplatin (Neoadjuvant Treatment) and Durvalumab (Adjuvant Treatment) in Patients With MIBC (ClinicalTrials.gov identifier NCT03732677); NITIMB, Durvalumab and Tremelimumab in Treating Patients With Muscle-Invasive Urothelial Cancer That Cannot Be Treated With Cisplatin-Based Therapy Before Surgery (ClinicalTrials.gov identifier NCT02811240); PANDORE, Study Evaluating Neoadjuvant Pembrolizumab Monotherapy in Patients With Muscle-Invasive Bladder Cancer to Explore in Vivo the Mechanisms of Action of Pembrolizumab (ClinicalTrials.gov identifier NCT03212651); PECULIAR, Pembrolizumab-Epacadostat Combination to Treat Muscle-Invasive Bladder Urothelial Cancer: PECULIAR Study (ClinicalTrials.gov identifier NCT03832673).
immune checkpoint blockade (Fig. 2A). Combined inhibition of PD-1/PD-L1 and CTLA-4 may lead to immunogenic intensification based on their complementary mechanisms of action on T-cell activation and effector T-cell response. In fact, dual ICIs have become a standard treatment approach in other solid tumors, such as melanoma and renal cell carcinoma. In the first report of neoadjuvant dual ICIs, durvalumab plus tremelimumab was given to cisplatin-ineligible patients with cT2-cT4aN0M0 disease. Of the 21 patients who underwent cystectomy, 9 (43%) had a pCR, and 2 additional patients had nonmuscle-invasive disease. The combination was well tolerated, with grade 3 immune-related AEs (irAEs) in 17% of patients, most commonly consisting of hepatitis. Ipilimumab plus nivolumab was also studied in an early phase clinical trial in patients with MIBC (14 with cT3-cT4aN0 disease, 10 with cN+ disease). Grade 3 or 4 irAEs occurred in 54% of patients, leading to treatment discontinuation after 2 cycles in 6 patients. Among the 22 patients who underwent cystectomy, 10 (45%) achieved a pCR, and 3 additional patients had nonmuscle-invasive cancer. Larger randomized trials are needed to determine whether neoadjuvant dual immune checkpoint blockade will have a role in the treatment of MIBC.

Bladder-Sparing Approaches for MIBC

Bladder cancer is largely a disease of older individuals, and comorbidities or individual treatment preferences may lead to an unfavorable risk:benefit proportion with RC. In fact, observational studies have reported that from 47% to 51% of patients with MIBC receive no curative-intent treatment. Trimodal therapy (TMT), consisting of maximal TURBT followed by concurrent chemotherapy and RT, has been extensively studied as a bladder-sparing approach to MIBC. In this setting, chemotherapy is given concurrently with RT as a radiosensitizer. RT alone may be curative for MIBC and is associated with a 5-year OS rate of 35% to 40%. The BC2001 trial (A randomized phase III study of radiotherapy with and without synchronous chemotherapy in muscle invasive bladder cancer; Cancer Research UK Clinical Trial CRUK/01/004), a phase 3 study of 360 patients, demonstrated better outcomes with RT with concurrent 5-fluorouracil (5-FU) plus mitomycin over RT alone. With a median follow-up of 118 months, the concurrent use of 5-FU plus mitomycin with RT improved cancer-specific survival (HR, 0.73; 95% CI, 0.54-0.99; P = .043), improved locoregional control (2-year relapse rate, 18% vs 32%; P = .01 [HR, 0.59; 95% CI, 0.41-0.83; P = .003]), and showed lower rates of salvage cystectomy (2-year rate, 11% vs 17%; P = .03). A pooled analysis of 6 Radiation Therapy Oncology Group (RTOG) studies and 2 large institutional studies also supported the use of CCRT over RT alone, with a survival benefit at 5 and 10 years. Of important note, appropriate patient selection is necessary for the proper implementation of TMT. Giacalone et al showed that refining the criteria for patient selection to cT2N0M0 disease, complete TURBT, no hydronephrosis, no CIS, and unifocal tumor improved the 5-year OS rate from 53% to 75%, and the rate of salvage cystectomy declined from 29% to 16%.

Several different chemotherapeutic agents, including cisplatin, paclitaxel, 5-FU, and mitomycin, have been explored in combination with RT for MIBC. For cisplatin-ineligible patients, gemcitabine is an acceptable alternative based on a 93% clinical CR rate and 5-year OS and cancer-specific survival of 59% and 89%, respectively, in a pooled analysis of multiple phase 1/2 trials. The incorporation of ICIs into TMT (Fig. 2B) is under investigation based on the potential ability of RT to enhance antitumor immune activity through tumor cell killing and subsequent release of tumor neoantigens. The outcomes of these studies may ultimately lead to more widespread use of bladder-sparing TMT as a treatment for MIBC.

Improving Outcomes of Cisplatin-Eligible Patients

Although cisplatin-based chemotherapy followed by RC improves survival, for some patients, residual cancer remains. In fact, Bhindi et al, in a retrospective analysis of patients with MIBC who received either NAC plus RC or RC alone, among patients with residual cancer, those who received NAC had worse disease control and survival. The aggressive nature of the disease in this subgroup of patients, who are refractory to NAC, calls for a
need to optimize cisplatin-based chemotherapy. One potential option is to implement chemoimmunotherapy based on the immunomodulatory properties of chemotherapy (Fig. 2A).\textsuperscript{106} Holmes et al demonstrated the first signal of antitumor activity and manageable toxicity with neoadjuvant chemoimmunotherapy in the phase 1b/2 trial of pembrolizumab with GC in patients with cT2–cT4aN0M0 UC/mixed histology carcinoma. In the 40 evaluable patients, one patient did not undergo RC because of a severe AE (thrombocytopenia purpura).\textsuperscript{107} There were 11 grade 3 or 4 AEs, most commonly hyponatremia, thromboembolism, and renal insufficiency. The pathologic nonmuscle-invasive rate was 60%; and, at a median follow-up of 14 months, the estimated 12-month relapse-free and disease-specific survival rate was 80% and 97%, respectively.\textsuperscript{107} Gupta et al evaluated neoadjuvant nivolumab in combination with GC followed by RC in patients with MIBC. In their report of 41 patients (cT2N0, 90%; cT3N0, 7%; cT4N1, 3%), pathologic downstaging (≤pT1N0) and pCR occurred in 66% and 49% of patients, respectively.\textsuperscript{108} In terms of safety, grade 3 and 4 AEs occurred in 20% of patients, mostly attributed to chemotherapy, including thrombocytopenia, neutropenia, and renal insufficiency. Furthermore, there were no surgical complications or delays in the time to RC. Galsky and colleagues are studying the same combination, although the trial design integrates the option of selective bladder-sparing based on clinical response to neoadjuvant treatment. There are now 3 ongoing randomized phase 3 studies of neoadjuvant cisplatin-based chemoimmunotherapy: nivolumab (ENERGIZE: A Study of Chemo Only Versus Chemo Plus Nivo With or Without BMS-986205, Followed by Post-Surgery Therapy With Nivo or Nivo and BMS-986205 in Patients With MIBC; ClinicalTrials.gov identifier NCT03661320), durvalumab (NIAGARA: Durvalumab + Gemcitabine/Cisplatin [Neoadjuvant Treatment] and Durvalumab [Adjuvant Treatment] in Patients With MIBC; ClinicalTrials.gov identifier NCT03732677), and pembrolizumab (KEYNOTE-866: Perioperative Pembrolizumab [MK-3475] Plus Neoadjuvant Chemotherapy Versus Perioperative Placebo Plus Neoadjuvant Chemotherapy for Cisplatin-Eligible Muscle-Invasive Bladder Cancer [MIBC]; ClinicalTrials.gov identifier NCT03924856).

Another potential solution to optimize cisplatin-based NAC is the addition of ICI in the adjuvant setting (Fig. 2C). In the first reported study of this approach, atezolizumab (IMVigor010: A Study of Atezolizumab Versus Observation as Adjuvant Therapy in Participants With High-Risk Muscle-Invasive Urothelial Carcinoma [UC] After Surgical Resection; ClinicalTrials.gov identifier NCT02450331) did not meet its primary endpoint of improved disease-free survival compared with observation, as reported in a press release\textsuperscript{109}; no further data are currently available. Three other phase 3 trials are currently underway in this setting including pembrolizumab vs observation (AMBASSADOR: Testing MK-3475 [Pembrolizumab] After Surgery for Localized Muscle-Invasive Bladder Cancer and Locally Advanced Urothelial Cancer; ClinicalTrials.gov identifier NCT03244384), durvalumab (NIAGARA), and nivolumab vs placebo (CheckMate 274: An Investigational Immuno-Therapy Study of Nivolumab, Compared to Placebo, in Patients With Bladder or Upper Urinary Tract Cancer, Following Surgery to Remove the Cancer; ClinicalTrials.gov identifier NCT02632409).

**Advanced Urothelial Carcinoma**

Advanced UC, comprised of locally advanced UC and mUC, is generally considered an incurable disease. To date, cisplatin-based chemotherapy remains the first-line treatment standard for advanced UC. Carboplatin-based regimens have been substituted in patients for whom the risks of cisplatin-based chemotherapy are believed to outweigh the potential benefits.\textsuperscript{71} Second-line treatment options for advanced UC have historically been limited. A better understanding of the biology of UC has led to several treatment advances over the last 5 years, including ICIs, fibroblast growth factor receptor (FGFR) inhibitors, and antibody-drug conjugates (ADCs). The timeline for approval of these novel therapies is detailed in Figure 3.

**Platinum-Based Chemotherapy Has Remained the First-Line Option**

The impact of cisplatin-based combination chemotherapy on improving survival for patients with bladder cancer was first demonstrated in the early 1990s, when MVAC demonstrated a survival benefit over cisplatin alone.\textsuperscript{110} The use of MVAC has been limited because of toxicities, including neutropenia, mucositis, and peripheral neuropathy, and a 3% to 4% mortality rate.\textsuperscript{110} As a result, other options were investigated, such as GC and ddMVAC. In phase 2 studies, GC had clinical activity similar to that of MVAC and a better toxicity profile.\textsuperscript{111,113} Subsequently, a phase 3 trial, although it was not designed as a noninferiority study, showed a similar objective response rate (ORR) (GC vs MVAC, 49% vs 46%, respectively) and a similar OS with the 2 regimens.\textsuperscript{35,36} ddMVAC was also shown to be better tolerated compared with classical dosing of MVAC; and, although there were no significant difference in OS outcomes between the regimens, the subset of patients who experienced durable disease control favored ddMVAC.\textsuperscript{39,40} When ddMVAC was compared with ddGC in a randomized phase 3 study, there was no difference in median OS.\textsuperscript{41} Taxanes, such as paclitaxel\textsuperscript{114} and larotaxel,\textsuperscript{115} have also been extensively studied in combination with GC; however, because of the higher incidence of serious toxicities, such as neutropenia and fatigue, and a lack
of OS benefit, the triplet regimens have not been embraced clinically. On the basis of these results, GC and ddMVAC have been widely adopted as first-line options for mUC.

For patients who are ineligible for cisplatin, GCa was evaluated in the EORTC 30986 trial (Randomized Phase II/III Study Assessing Gemcitabine/Carboplatin and Methotrexate/Carboplatin/Vinblastine in Previously Untreated Patients With Advanced Urothelial Cancer Ineligible for Cisplatin-Based Chemotherapy; ClinicalTrials.gov identifier NCT00014274). In this phase 2/3 study, De Santis et al compared GCa with methotrexate/carboplatin/vinblastine (M-CAVI) in 238 previously untreated patients who had 2mUC with impaired renal function (a glomerular filtration rate between 30 and 60 mL per minute) and/or a performance status ≥2. At a median follow-up of 4.5 years, there was no difference in the ORR or OS between the 2 cohorts, although GCa was much better tolerated, with a lower rate of severe acute toxicities.116 Unfortunately, the median OS in patients with GCa was only approximately 8 or 9 months. Subsequently, vinflunine, an active agent against UC that is safe in patients with renal insufficiency,117 was evaluated in combination with carboplatin compared with vinflunine plus gemcitabine (VG).118 The clinical activity was similar in both groups with a more favorable hematological toxicity profile in the VG group.118 Most recently, the VINGEM study (A Trial With Vinflunine in Patients With Metastatic Bladder Cancer and Impaired Renal Function; ClinicalTrials.gov identifier NCT02665039) investigated VG compared with GCa in 59 patients who had a CrCl of 30 to 60 mL per minute and a performance status ≤1. The primary endpoint of improvement in PFS was not met; however, compared with GCa, VG had a higher CR rate (22% vs 3%).119 Conversely, patients who received VG had higher rates of grade 3 and 4 neutropenia (VG vs GCa, 62% vs 43%) and febrile neutropenia (VG vs GCa, 31% vs 7%).119 Currently, GCa remains the preferred cytotoxic chemotherapy regimen for first-line treatment of cisplatin-ineligible patients with mUC.

IcIs Change the Treatment Paradigm for mUC

In retrospect, several lines of evidence support the exploration of immune checkpoint blockade in UC, including the relatively high tumor mutational burden associated with this disease.56,120 However, aside from a small body of literature suggesting that the antitumor immune response may play an important role in the outcomes of patients with advanced UC,121 the clinical activity of PD-1/PD-L1 blockade in mUC observed in phase 1 studies was largely unexpected and led to rapid exploration in larger trials. Currently, 5 ICIs (atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab) are approved by the US Food and Drug Administration (FDA) for the treatment of patients with advanced UC who progress despite platinum-based chemotherapy, and 2 ICIs (atezolizumab...
and pembrolizumab) are approved for first-line treatment of cisplatin-ineligible patients. The results of pivotal studies leading to these approvals are listed in Table 2.120,122-128

In 2016, atezolizumab was the first ICI reported to have durable antitumor activity in a subset of patients with advanced UC who progressed on platinum-based chemotherapy. This was based on IMvigor210 (A Study of Atezolizumab in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer [Cohort 2]; ClinicalTrials.gov identifier NCT02108652), a phase 2 study of atezolizumab consisting of 2 patient cohorts: platinum-refractory and treatment-naive, cisplatin-ineligible. In the platinum-refractory population, Rosenberg et al demonstrated an ORR of 15% (95% CI, 11%-19%); furthermore, 38 of 45 responders (84%) had an ongoing response at a median follow-up of 11.7 months.120 Grade 3 or 4 aEs occurred in 50 patients (15%), and the most common was fatigue (N = 5). In addition, grade 3 or 4 irAEs occurred in 15 patients (5%), including pneumonitis, hepatitis, and dermatitis.120 On the basis of durable activity and good tolerability, atezolizumab received accelerated FDA approval in May 2016 for patients with platinum-refractory, advanced UC. The accelerated approval designation was introduced in 1992 to allow for the use of surrogate endpoints (eg, ORR, duration of response) that reasonably predict clinical benefit, hence allowing for faster approval of drugs in areas of unmet need. However, the accelerated approval pathway stipulates the conduct of a follow-up definitive trial. IMvigor211 (A Study of Atezolizumab Compared With Chemotherapy in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer; ClinicalTrials.gov identifier NCT02302807), was a phase 3 study of 931 patients with mUC who progressed despite platinum-based chemotherapy and were randomized to either atezolizumab or investigator’s choice of chemotherapy (docetaxel, paclitaxel, or vinflunine). The study used a hierarchical, hypothesis-testing strategy, such that an OS difference in the PD-L1–high population, and the PD-L1 biomarker did not perform as expected, with better outcomes for both study arms in the PD-L1–high population. There was a significant improvement in OS with atezolizumab in the entire

**TABLE 2. Pivotal Clinical Trials of Immune Checkpoint Inhibitors for Advanced Urothelial Cancer**

| STUDY                                      | MONTH/YEAR | ELIGIBILITY                        | NO. | PHASE | INTERVENTION | PRIMARY ENDPOINT (95% CI) |
|--------------------------------------------|------------|------------------------------------|-----|-------|--------------|---------------------------|
| Rosenberg 2016120 (IMvigor210)             | 05/2016    | Platinum-ineligible or refractory  | 311 | 2     | Atezolizumab | ORR: All, 15% (11%-19%); IC1/IC2/IC3, 18% (13%-24%); IC2/IC3, 26% (18%-36%) |
| Sharma 2007122 (CheckMate-032)            | 11/2016    | Platinum-ineligible or refractory  | 78  | 1/2   | Nivolumab    | ORR: All, 24% (15%-35%)   |
| Balar 2017123 (IMvigor210)                 | 01/2017    | First-line, cisplatin-ineligiblea | 119 | 2     | Atezolizumab | ORR: All, 23% (16%-31%); PD-L1 ≥ 5%, 28% (14%-47%); PD-L1 < 5%, 22% (14%-32%) |
| Bellmunt 2017124 (KEYNOTE-045)            | 03/2017    | Platinum-ineligible or refractory  | 542 | 3     | Pembrolizumab vs chemotherapy | OS: All, HR, 0.73 (0.59-0.91);  P = .002; CPS ≥ 10, HR, 0.57 (0.37-0.88); P = .005; CPS < 10, HR, 0.80 (0.61-1.05) |
| Apolo 2017,125 Patel 2018128 (JAVELIN Solid Tumor trial) | 07/2017; 01/2018 | Platinum-ineligible or refractory | 242 | 1b   | Avelumab     | ORR: All, 17% (11%-24%); PD-L1 ≥ 5, 24% (14%-36%); PD-L1 < 5, 13% (7%-23%) |
| Powles 2017127                             | 09/2017    | Platinum-ineligible or refractory  | 191 | 1/2   | Durvalumab   | ORR: All, 17% (11%-24%); PD-L1 ≥ 25%, 28% (19%-38%); PD-L1 < 25%, 5% (1%-13%) |
| Balar 2017128 (KEYNOTE-052)                | 11/2017    | First-line, cisplatin-ineligibleb | 370 | 2     | Pembrolizumab | ORR: All, 24% (20%-29%); CPS ≥ 10, 39% (28%-50%); CPS 1-10, 20% (14%-28%); CPS < 1, 11% (4%-24%) |

Abbreviations: CheckMate-032, A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors (ClinicalTrials.gov identifier NCT01928394); CPS, combined positive score (percentage of tumor and immune cells with PD-L1 expression × 100); IC, immune cell group (corresponding to level of PD-L1 expression on tumor cells); IMvigor210, A Study of Atezolizumab in Participants With Locally Advanced or Metastatic Urothelial Bladder Cancer (Cohort 2); ClinicalTrials.gov identifier NCT02108652); JAVELIN Solid Tumor trial, Avelumab in Metastatic or Locally Advanced Solid Tumors (ClinicalTrials.gov identifier NCT01772004); KEYNOTE-045, A Study of Pembrolizumab (MK-3475) Versus Paclitaxel, Docetaxel, or Vinflunine for Participants With Advanced Urothelial Cancer (ClinicalTrials.gov identifier NCT02156436); KEYNOTE-052, Study of Pembrolizumab (MK-3475) in Participants With Advanced Urothelial Cancer (ClinicalTrials.gov identifier NCT02335428); ORR, objective response rate; OS, overall survival.

aThe data monitoring committee of this study found early deaths in patients harboring <5% PD-L1 expression, thus approval was restricted to first-line cisplatin-ineligible patients harboring >5% PD-L1 expression.

bThe data monitoring committee of this study found early deaths in patients who had a CPS <10, thus approval was restricted to first-line cisplatin-ineligible patients who had a CPS ≥10.
Despite the success of single-agent ICI, only a subset of patients achieves long-term durable responses. Novel combination strategies with chemotherapy, targeted therapy, and other immunotherapies have been pursued in an effort to extend the benefits of ICI to a larger patient population. Cytotoxic chemotherapy has immunogenic potential because of several factors and has already been successfully implemented in combination with ICIs in non–small cell lung cancer. Early efforts from Galsky and colleagues demonstrated that GC with ipilimumab did not clearly improve OS compared with historical controls but did lead to an expansion of CD4-positive and CD8-positive T cells in the peripheral blood postipilimumab that was associated with durable disease control.

Several randomized phase 3 studies have been initiated to explore the potential benefits of first-line PD-1/PD-L1 blockade versus standard platinum-based chemotherapy versus a combination of these treatments. The IMvigor130 trial (Study of Atezolizumab as Monotherapy and in Combination With Platinum-Based Chemotherapy in Participants With Untreated Locally Advanced or Metastatic Urothelial Carcinoma; ClinicalTrials.gov identifier NCT02807636) showed an improved PFS with atezolizumab plus platinum-based chemotherapy versus platinum-based chemotherapy alone (stratified HR, 0.82; 95% CI, 0.70–0.96; = .007); however, the prespecified threshold for statistical significance at the interim OS analysis was not met (HR, 0.83; 95% CI, 0.69–1.00; = .27), and the trial is ongoing until the final OS analysis. The safety profile of the chemoimmunotherapy arm was similar to that of the chemotherapy-alone arm. Conversely, in a similarly designed trial (KEYNOTE-361: Study of Pembrolizumab With or Without Platinum-Based Combination Chemotherapy Versus Chemotherapy Alone in Urothelial Carcinoma; ClinicalTrials.gov identifier NCT02853305), pembrolizumab in combination with chemotherapy did not meet its prespecified dual primary endpoints of OS and PFS compared with chemotherapy. Interestingly, the data and safety monitoring committees of both IMvigor130 and KEYNOTE-361, before the trials completed accrual, independently identified that patients who had low PD-L1–expressing tumors who were enrolled on these studies and were randomized to single-agent PD-1/PD-L1 blockade were experiencing a higher frequency of deaths compared with patients who were randomized to standard chemotherapy. These findings led the FDA and the European Medical Agency to change the label for the first-line use of atezolizumab and pembrolizumab to the first-line treatment of cisplatin-ineligible patients with mUC and to restrict use to patients with high PD-L1–expressing tumors. Thus, PD-L1 testing is crucial in determining whether cisplatin-ineligible patients can be spared from platinum agents.
Other ongoing phase 3 studies exploring the integration of PD-1/PD-L1 blockade into first-line treatment for patients with mUC include CheckMate 901 (Study of Nivolumab in Combination With Ipilimumab or Standard of Care Chemotherapy Compared to the Standard of Care Chemotherapy Alone in Treatment of Participants With Untreated Inoperable or Metastatic Urothelial Cancer; ClinicalTrials.gov identifier NCT03036098; nivolumab plus GC vs ipilimumab plus nivolumab vs cisplatin/carboplatin plus gemcitabine) and NILE (Study of Durvalumab Given With Chemotherapy, Durvalumab in Combination With Tremelimumab Given With Chemotherapy, or Chemotherapy in Patients With Unresectable Urothelial Cancer; ClinicalTrials.gov identifier NCT03682068; durvalumab plus cisplatin/carboplatin plus gemcitabine vs durvalumab plus tremelimumab plus cisplatin/carboplatin plus gemcitabine vs cisplatin/carboplatin plus gemcitabine). Chemoimmunotherapy is also being investigated in combination with enfortumab vedotin (EV), an antibody-drug conjugate (ADC); specifically, EV plus pembrolizumab plus chemotherapy versus chemotherapy (EV-302: Enfortumab Vedotin and Pembrolizumab, With or Without Chemotherapy, vs Chemotherapy Alone in Untreated Locally Advanced or Metastatic Urothelial Cancer; ClinicalTrials.gov identifier NCT04223856). The emergence of EV in mUC treatment is discussed in a below. Collectively, these studies will determine whether chemoimmunotherapy will be established as standard first-line treatment for patients with advanced UC.

Similar to trials in the neoadjuvant setting, dual ICIs are being investigated in patients with advanced UC. In the CheckMate 032 study (A Study of Nivolumab by Itself or Nivolumab Combined With Ipilimumab in Patients With Advanced or Metastatic Solid Tumors; ClinicalTrials.gov identifier NCT01928394), 2 cohorts received ipilimumab plus nivolumab at different doses. The highest ORR was 38.5% with ipilimumab 3 mg/kg and nivolumab 1 mg/kg, and response rates with respect to ipilimumab were dose-dependent.139 Data from phase 3 the CheckMate 901 study will guide whether ipilimumab plus nivolumab will become a standard approach in patients with treatment-naive, advanced UC. Durvalumab plus tremelimumab is another dual immune checkpoint blockade strategy that showed promising clinical activity in a phase 1 study of platinum-refractory patients, particularly in those with high PD-L1 expression (29.4% vs 15.1%).140 As a result, the DANUBE trial (Study of MEDI4736 [Durvalumab] With or Without Tremelimumab Versus Standard of Care Chemotherapy in Urothelial Cancer; ClinicalTrials.gov identifier NCT02516241), a phase 3 study of durvalumab versus durvalumab plus tremelimumab versus chemotherapy, was undertaken in patients with treatment-naive, advanced UC. However, the study did not meet its primary endpoints of improving OS compared with chemotherapy for single-agent durvalumab in patients with high PD-L1 expression (≥25%) or for durvalumab plus tremelimumab in patients irrespective of their PD-L1 status.141 Another important question with regard to dual ICIs is whether to administer the 2 agents concurrently or sequentially. A phase 2 study of combined durvalumab and tremelimumab versus sequential durvalumab and tremelimumab versus durvalumab is ongoing in platinum-refractory patients with advanced UC to answer this question (Study of Tremelimumab in Patients With Advanced Solid Tumors; ClinicalTrials.gov identifier NCT02527434).

ICIs are also being explored as maintenance therapy for patients who achieve disease control with platinum-based chemotherapy. In the current paradigm, after 6 cycles of chemotherapy, patients undergo radiographic surveillance off-treatment until disease progression. In the Hoosier Cancer Research Network GU14-182 study (Testing the PD-1 Inhibitor Pembrolizumab as Maintenance Therapy After Initial Chemotherapy in Metastatic Bladder Cancer; ClinicalTrials.gov identifier NCT02500121), patients who achieved at least stable disease after up to 8 cycles of first-line platinum-based chemotherapy for advanced UC received either pembrolizumab (N = 55) or placebo (N = 52). At a median follow-up of 14.7 months, 50% of patients crossed over to receive pembrolizumab. PFS was significantly longer in patients who received pembrolizumab compared with those who received placebo (HR, 0.64; 95% CI, 0.41-0.98; P = .038).142 A similarly designed phase 3 study exploring switch maintenance PD-L1 inhibition with avelumab (JAVELIN Bladder 100: A Study of Avelumab in Patients With Locally Advanced or Metastatic Urothelial Cancer; ClinicalTrials.gov identifier NCT02603432) recently reported an improvement in OS with this approach.143 This is the first randomized trial to date demonstrating an OS benefit with early integration of ICI and will likely affect standard care in the near term.

FGFR Inhibition

FGFR gene amplification and overexpression have oncogenic potential with multiple downstream effects, including cell proliferation, survival, migration, invasion, and angiogenesis.144 Although FGFR alterations, particularly FGFR3, are much more common in NMIBC, they can be present in approximately 20% of more advanced stage UC.54,56,145 Furthermore, FGFR3 alterations are enriched in the TCGA luminal subtype (cluster I) of UC. Thus, tumors harboring FGFR3 alterations are potentially vulnerable to FGFR3-targeted therapies.

Initially, dovitinib, a multityrosine kinase inhibitor, did not have clinical activity in patients with FGFR3-altered,
platinum-refractory, advanced UC.\textsuperscript{146} However, the lack of activity with first-generation FGFR3 inhibition, in retrospect, was likely related to poor potency and selectivity of the molecules being investigated. In contrast, a phase 1 basket trial of an FGFR1, FGFR1, and FGFR3 inhibitor, BGJ398, led to disease control in approximately 32% of patients across several tumors, including 3 partial responses in patients with FGFR3-mutated, advanced UC.\textsuperscript{147} Consequently, BCgJ398 use in a UC-specific arm showed a high level of clinical activity (ORR, 38%; disease control rate, 75%).\textsuperscript{148}

This ushered in the clinical development of several FGFR inhibitors for patients with advanced UC. Erdafitinib, a pan-FGFR inhibitor, is the most extensively studied and is currently the only FDA-approved FGFR inhibitor to treat advanced UC. A phase 2 study of erdafitinib in patients with FGFR3-mutated, platinum-refractory, advanced UC showed an impressive ORR of 42% (CR, 3%; partial response, 39%) and disease control in 80% of patients.\textsuperscript{149} Furthermore, in those previously treated with ICIs, clinical responses were seen in 70% of patients.\textsuperscript{149} This study included patients who had one or more of the following alterations: FGFR3 (R248C, S249C, Y373C, G370C) or FGFR gene fusions (FGFR3-TACC3, FGFR3-BA1AP2L1, FGFR2-BICC1, FGFR2-CASP7). On the basis of these results, erdafitinib was FDA-approved in March 2018 for patients with FGFR2-mutated and FGFR3-mutated, advanced UC that progresses despite prior platinum-based chemotherapy. Of importance, patients who are treated with FGFR3 inhibitors require monitoring for common AEs, including hyperphosphatemia, stomatitis, and hand-foot syndrome. In addition, erdafitinib carries a warning for ocular disorders, including central serous retinopathy/retinal pigment epithelial detachment, thus monthly ophthalmologic examinations should be performed in the first 4 months of treatment and every 3 months thereafter. In addition to erdafitinib, several novel FGFR inhibitors (pemigatinib, rogaratinitib, infgratinitib, derazantib, debio 1347, AZD4547, and TAS-120) and an FGFR3-specific monoclonal antibody (MoAb) (vofatamab) are under investigation at various stages of clinical development.

**Antibody-Drug Conjugates**

ADCs were first developed for cancer in early 2000s and now are approved for several hematologic malignancies, including lymphoma and B-cell acute lymphoblastic leukemia. ADCs consist of 3 components: an MoAb against a commonly expressed cancer cell target, a protease-cleavable linker, and a chemotherapeutic agent. The cytotoxic agent is released inside cells only after internalization of ADCs and subsequent lysosomal linker cleavage. Thus this formulation leads to the delivery of high doses of chemotherapy in a targeted manner. UC currently has several highly expressed proteins on the cell surface, including SLITRK6, Nectin-4, Trop-2, and Her-2, thus making ADCs a logical therapeutic strategy. ASG-15ME, which contains an antibody for SLITRK6 (a type I transmembrane neuronal receptor) and microtubule-disrupting chemotherapy called monomethyl auristatin E (also known as vedotin), was among the first reported ADCs in heavily pretreated patients with UC. In a phase 1 trial, reversible ocular AEs occurred in 29.4% of patients and among all dosing levels, and 37.5% of patients (N = 18) achieved a radiographic response.\textsuperscript{150}

EV, also known as ASG-22ME, is a MoAb targeting nectin-4 and is linked to vedotin. Nectin-4 is a cell adhesion molecule that is highly expressed in several cancers, including UC.\textsuperscript{151} In the initial phase 1 dose-escalation/dose-expansion study, which included a cohort of 71 heavily pretreated patients with advanced UC, Petrylak et al reported an ORR of 40% (95% CI, 27.6%-53.5%). Furthermore, those who received the recommended phase 2 dose (1.25 mg/kg) had even higher responses.\textsuperscript{151} Grade ≥3 AEs occurred in 19 patient (28%), and the most common were fatigue (50%), alopecia (48%), and decreased appetite (41%). Other common side effects were rash, pruritis, diarrhea, nausea, hypophosphatemia, and peripheral neuropathy. In an updated analysis of 155 patients, of whom 112 received EV at the recommended phase 2 dose, Rosenberg and colleagues demonstrated an ORR of 33% (95% CI, 24.7%-42.9%), including 3 CRs.\textsuperscript{152} The median duration of response was 24.3 weeks (95% CI, 16.3-47.3 weeks) and PFS was 23.1 weeks (95% CI, 20.1-24.1 weeks). The most common grade ≥3 AEs were anemia (7%), hyponatremia (6%), urinary tract infection (6%), and hyperglycemia (5%). That study led to an accelerated FDA approval in December 2019 for patients with advanced UC previously treated with platinum-based chemotherapy and PD-1/PD-L1 inhibitors. EV has also been explored in the first-line setting combined with pembrolizumab in a phase 1/2 study of 45 patients with mUC.\textsuperscript{153} The ORR in that study was an impressive 73%, including a 15.6% CR rate. With a median follow-up of 10.4 months, 55% of patients had an ongoing response. Side effects of this combination were similar to the individual toxicities of each drug. On the basis of these findings, the EV-302 phase 3 study will evaluate this combination compared with gemcitabine plus platinum chemotherapy.

Other exciting ADCs currently in an early phase of clinical development include sacituzumab govitecan and DS-8201a. Sacituzumab govitecan targets Trop-2, which is highly expressed across several tumors, and delivers a potent topoisomerase I inhibitor known as SN-38. In an interim analysis of a phase 1/2 basket study in patients with advanced solid tumors, 45 patients who previously received platinum-based chemotherapy and/or an ICI for advanced
UC were evaluated and experienced an ORR of 31% with 2 CRs.\textsuperscript{154} Common grade ≥3 AEs included neutropenia (38%), anemia (11%), hypophosphatemia (11%), diarrhea (9%), fatigue (9%), and febrile neutropenia (7%). A phase 2 study in advanced UC (TROPHY-U-01: Phase II Open Label Study of IMMU-132 in Metastatic Urothelial Cancer; ClinicalTrials.gov identifier NCT03547973) is ongoing.

DS-8201a targets Her-2, which is expressed on 37% to 50% of UCs\textsuperscript{155} and is linked to DXd, a novel topoisomerase I inhibitor. DS-8201a is currently in phase 1 testing across several solid tumors (Study of DS-8201a in Subjects With Advanced Solid Malignant Tumors; ClinicalTrials.gov identifier NCT02564900) and is also being evaluated in combination with nivolumab (Trastuzumab Deruxtecan With Nivolumab in Advanced Breast and Urothelial Cancer; ClinicalTrials.gov identifier NCT03523572).

**Antiangiogenic Therapy**

Vascular endothelial growth factor receptor 1 (VEGF1) and VEGFR2 and their ligands (VEGF-A through VEGF-D) promote angiogenesis and play a key role in the pathogenesis and progression of UC.\textsuperscript{156} Many VEGF/VEGFR inhibitors have been tested in advanced UC as single-agents, with modest antitumor activity.\textsuperscript{157-162} On the basis of other solid tumors,\textsuperscript{163} VEGF/VEGFR inhibitors may be more effective in combination with chemotherapy. However, in a placebo-controlled, phase 3 trial evaluating GC plus bevacizumab (a VEGF MoAb), Rosenberg and colleagues reported no improvement in OS from the combination compared with placebo-months (Study of EMN001 in Cancer Patients With Advanced UC; ClinicalTrials.gov identifier NCT01672021).

Another possible combination involving VEGF/VEGFR inhibitors is with ICIs based on their potential immunomodulatory properties.\textsuperscript{166,167} Cabozantinib, a VEGFR2/c-MET/RET tyrosine kinase inhibitor, has been studied in combination with nivolumab (with or without ipilimumab) in a phase 1 expansion cohort of patients with platinum-refractory, advanced UC. Interestingly, this study included both ICI-naive and ICI-refractory patients. In the ICI-naive population (N = 26), the ORR for cabozantinib plus nivolumab (N = 15) and for combined cabozantinib, nivolumab, and ipilimumab (N = 11) was 50% and 22%, respectively.\textsuperscript{168} Of the 7 ICI-refractory patients, 2 had a PR, suggesting the potential ability of this combination to overcome ICI resistance. Grade 3 or 4 AEs occurred in 69% of patients, most commonly fatigue, elevated lipase, and hypophosphatemia, and severe irAEs leading to discontinued treatment occurred in 3 patients. Further investigation of VEGF tyrosine kinase inhibitor/ICI combinations is ongoing.

**Conclusions**

Over the last decade, there has been a transformation in our understanding of the pathogenesis and management of UC. Although cisplatin-based chemotherapy remains the standard therapy in the perioperative and first-line metastatic settings, novel therapies for UC have finally arrived and are rapidly altering treatment paradigms. This includes the approvals of 5 ICIs in the platinum-refractory setting and of 2 ICIs in the first-line setting for patients who are deemed cisplatin-ineligible and harbor tumors with high PD-L1 expression. Most recently, erdafitinib and EV have been approved for patients with platinum-refractory, advanced UC. The next decade will build upon these recent achievements and focus on moving these novel therapies into earlier disease settings, optimizing sequencing and combinations of approved therapies, improving patient selection, and identifying novel therapeutic targets.
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