Chapter 19
Treatment of Metastatic Bladder Cancer

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Introduction

The treatment options for patients with locally advanced or metastatic bladder cancer (BC) have been limited for decades. The main first-line treatment has been platinum-based chemotherapy, and the role of second-line chemotherapy had been limited until the development of immune checkpoint inhibitors. Approximately 25% of patients with bladder cancer present with muscle-invasive disease, of whom half may ultimately progress to metastatic disease, while ~5% present with metastatic disease de novo [1]. The most common histology of cancer in the urinary tract is urothelial carcinoma (UC), and the bladder is the most common primary site. UC consists of approximately 90% of BC, and the evidence of treatment of BC is mainly based on the trials for UC [2]. The median overall survival (OS) of patients with metastatic BC was about 3 months prior to the development of chemotherapeutic regimens with activity in this disease, and more contemporary clinical trials report median OS of ~15 months [3, 4]. Several clinical factors have been associated with prognosis in prior studies. The Karnofsky or Eastern Cooperative Oncology Group performance status (KPS $\leq$ 80% or ECOG PS > 1) and visceral metastases (lung, liver, or bone) were found as prognostic factors among patients who received methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) or paclitaxel, gemcitabine, and cisplatin (PGC) in the first-line setting [5, 6]. In the second-line setting, a study

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K. L. Stratton, A. K. Morgans (eds.), *Urologic Oncology*,
https://doi.org/10.1007/978-3-030-89891-5_19

evaluating vinflunine for platinum-refractory patients showed that anemia (hemoglobin <10 g/dL), liver metastases, and ECOG PS (>0) were related to poor prognosis [7]. Molecular features associated with prognosis that have been extensively validated have been more elusive though molecular subtypes of bladder cancer defined by gene expression profiling so seem to confer some prognostic information.

First-Line Treatment for Metastatic Bladder Cancer

The first-line treatment for patients with locally advanced or metastatic BC has been limited until the development of immune checkpoint blockade in the late 2010s. Currently, gemcitabine plus cisplatin (GC) and MVAC are the main options for cisplatin-eligible patients (Fig. 19.1), and carboplatin-based chemotherapy (i.e., gemcitabine plus carboplatin) has been the mainstay of treatment for patients ineligible for cisplatin. Programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) blockade with pembrolizumab or atezolizumab is a potential option for cisplatin-ineligible patients harboring tumors with increased PD-L1

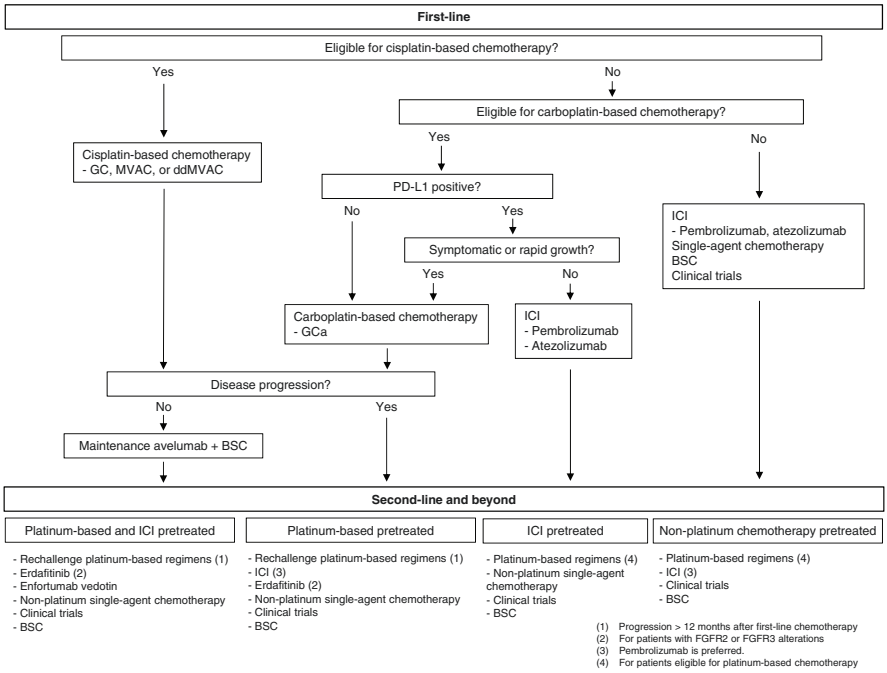

Fig. 19.1 Treatment algorithm for metastatic urothelial cancer. Abbreviation: GC gemcitabine and cisplatin, MVAC methotrexate, vinblastine, doxorubicin and cisplatin, ddMVAC dose-dense MVAC, GCa gemcitabine and carboplatin, ICI immune checkpoint inhibitor, BSC best supportive care, PD-L1 programmed death-ligand 1

expression though initial chemotherapy with switch maintenance PD-1/PD-L1 blockade has emerged as a preferred strategy. For patients that are "chemotherapy ineligible," PD-1/PD-L1 blockade remains a potential treatment option.

Treatment for Cisplatin-Eligible Patients

In the 1990s, cisplatin-based chemotherapy was shown to improve the OS in patients with advanced UC. At first, MVAC showed survival improvement when compared with cisplatin alone [8]. MVAC had toxicities such as myelosuppression and mucositis. Several platinum-based doublets with newer cytotoxic drugs, such as the combination of GC, were subsequently explored in phase 2 trials demonstrating promising activity [9]. A phase 3 trial comparing GC with MVAC showed a similar response rate and OS, albeit with less toxicity with GC, and GC became a standard first-line regimen [4, 10]. Dose-dense MVAC (ddMVAC) with granulocyte colony-stimulating factor demonstrated less toxicity and potentially better long-term survival rates compared with classical MVAC in a phase 3 trial [11]. Dose-dense GC was also compared with ddMVAC but no OS difference was observed [12]. GC was compared with paclitaxel plus GC (PGC) in a phase 3 trial (EORTC study 30987). Although subgroup analyses showed an OS improvement among patients who met all eligibility criteria and patients with primary BC, PGC had more toxicities and showed no significant survival benefit in the overall population [13]. Together, these series of single-arm and randomized studies have solidified the role of GC and ddMVAC as standard first-line options for cisplatin-eligible patients with metastatic UC (Table 19.1).

Treatment for Cisplatin-Ineligible Patients

Carboplatin-Based Chemotherapy

The risks versus benefits of cisplatin-based chemotherapy for patients with metastatic UC require individualized shared medical decisions. However, criteria for "cisplatin-ineligibility" have been harmonized for clinical trial eligibility purposes which can also offer some guidance for routine clinical care which include the following: ECOG PS >1, glomerular filtration rate (GFR) $\leq$60, grade $\geq$2 hearing loss, grade $\geq$2 peripheral neuropathy, and the New York Heart Association $\geq$ III heart failure [14]. Renal impairment, common in patients with UC based on age-associated physiologic declines in GFR, age- and smoking-related comorbidities, and potential tumor-related ureteral obstruction, is the most common reason for "cisplatin ineligibility." The development of chemotherapeutic regimens that balance safety and efficacy for this subset of patients with metastatic UC has been pursued for decades. A phase 2/3 randomized controlled trial (RCT) which compared gemcitabine plus

Table 19.1 Standard treatment regimens for locally advanced or metastatic urothelial cancer

Study	Eligibility	Number	Phase	Intervention	Treatment detail	Response rate (%)	Median PFS (months)	Median OS (months)	Reference
First-line regimens									
Loehrer 1992	NA	269	III	MVAC vs cisplatin	MVAC (methotrexate 30 mg/m^2 on days 1, 15, 22; vinblastine 3 mg/m^2 on day 2, 15, 22; doxorubicin 30 mg/m^2 on day 2; cisplatin 70 mg/m^2 on day 2, every 28 days)	39 vs 12	10.0 vs 4.3	12.5 vs 8.2	[8]
von der Maase 2000	NA	405	III	GC vs MVAC	GC (gemcitabine 1000 mg/m^2 on days 1, 8, 15; cisplatin 70 mg/m^2 on day 2, every 21 days)	49 vs 46	7.7 vs 8.3	14.0 vs 15.2	[10]
Sternberg 2006	NA	263	III	ddMVAC vs MVAC	ddMVAC (methotrexate 30 mg/m^2 on days 1; vinblastine 3 mg/m^2 on day 2; doxorubicin 30 mg/m^2 on day 2; cisplatin 70 mg/m^2 on day 2 with G-CSF on days 3–7, every 15 days)	64 vs 50	9.5 vs 8.1	15.1 vs 14.9	[11]
Bellmunt 2012	NA	626	III	PGC vs GC	PGC (paclitaxel 80 mg/m^2 on days 1, 8; gemcitabine 1000 mg/m^2 on days 1, 8, 15; cisplatin 70 mg/m^2 on day 2, every 21 days)	55.5 vs 43.6	8.3 vs 7.6	15.8 vs 12.7	[13]

De Santis 2012	With renal dysfunction	238	II/III	GCa vs M-CAVI	GCa (gemcitabine 1000 mg/m^2 on days 1, 8; carboplatin AUC 4.5 on day 1, every 21 days) M-CAVI (methotrexate 30 mg/m^2 on days 1, 15, 22; carboplatin AUC 4.5 on day 1; vinblastine 3 mg/m^2 on days 1, 15, 22, every 28 days)	41.2 vs 30.3	5.8 vs 4.2	9.3 vs 8.1	[15]
Vuky 2020	Cisplatin-ineligible	374	II	Pembrolizumab	Pembrolizumab (200 mg on day 1, every 21 days)	28.6	2.2	11.3	[19]
Balar 2017	Cisplatin-ineligible	123	II	Atezolizumab	Atezolizumab (1200 mg on day 1, every 21 days)	23.0	2.7	15.9	[17]
Powles 2020	Disease-controlled with platinum-based chemotherapy	700	III	Maintenance avelumab vs BSC	Maintenance avelumab: four to six cycles of GC or GCa following avelumab (10 mg/kg on day 1, every 14 days)	–	3.7 vs 2.0	21.4 vs 14.3	[21]
Second-line regimens (for patients with progression after platinum-based chemotherapy)									
Fradet 2019	NA	542	III	Pembrolizumab vs chemotherapy[a]	Pembrolizumab (200 mg on day 1, every 21 days) Paclitaxel (175 mg/m^2 on day 1), docetaxel (75 mg/m^2 on day 1), or vinflunine (320 mg/m^2 on day1), every 21 days	21.1 vs 11.0	2.1 vs 3.3	10.1 vs 7.3	[25]
Powles 2018	NA	931	III	Atezolizumab vs chemotherapy[b]	Atezolizumab (1200 mg on day 1, every 21 days) Paclitaxel (175 mg/m^2 on day 1), docetaxel (75 mg/m^2 on day 1), or vinflunine (320 mg/m^2 on day1), every 21 days	13.4 vs 13.4	2.1 vs 4.0	8.6 vs 8.0	[23]

(continued)

Table 19.1 (continued)

Study	Eligibility	Number	Phase	Intervention	Treatment detail	Response rate (%)	Median PFS (months)	Median OS (months)	Reference
Sharma 2017	NA	270	II	Nivolumab	Nivolumab (3 mg/kg, every 14 days)	19.6	2.0	8.74	[27]
Patel 2018	NA	249	I	Avelumab	Avelumab (10 mg/kg, every 14 days)	17.0	6.6	6.5	[29]
Powles 2017	NA[c]	191	I/II	Durvalumab	Durvalumab (10 mg/kg every 14 days)	17.8	1.5	18.2	[30]
	Later regimens								
Loriot 2019	FGFR alteration and progression after one or more chemotherapies[b]	99	II	Erdafitinib	Erdafitinib (8 mg daily, can be increased to 9 mg daily if serum phosphate level < 5.5 mg/dL on day 14)	40	5.5	13.8	[39]
Rosenberg 2019	Previously treated with platinum-based regimen and anti-PD-1/L1 therapy.	125	II	Enfortumab vedotin	Enfortumab vedotin (1.25 mg/kg on days 1, 8, 15, every 28 days)	44	5.8	11.7	[42]
Bellmunt 2009	Previously treated with platinum-based regimen	370	III	Vinflunine vs BSC	Vinflunine (320 mg/m^2 on day 1, every 21 days)	8.6 vs 0	3.0 vs 1.5	6.9 vs 4.3	[31]

Abbreviation: *NA* not available; *FGFR* fibroblast growth factor receptor; *PD-1* programmed cell death protein 1; *PD-L1* programmed death-ligand 1; *MVAC* methotrexate, vinblastine, doxorubicin, and cisplatin; *GC* gemcitabine and cisplatin; *ddMVAC* dose-dense MVAC; *PGC* paclitaxel, gemcitabine, and cisplatin; *GCa* gemcitabine and carboplatin; *M-CAVI* methotrexate, carboplatin, and vinblastine; *BSC* best supportive care; *PFS* progression-free survival; *OS* overall survival

[a]Investigators' choice from paclitaxel, docetaxel, or vinflunine

[b]The study did not specify previous exposure to PD-1/PD-L1 inhibitors as inclusion criteria

[c]The study did not selectively include patients with progression after platinum-based regimen. Nevertheless, 99.5% of patients included had received prior chemotherapy, and 95% of them had received platinum-based chemotherapy

carboplatin (GCa) with methotrexate, carboplatin, and vinblastine (M-CAVI) showed less toxicity and higher response rate in GCa than M-CAVI (overall response rate (ORR), 42% vs 30%) although no significant difference in ORR and OS was observed (EORTC study 30986) [15]. A recent phase 2 RCT evaluating the efficacy of vinflunine plus gemcitabine (VG) compared with GCa showed higher ORR in VG than GCa, but no significant difference was observed in OS and progression-free survival (PFS) [16]. Therefore, GCa has become a favored first-line regimen for cisplatin-ineligible patients with metastatic UC.

Immune Checkpoint Blockade

PD-1/PD-L1 inhibitors demonstrated early after in UC in expansion cohorts of phase I studies in solid tumors leading to the rapid initiation of larger studies. Atezolizumab, a PD-L1 inhibitor, was evaluated in the IMvigor210 phase 2 trial. In cohort 1 of this study, 119 cisplatin-ineligible chemotherapy-naïve patients with locally advanced or metastatic UC regardless of PD-L1 expression status were enrolled, and atezolizumab demonstrated an ORR of 23%, median PFS of 2.7 months, and median OS of 15.9 months [17]. Another trial (KEYNOTE-052) which evaluated the efficacy of pembrolizumab, a PD-1 inhibitor, for 370 cisplatin-ineligible patients showed an ORR of 29% with CR of 9%, median PFS of 2.2 months, and median OS of 11.3 months. Notably, ORR was 47% in patients with high PD-L1 expression (combined positive score (CPS) $\geq$10%) and 20% in patients with CPS <10%, respectively [18, 19]. Based on these results, atezolizumab and pembrolizumab were approved by the US Food and Drug Administration (FDA) in 2017 for cisplatin-ineligible patients regardless of the PD-L1 expression status in the first-line setting. However, the interim results of two phase 3 studies (IMvigor130 and KEYNOTE-361) which compared PD-1/PD-L1 inhibitors plus chemotherapy, PD-L1/PD-L1 inhibitor monotherapy, and chemotherapy showed poorer survival outcomes among patients with low PD-L1 expressing tumors who received PD-1/PD-L1 inhibitor monotherapy than those who received platinum-based chemotherapy. Therefore, for cisplatin-ineligible patients, the FDA prescribing label was changed to limit atezolizumab and pembrolizumab to patients with tumor harboring high levels of PD-L1 expression based on the appropriate assay for the particular PD-1/PD-L1 inhibitor. The FDA prescribing label did permit the use of these therapies for patients deemed "platinum-ineligible" (i.e., "chemotherapy-ineligible") regardless of the PD-L1 expression status. The evidence to select either carboplatin-based chemotherapy or PD-1/PD-L1 inhibitor monotherapy for cisplatin-ineligible patients is insufficient. Because of the higher response rate in carboplatin-based chemotherapy (ORR, 41.2% in EORTC Study 30986) compared with that in PD-1/PD-L1 inhibitor monotherapy (ORR, around 20% in IMvigor210 and KEYNOTE-052), patients with rapid progression or visceral crisis might be better to be treated with carboplatin-based chemotherapy. However, the incidence of grade 3 or more adverse events (AEs) is higher in chemotherapy, and patients with poor performance status or slower tumor growth may prefer PD-1/PD-L1 inhibitor monotherapy.

Maintenance Immune Checkpoint Blockade

Standard first-line platinum-based chemotherapy for metastatic UC is typically administered for up to six cycles, in the absence of prohibitive side effects or disease progression, and then discontinued due to the likelihood of cumulative side effects in the absence of additional benefit. Given the generally short duration of response upon discontinuation of chemotherapy, and the efficacy of PD-1/PD-L1 blockade as second-line treatment, initiating immune checkpoint blockade upon cessation of chemotherapy in a switch maintenance approach has been explored. In a phase 2 trial (GU14-182) which compared switch maintenance pembrolizumab with placebo subsequently after platinum-based chemotherapy, pembrolizumab demonstrated an improvement in PFS (5.4 versus 3.0 month; hazard ratio, HR 0.64 [95% confidence interval, CI, 0.41–0.98]) [20]. In parallel, the strategy to use avelumab, a PD-L1 inhibitor, as maintenance therapy was studied in a phase 3 trial (JAVELIN Bladder 100) [21]. Patients who received four to six cycles of GC/GCa without disease progression were randomly assigned to receive best supportive care with or without maintenance avelumab. Maintenance avelumab prolonged OS and PFS in the overall population (OS: 21.4 versus 14.3 months; HR 0.56 [95% CI 0.40–0.79]; PFS: 3.7 versus 2.0 months; HR 0.62 [95% CI 0.52–0.75]) and in the PD-L1-positive population. As a result, maintenance immune checkpoint blockade after initial platinum-based chemotherapy has been embraced as a standard treatment approach.

Treatment in the Second-Line and Beyond Setting

Cytotoxic chemotherapy, typically with taxanes, had been a common approach for patients with metastatic UC progressing despite first-line chemotherapy. However, ORR with this approach was relatively low and better strategies were pursued. An understanding of the tumor microenvironment and the molecular features of UC has led to the development of multiple new therapeutic classes in the second-line and beyond setting.

Immune Checkpoint Blockade

Traditionally, single-agent cytotoxic chemotherapy was the main treatment option in the second-line and beyond setting before the development of immunotherapy. The development of immune checkpoint blockade led to the expansion of therapeutic options and changed the second-line and beyond treatment scheme. Currently, five anti-PD-1/PD-L1 antibodies (pembrolizumab, atezolizumab, nivolumab, durvalumab, and avelumab) are FDA-approved in the second-line setting. Atezolizumab

was first approved as it showed promising activity among patients with advanced UC progressed during or after the previous platinum-based chemotherapy in the early-phase trials [22]. Several cancer cell and tumor microenvironment features were associated with a high likelihood of response to atezolizumab, such as PD-L1 expression, tumor mutational burden, and molecular subtype, but none of these has been integrated into clinical decision-making [22]. The efficacy of atezolizumab was subsequently confirmed by the phase 3 trial (IMvigor211) that compared atezolizumab with conventional single-agent chemotherapy (paclitaxel, docetaxel, or vinflunine). Although this study did not meet its primary endpoint in patients with PD-L1 high expressing tumors, there was a suggestion of better outcomes with atezolizumab versus chemotherapy in the intent-to-treat population though this was considered exploratory given the hierarchical statistical analysis plan (i.e., improved OS needed to be demonstrated in the patients with PD-L1 high expressing tumors before hypothesis testing could formally occur in the intent-to-treat population) [23]. In contrast with atezolizumab, pembrolizumab improved the median OS (10.1 versus 7.3 months; HR 0.7 [95% CI 0.57–0.85]) in platinum-refractory patients compared with chemotherapy (paclitaxel, docetaxel, or vinflunine) in the phase 3 trial (KEYNOTE-045). Pembrolizumab also demonstrated better response rate (21% vs 11%) and less severe toxicity (17% vs 50%) [24, 25]. Pembrolizumab in patients with high PD-L1 expression (CPS $\geq$ 10) achieved similar ORR (20.3%) to the overall population, suggesting OS benefit was independent of the PD-L1 expression level. Other immune checkpoint inhibitors including nivolumab (PD-1 inhibitor), avelumab (PD-L1 inhibitor), and durvalumab (PD-L1 inhibitor) were also shown to have promising efficacy in early-phase clinical trials which resulted in FDA approval. The phase 1/2 CheckMate 032 trial evaluating nivolumab monotherapy for recurrent or platinum-ineligible patients showed 24% of ORR regardless of PD-L1 expression [26]. Another phase 2 CheckMate 275 trial assessing nivolumab monotherapy showed a similar ORR (19.6%) and median OS of 8.7 months [27]. This trial found that higher tumor mutational burden was associated with improved ORR, PFS, and OS [28]. Avelumab and durvalumab were also found to have adequate ORR (17% with avelumab and 17% with durvalumab) in early-phase clinical trials regardless of the PD-L1 expression status [29, 30].

Chemotherapy

Given the results of KEYNOTE-045 and IMvigor211 trials, single-agent chemotherapy with taxanes (or vinflunine in countries where this therapy is available) is now usually reserved for patients with contraindications to immune checkpoint inhibitors though newer therapies have further decreased the use of these therapies. In Europe, vinflunine is approved for second-line use based on the phase 3 trial result which compared vinflunine with best supportive care among 370 patients previously treated with platinum-based chemotherapy. This trial demonstrated no significant difference in OS (6.9 versus 4.6 months; HR 0.88 [95%CI 0.69–1.12])

though a trend toward better outcomes was observed [31]. Other agents such as taxanes, gemcitabine, and ifosfamide were shown in previous studies to have 10–20% response rate [32–35].

FGFR Inhibitors

Fibroblast growth factor receptor (FGFR) is known to control cell proliferation, survival, migration, and differentiation in cancer cells [36]. Alterations of FGFR lead to oncogenesis which is seen among several cancer types including UC though UC harbors among the highest frequency of somatic FGFR3 alterations [36]. Generally, alterations of FGFR3 are seen in approximately 20% of patients with advanced UC, and FGFR2 or FGFR3 is commonly involved in the luminal I subtype [36, 37]. Initially, dovitinib, a multi-targeted inhibitor of tyrosine kinases including FGFR3, was investigated for platinum-refractory patients with or without FGFR mutations. However, this phase 2 trial did not show substantial activity with dovitinib [38]. Subsequently, more potent and selective FGFR3 inhibitors were developed and demonstrated activity on UC. Erdafitinib, a pan-FGFR inhibitor, was approved by the FDA for platinum-refractory patients as erdafitinib showed efficacy in patients with FGFR mutations (FGFR3 gene mutation or FGFR2/3 gene fusions) with 42% of ORR, median PFS of 5.5 months, and median OS of 13.8 months, respectively. Of note, about 70% of patients who were previously treated with immune checkpoint blockade gained response in this trial [39]. In any grade AEs, hyperphosphatemia was seen in 77% of patients, followed by stomatitis (58%) and diarrhea (50%). Other important AEs with erdafitinib are hand-foot syndrome, nail changes (onycholysis, 18%; paronychia, 17%; nail dystrophy, 16%; nail disorder, 8%), and ocular events including dry eye and central serous retinopathy which require dry eye prophylaxis with ocular demulcents and regular ophthalmologic examinations during the first 4 months of treatment and every 3 months afterward [39]. Several studies are ongoing to evaluate other pan-FGFR inhibitors and an FGFR3-specific antibody to develop therapeutic options for patients with FGFR alterations.

Enfortumab Vedotin

Enfortumab vedotin is an antibody-drug conjugate (ADC) that is composed of an anti-nectin-4 monoclonal antibody conjugated to monomethyl auristatin E (called vedotin), a micro-tubule-disrupting agent [40]. Nectin-4 is a transmembrane protein and related to oncogenesis in cancer cells. Several solid tumors such as urothelial, breast, gastric, and lung carcinoma are known to have high expression of Nectin-4 [41]. A phase 2 trial (EV-201) demonstrated the efficacy of enfortumab vedotin in 125 patients with locally advanced or metastatic UC who had progression after

platinum-based chemotherapy and immunotherapy, resulting in FDA approval in 2019. This study showed an ORR of 44%, median PFS of 5.8 months, and median OS of 11.7 months [42]. Grade ≥3 treatment-related adverse events (TRAEs) were seen in 54% of patients, and the common grade ≥3 TRAEs were neutropenia (8%), anemia (7%), and fatigue (6%). Currently, a phase 3 trial that compares enfortumab vedotin with chemotherapy (paclitaxel, docetaxel, or vinflunine) for patients previously treated with platinum-based chemotherapy and immunotherapy is ongoing (EV-301, NCT03474107). Concurrently, another phase 3 trial (EV-302, NCT04223856) will compare enfortumab vedotin plus pembrolizumab with GC/GCa in the first-line setting.

Future Perspective of Treatment

Combination Treatment with Immunotherapy

To explore the potential benefits of the combination therapy using immune checkpoint inhibitors and other agents, several phase 3 trials are ongoing both in the first-line and the later line settings. Especially, the IMvigor130 trial comparing atezolizumab, atezolizumab plus GC/GCa, and GC/GCa showed significant improvement of PFS with atezolizumab plus GC/GCa compared with GC/GCa (stratified HR 0.82 [95% CI 0.70–0.96]) but did not show OS benefit in the interim analysis (stratified HR 0.83 [95% CI 0.69–1.0]). This study is ongoing and the final OS analysis is awaited [43]. Another phase 3 study, KEYNOTE-361, compared pembrolizumab plus GC/GCa versus GC/GCa. Although there was a trend toward improvement in PFS (HR 0.78 [95% CI 0.65–0.93]) and OS (HR 0.86 [95% CI 0.72–1.02]) for patients treated with pembrolizumab plus GC/GCa, the study results did not reach statistical significance per the pre-specified statistical plan [44]. Another potential combination is the dual immune checkpoint inhibitors as the efficacy of this strategy was shown in other cancers such as renal cell carcinoma and lung cancer [45, 46]. Nivolumab plus ipilimumab (a cytotoxic T-lymphocyte antigen 4 [CTLA-4] inhibitor) was investigated in the CheckMate 032, phase 2 trial. In this study, 274 patients who showed progression on prior platinum-based chemotherapy were assigned to either nivolumab monotherapy or nivolumab plus ipilimumab which had two cohorts with different dose. Nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) provided the greatest efficacy among three cohorts in ORR (38.8%), PFS (4.9 months), and OS (15.3 months) [47]. Currently, a phase 3 trial comparing nivolumab plus ipilimumab versus platinum-based chemotherapy in the first-line setting is ongoing (CheckMate 901, NCT03036098). Dual immune checkpoint inhibitors in the first-line setting were also investigated in the DANUBE trial (NCT02516241) which compared durvalumab (PD-L1 inhibitor) versus durvalumab plus tremelimumab (CTLA-4 inhibitor) versus GC/GCa. However, this study did not meet the primary endpoint that was the OS benefit from durvalumab monotherapy compared with GC/GCa in the high PD-L1 expression group and OS benefit

from durvalumab plus tremelimumab compared with GC/GCa regardless of PD-L1 expression status [48]. There is another study, the NILE trial (NCT03682068), which evaluates the efficacy of durvalumab plus GC/GCa, durvalumab plus tremelimumab with GC/GCa, and GC/GCa alone. This study is ongoing and will provide insights into the efficacy of dual immune checkpoint inhibitors with chemotherapy.

Molecular-Targeted Therapy and ADC

In addition to immunotherapy, other therapeutic agents have been explored. Angiogenesis inhibitors targeting the vascular endothelial growth factor (VEGF) pathway were investigated for advanced or metastatic BC. Ramucirumab, a monoclonal antibody that inhibits the VEGF receptor-2 (VEGFR2), was explored in a phase 3 trial (RANGE). Ramucirumab plus docetaxel was compared with docetaxel alone for platinum-refractory patients. Although PFS was significantly longer in ramucirumab plus docetaxel therapy (4.1 versus 2.8 months; HR 0.70 [95% CI 0.57–0.85]), it did not improve OS (9.4 versus 7.9 months; HR 0.89 [95% CI 0.72–1.09]) [49]. Bevacizumab, a monoclonal antibody targeting VEGF-A, plus GC was evaluated in the first-line setting in a phase 3, CALGB 90601 trial. Similarly, this combination improved PFS (HR 0.77 [95%CI 0.63–0.93]) but did not prolong OS (HR 0.87 [95% CI 0.72–1.06]) compared with GC alone [50]. Although these trials showed the potential efficacy of angiogenesis inhibitors, no agents are currently approved. The combination of angiogenesis inhibitors with PD-1/PD-L1 blockade has also been evaluated. Cabozantinib, a multi-targeted inhibitor of tyrosine kinases including VEGFR2, with nivolumab alone or with ipilimumab demonstrated a modest ORR in a phase 1 trial [51]. Lenvatinib, another multi-targeted inhibitor of tyrosine kinase including VEGFR1-3, with pembrolizumab demonstrated 25% of ORR for solid tumors in a phase 1 trial [52]. A phase 3 trial comparing lenvatinib plus pembrolizumab with pembrolizumab alone for platinum-ineligible patients in the first-line setting is ongoing (NCT03898180). Other potential options are ADCs. Sacituzumab govitecan, a Trop-2-directed antibody conjugated to a topoisomerase I inhibitor (SN-38), has been widely investigated for solid tumors and obtained approval for previously treated metastatic triple-negative breast cancer in 2020 [53]. Two cohorts of a basket phase 2 trial (NCT03547973) showed an ORR of ~30% in patients with metastatic UC who progressed after platinum-based chemotherapy and immunotherapy and in platinum-ineligible patients with immunotherapy failure [54, 55]. The cohort 3 of this study which evaluates sacituzumab govitecan plus pembrolizumab for patients after failure of platinum-based chemotherapy or immunotherapy and a phase 3 trial (NCT04527991) which compares sacituzumab govitecan with chemotherapy (docetaxel, paclitaxel, or vinflunine) after the failure of platinum-based chemotherapy and immunotherapy are ongoing. Another promising candidate of ADC is trastuzumab deruxtecan, composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody linked to a cytotoxic

topoisomerase I inhibitor. Approximately 30% to 50% of UC is known to express HER2 [56]. It showed clinical efficacy among HER2-positive solid tumors such as breast and gastric cancer [57–59]. A phase 2 trial for HER2 expressing tumors including BC (NCT04482309) and another trial evaluating trastuzumab deruxtecan plus nivolumab for breast cancer and UC (NCT03523572) are now conducted.

Treatment for Metastatic Non-urothelial Bladder Cancer

Since the majority of BC is UC and most clinical trials have been conducted for patients with UC, there is a lack of evidence regarding treatment options for patients with locally advanced or metastatic non-urothelial BC. There are no standardized therapeutic options for this population. Therefore, patients with non-urothelial histology are encouraged to get molecular profiling techniques including next-generation sequencing and participate in the clinical trials. If there is a lack of trials, this population can be treated with GC/GCa, ifosfamide plus paclitaxel plus cisplatin, or paclitaxel plus carboplatin plus gemcitabine based on the results of phase 2 studies in the first-line setting [60–62].

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