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GENITOURINARY CANCERS (DP PETRYLAK AND JW KIM, SECTION EDITORS)

Current Status and Future Direction of Immunotherapy in Urothelial Carcinoma

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Abstract

Purpose of Review Since 2016, five new programmed cell death protein 1/ligand 1 (PD-1/L1) checkpoint inhibitors have been approved for metastatic urothelial carcinoma. This review will summarize the data supporting the widespread use of these agents and highlight areas of ongoing clinical development.

Recent Findings PD-1/L1 axis inhibition has demonstrated clear superiority to chemotherapy for the treatment of metastatic urothelial cancer in the second-line setting. A multitude of ongoing studies are investigating the feasibility and efficacy of incorporating established and novel immunotherapies into earlier lines of therapy, including non-metastatic muscle-invasive bladder cancer and even non-muscle-invasive disease. Early-phase clinical trials have begun to explore the safety and activity of novel immune-oncology combinations across a range of clinical settings.

Summary Immunotherapy has a clearly defined role in the treatment of metastatic urothelial cancer both in the platinum-refractory setting and in the first-line cisplatin-ineligible setting. Ongoing clinical trials will dictate how to best incorporate immunotherapy into earlier lines of therapy and define the safety and activity of novel immunotherapy agents and combinations.

Keywords Immunotherapy · Urothelial carcinoma · Bladder cancer · PD-1 · PD-L1 · CTLA-4

Introduction

With over 80,000 new cases annually in the USA, urothelial cancer (UC) is the fourth most common cancer among men [1]. The natural history of urothelial bladder cancer (UBC) is conceptualized by a model in which dysplastic cells within the urothelium accumulate somatic alterations and acquire an invasive phenotype, a process triggered most commonly by chronic exposure to carcinogens in tobacco smoke. These malignant cells then invade outward from the inner lining of the bladder, through the lamina propria, the muscularis propria, and the perivesical adipose tissue [2]. Ultimately, advanced tumors invade local structures (e.g., the prostate) and metastasize. Although most urothelial carcinomas arise from the bladder, a minority (~ 10%) arise from the upper tract [3]. The current treatment paradigm for urothelial carcinoma distinguishes between muscle-invasive (MIBC) and non-muscle-invasive bladder cancer (NMIBC). While NMIBC may be managed by transurethral resection and intravesical bacille Calmette-Guérin (BCG) [4], MIBC poses a significant risk of metastasis [5]. The current standard of care for MIBC includes neoadjuvant cisplatin-based chemotherapy followed by surgical resection [6]. Until recently, cytotoxic chemotherapy constituted the only systemic treatment option for MIBC and advanced urothelial cancer [6–8]. In 2014, promising responses were reported [9] among a small expansion cohort of a phase 1a clinical trial of the programmed cell death ligand 1 (PD-L1) antibody, atezolizumab. Subsequent clinical development of both PD-L1 and programmed cell death protein 1 (PD-1) antibodies in phase I, II, and III studies culminated in FDA approval of five agents, and these agents have become standard of care for advanced UC.

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Metastatic Urothelial Carcinoma

Metastatic urothelial cancer (mUC) carries a grim prognosis. It is the 8th leading cause of cancer-related mortality among US men and accounts for approximately 18,000 deaths annually [1]. Data from the preimmunotherapy era suggest a median overall survival (OS) of approximately 12–16 months [8, 10] with cisplatin-based chemotherapy with few long-term survivors. After failure of first-line chemotherapy, mUC is a universally fatal malignancy with a median survival of 6–7 months. Immune checkpoint inhibitors have revolutionized bladder cancer care with remarkably favorable toxicity profiles and durable responses in up to 20% of patients in the second-line setting. Since 2016, five new checkpoint inhibitors targeting PD-1 or PD-L1 have garnered FDA approval (Table 1) for the treatment of advanced UC.

Second-Line Therapy for Metastatic Disease

Checkpoint blockade immunotherapy for UC was first investigated in the second-line setting among patients with platinum-refractory disease. The prognosis after failure of platinum-based chemotherapy is dismal, with overall survival approximating 7 months [11]. IMvigor 210 was an international, multi-cohort, single-arm, phase II study of the PD-L1 antibody atezolizumab (1200 mg every 3 weeks) for the treatment of advanced UC. The primary end point was objective response (ORR), and results were stratified by the degree of PD-L1 expression on tumor-infiltrating immune cells (ICs), utilizing the Ventana SP142 assay [12]. Patients were enrolled in two cohorts; cohort 2 [13••] consisted of patients with platinum-refractory mUC. In this cohort, atezolizumab achieved an ORR of 15% (5% complete responses (CRs)). The IC2/3 subgroup (patients with tumor-infiltrating immune cell PD-L1 expression ≥ 5%) was enriched for responses (26% ORR, 11% CR). Most notable, however, was the durability of these responses, with the majority ongoing at 10 months. Based on the duration of response and the high unmet need among these patients, the FDA, in 2016, granted accelerated approval for atezolizumab as second-line therapy in patients with platinum-refractory advanced UC.

IMvigor211 [14•] was the potentially confirmatory phase 3 trial of atezolizumab versus investigators' choice chemotherapy for platinum-refractory mUC. This trial was designed to detect a difference in OS specifically among the IC2/3 subgroup, with outcomes analyzed hierarchically. A total of 931 patients were randomized to atezolizumab or chemotherapy (vinflunine, paclitaxel, or docetaxel). In contrast to previous clinical trials of second-line chemotherapy in mUC demonstrating a median OS of 6–7 months [15, 16], the IC2/3 chemotherapy arm of IMvigor211 demonstrated an OS of 10.6 months, and the study failed to meet its primary end point. Investigators hypothesize that the prognostic

Table 1 FDA-approved immune checkpoint inhibitors for advanced urothelial cancer with corresponding efficacy and biomarker data

Target	Agent	Approved indication	Study	Line of therapy	Phase	Patients	Response rate			PD-L1 assay	PD-L1 cutoffs
							Overall (%)	PD-L1-high (%)	PD-L1-low (%)		
PD-L1	Atezolizumab	°1 L (Cisplatin-ineligible and PD-L1 ≥ 5%)	IMvigor210 Cohort 1	1 L	2	119	23	28	21	Ventana SP142	< 1% or ≥ 5%, immune cells
		°1 L (Platinum-ineligible) °2 L	IMvigor210 Cohort 2	≥ 2 L	2	310	15	26	8		< 1% or ≥ 5%, immune cells
			IMvigor211	2 L	3	459	13	23	N/A		≥ 5%, immune cells
	Durvalumab	2 L	Study 1108	≥ 1 L	1/2	191	18	28	5	Ventana SP263	25%, tumor and/or immune cells
	Avelumab	2 L	JAVELIN	≥ 2 L	1	161	17	24	13	Dako 73–10	5%, tumor cells
PD-1	Pembrolizumab	°1 L (Cisplatin-ineligible and CPS ≥ 10%)	KEYNOTE-052	1 L	2	370	24	39	20	Dako 22C3	10%, combined positive score
		°1 L (Platinum-ineligible) °2 L	KEYNOTE-045	2 L	3	270	21	22	N/A		≥ 10%, combined positive score
	Nivolumab	2 L	CheckMate 032	≥ 2 L	1/2	78	24	24	26	Dako	1%, tumor cells
			CheckMate 275	≥ 2 L	2	265	20	28 (24)	16 (16)	28.8	5% (and 1%), tumor cells

N/A not available

implications of high PD-L1 expression lead to unexpectedly long survival in the chemotherapy arm, thus under-powering the study. This rationale is supported by a post-hoc survival analysis demonstrating a statistically significant survival benefit among the overall cohort.

Following early-phase clinical trials [17, 18] characterizing the safety and efficacy of the PD-1 antibody pembrolizumab, KEYNOTE-045 [19••] demonstrated superiority of pembrolizumab (200 mg every 3 weeks) over chemotherapy with respect to OS. KEYNOTE-045 was a randomized phase 3 trial similar to IMvigor211. In contrast to IMvigor211, KEYNOTE-045 was designed to detect a difference in OS and PFS primarily among the entire cohort. Pembrolizumab achieved a median survival of 10.3 months versus 7.4 months with chemotherapy. However, unlike IMvigor211, the OS benefit of pembrolizumab was observed irrespective of PD-L1 status. Whereas IMvigor211 utilized the Ventana SP142 assay, KEYNOTE 045 relied upon the Dako PD-L1 IHC 22C3 pharmDx assay which measures, not simply of the percentage of PD-L1 positive immune cells, but of the combined positive score, defined as the ratio of the number of PD-L1 expressing cells (both immune and tumor) to the total number of tumor cells [17]. Interestingly, unlike IMvigor211 in which the chemotherapy arm fared better in the PD-L1-high subgroup, the PD-L1-high subgroups of KEYNOTE-045 did not exhibit a longer survival in either treatment arm.

CheckMate 275 [20••] was a single-arm phase 2 study of the PD-1 antibody nivolumab (3 mg/kg every 2 weeks) for the treatment of platinum-refractory mUC, similar to IMvigor 210 cohort 2. Objective response rates were similar to those observed in IMvigor210, with a 19.6% ORR (2%CR), and the median duration of response not reached at a median follow-up of 7 months. Given the unmet need in the second-line setting, nivolumab was granted accelerated approval in 2017. CheckMate 275 also analyzed outcomes with respect to PD-L1 status as measured by the Dako 22C3 assay. Although investigators found a statistically significant improvement in OS among the PD-L1 ≥ 1% subgroup, responses were observed in all PD-L1 subgroups.

Given the first-ever PD-L1 inhibitor, atezolizumab, was initially approved in mUC, this disease has also been at the forefront of clinical development for other PD-L1 antibodies. Study 1108 [21, 22••] was a single arm phase I/II study of the PD-L1 antibody durvalumab (10 mg/kg every 2 weeks) with an expansion cohort of 191 patients with platinum-refractory mUC. In addition to demonstrating an objective response rate of 31% in the UC expansion cohort, investigators validated the Ventana SP263 assay for PD-L1 expression, selecting a cutoff of 25% PD-L1 positivity on either the tumor cells or the immune cells [23]. Patients with PD-L1-high tumors achieved a response rate of 46% and OS of 20 months compared to 8 months in the PD-L1-low subgroup. Durvalumab was subsequently granted FDA-approval based on the results of study 1108. Again, however, objective responses were observed even among the PD-L1-low subgroup.

A third PD-L1 antibody, avelumab, was also granted accelerated approval for mUC after progression on platinum-based chemotherapy based on the findings of a bladder cancer cohort of JAVELIN phase I program. JAVELIN [24••] was a multi-cohort phase 1 trial which enrolled patients on both a platinum-naïve cohort and a platinum-refractory cohort, with a primary end point of ORR. Outcomes were stratified by PD-L1 status as defined by the Dako 73-10 assay. Among 161 patients (across both cohorts), the ORR was 17%, with high PD-L1 expression again enriching for response (24% versus 14% in the PD-L1-low subgroup).

First-Line Immunotherapy for Cisplatin-Ineligible Patients

Among patients with locally advanced or metastatic UC, cisplatin-based chemotherapy [25] remains the standard of care in the first-line setting at the time of publication. However, first-line chemotherapy is often not well-tolerated and is associated with a short duration of response. Furthermore, up to two thirds of patients are unfit for cisplatin-based chemotherapy [26], and carboplatin-based alternative regimens are associated with an overall survival of less than 1 year [27].

IMvigor210 cohort 1 [28••] consisted of 119 systemic treatment-naïve patients with locally advanced or metastatic UC who were ineligible for cisplatin. Patients were most commonly ineligible for cisplatin based on renal impairment (70%) and ECOG performance status (20%), but many were also ineligible on the basis of hearing loss and neuropathy. At baseline, these patients exhibited poor prognostic features, with a sizable fraction of octogenarians and a preponderance of visceral metastases. Similar to IMvigor210 cohort 2, the primary end point was ORR, and outcomes were stratified by PD-L1 expression on immune cells. As expected, the ORR of 23% (9%CR, 13%PR) for first-line atezolizumab was numerically higher than that observed in the second line setting. Although the IC2/3 subgroup was slightly enriched for responses, 20% of the IC0 patients achieved a response. Importantly, 70% of these responses were ongoing at a median follow-up of 17 months. Based on these responses and the limited therapeutic options for patients unable to tolerate cisplatin, the FDA granted accelerated approval of first-line atezolizumab for cisplatin-ineligible patients with locally advanced or metastatic UC.

KEYNOTE-052 [29••] was a single-arm phase II trial of pembrolizumab in cisplatin-ineligible patients with mUC. A total of 370 patients were treated with first-line pembrolizumab, and response data were reported for the overall cohort and also stratified by PD-L1 status using the combined positive score. Results were similar to IMvigor210

cohort 1, with an ORR of 24%, and an ORR of 38% among patients with a combined positive score ≥ 10%. These data ultimately supported accelerated approval of pembrolizumab in the first-line, cisplatin-ineligible setting.

Further studies are investigating the combination of PD-1 or PD-L1 antibodies with cytotoxic chemotherapy in the first-line cisplatin-ineligible setting, including gemcitabine/carboplatin (NCT03390595) [30], nanoparticle albumin-bound paclitaxel (NCT03240016), and carboplatin or oxaliplatin (NCT03451331).

First-Line Checkpoint Inhibitor in Combination with Platinum-Based Chemotherapy

Following approvals for atezolizumab and pembrolizumab in the second-line and first-line cisplatin-ineligible settings, subsequent trials were initiated to more broadly assess the efficacy of PD-1/L1 blockade in the first-line setting. KEYNOTE-361 [31•] is an ongoing randomized phase 3 trial of pembrolizumab with or without gemcitabine/cisplatin (or gemcitabine/carboplatin) versus chemotherapy alone for the first-line treatment of metastatic urothelial cancer. IMvigor130 [32•] is a similarly designed ongoing trial of atezolizumab. Both trials specify that outcomes will be stratified by cisplatin-eligibility as well as by PD-L1 status. In May 2018, the FDA issued a safety alert for atezolizumab and pembrolizumab [33], reporting decreased survival relative to chemotherapy among the PD-L1-low subgroups. The accelerated approvals for these agents in the first-line cisplatin-ineligible setting were subsequently amended to exclude patients with PD-L1-low tumors, although first-line PD-1/L1 blockade is still an option for patients unable to tolerate carboplatin due to advanced age or comorbidities. Published data from these trials will be highly informative as to the importance of PD-L1 as a predictive biomarker in mUC.

Post-platinum Maintenance

Other trials are investigating anti-PD-1/L1 checkpoint inhibition as maintenance therapy following platinum induction in patients achieving a response. JAVELIN Bladder 100 (NCT02603432) [34] is a randomized open-label phase 3 trial of maintenance avelumab in patients who achieved disease stabilization with 4–6 cycles of first-line platinum-based chemotherapy. A multi-institution placebo-controlled phase 2 investigator-initiated trial of pembrolizumab is also underway in this clinical setting (NCT02500121).

Muscle-Invasive Bladder Cancer

Despite surgical resection, patients with MIBC remain at substantial risk of postoperative recurrence and death from mUC. Prior to the widespread incorporation of perioperative chemotherapy, the majority (52%) of patients undergoing radical cystectomy (RC) recurred within 5 years of surgery [35]. Furthermore, RC is associated with substantial morbidity [36]. Perioperative cisplatin-based chemotherapy improves survival when added to cystectomy for patients with MIBC; however, a significant proportion still recurs with and succumbs to metastatic disease [6, 7]. Given the success of anti-PD-1/L1 immunotherapy in mUC, ongoing trials are examining the role of immune checkpoint inhibition in non-metastatic MIBC.

Adjuvant

Currently, three phase 3 clinical trials are underway to assess the efficacy of checkpoint inhibitor monotherapy in the adjuvant setting with atezolizumab (IMvigor010, NCT02450331), nivolumab (CheckMate274, NCT02632409) [37], and pembrolizumab (AMBASSADOR, NCT03244384). While IMvigor010 and CheckMate274 are international studies powered for disease-free survival, AMBASSADOR is an National Cancer Institute (NCI)-sponsored trial pursuing a dual-primary end point of disease-free and overall survival.

Neoadjuvant

In the neoadjuvant setting, PURE-01 was a single-arm phase 2 study demonstrating encouraging efficacy of pembrolizumab in MIBC. A total of 50 patients were treated with three cycles of pembrolizumab followed by radical cystectomy. All 50 patients underwent surgery as planned, and investigators reported a 42% pathologic CR (pCR) rate and a 54% rate of pathologic downstaging. Additional studies (NCT03319745, NCT03212651) are also investigating pembrolizumab in the neoadjuvant setting. ABACUS is an investigator-initiated single-arm phase 2 study of preoperative atezolizumab in patients with MIBC (NCT02662309) [38]. In this study, 69 patients were enrolled and planned for two cycles of atezolizumab followed by surgery. Despite the fact that 20% of patients received only a single dose of atezolizumab (mostly due to adverse events) and 10% did not undergo cystectomy, atezolizumab achieved a clinically significant 29% pCR rate. Additional studies of neoadjuvant atezolizumab (NCT02451423) and avelumab (NCT03498196) are underway. In addition to anti-PD-1/L1 monotherapy, other neoadjuvant trials are examining the safety of checkpoint inhibitors in combination with cisplatin-based chemotherapy, including atezolizumab (NCT02989584), pembrolizumab (NCT02690558, NCT02365766) [39], nivolumab (NCT03294304) [40], and durvalumab (NCT03406650).

Cystectomy-Sparing Approaches

Although RC is considered the standard of care for MIBC, up to half of all MIBC patients are either unfit for surgery or decline it [41]. Historically, many of these patients have opted for observation and supportive care, with a minority electing trimodality therapy with maximal transurethral resection followed by chemoradiation [42]. Among patients with non-zero performance status, multiple comorbidities, or cisplatin ineligibility, strategies utilizing immunotherapy in place of chemotherapy offer the potential for disease control without substantial toxicity. Investigator-initiated trials of pembrolizumab (with (NCT02621151) and without (NCT03419130) radiosensitizing gemcitabine), nivolumab (NCT03421652), and durvalumab (NCT02891161) [43] are assessing the efficacy of checkpoint blockade with external beam radiation. Primary end points vary across these trials, ranging from safety to progression-free survival and cystectomy-free survival. More aggressive investigational regimens for relatively fit patients include pembrolizumab with cisplatin and radiation (NCT02662062) as well as definitive chemoradiation followed by adjuvant nivolumab (NCT03171025).

Non-muscle-Invasive Bladder Cancer

Patients with non-muscle-invasive bladder cancer (NMIBC) are typically managed with transurethral resection of the bladder tumor (TURBT) followed by intravesical BCG. Unfortunately, a subset of patients develops recurrent NMIBC and/or goes on to develop MIBC [44]. Therefore, a number of clinical trials are underway to investigate the utility of checkpoint blockade in NMIBC. Checkpoint inhibitor monotherapy is currently being examined as potential salvage therapy in BCG-refractory NMIBC, with trials ongoing for atezolizumab (NCT02844816) [45], pembrolizumab (KEYNOTE-057, NCT02625961) [46] (including intravesical pembrolizumab (NCT03167151)), and durvalumab (NCT02901548, NCT03258593). Most notably, in KEYNOTE-057, pembrolizumab achieved a 39% CR rate, with 73% of responses ongoing at a median follow-up of 14 months. Several other studies are examining the safety and efficacy of checkpoint blockade in combination with intravesical BCG, with specific trials being conducted for atezolizumab (NCT02792192), intravenous (NCT02324582) [47] and intravesical (NCT02808143) pembrolizumab, nivolumab (NCT03519256, CheckMate 9UT), and durvalumab—both with (NCT03317158) and without (NCT03528694, POTOMAC) radiation. Furthermore, a single-arm phase 2 investigator-initiated trial is assessing the efficacy of up-front pembrolizumab following TURBT for the prevention of recurrence in BCG-naive NMIBC (NCT03504163).

Immunotherapy Combinations and Novel Modalities

Checkpoint Inhibitors and Costimulatory Agonists

As of publication, no CTLA-4 antibody has been approved in urothelial cancer. CheckMate 032 (NCT01928394) [48] is a phase I/II study investigating the combination of ipilimumab and nivolumab in platinum-refractory advanced urothelial cancer (Table 2). A total of 130 patients were treated with either ipilimumab 3 mg/kg and nivolumab 1 mg/kg (IPI3 + NIVO1) or nivolumab 3 mg/kg and ipilimumab 1 mg/kg (NIVO3 + IPI1) every 3 weeks for four cycles, followed by nivolumab maintenance (3 mg/kg every 2 weeks). Interim analysis demonstrates ORRs of 38% and 27% with NIVO1 + IPI3 and NIVO3 + IPI1, respectively, suggesting clinical benefit with NIVO1 + IPI3. However, the addition of CTLA-4 blockade is associated with an increased incidence of immune-related adverse events (IRAEs), with approximately one-third of patients experiencing grade 3 or 4 toxicity. Based on encouraging activity, IPI3 + NIVO1 is being further investigated in CheckMate 901 [49] (Table 2), a randomized phase 3 trial of nivolumab with or without ipilimumab versus standard-of-care cisplatin- or carboplatin-based chemotherapy for the treatment of mUC in the first-line setting. This study is powered for survival, and results will be stratified by cisplatin eligibility and PD-L1 expression. Given the potential toxicity of anti-CTLA-4 therapy, TITAN (NCT03219775), a large phase 2 trial, seeks to spare PD-1-responsive patients the addition of anti-CTLA-4 using a tailored design. Additionally, ipilimumab/nivolumab is being examined in the neoadjuvant setting in two investigator-initiated feasibility trials among cisplatin-ineligible patients (NCT03520491, NCT03387761).

In addition to ipilimumab/nivolumab, ongoing trials are also evaluating the combination of the PD-L1 antibody durvalumab with the CTLA-4 antibody tremelimumab. In a phase 1 expansion cohort of 168 platinum-refractory mUC patients (NCT02261220; Table 2) [50], investigators found that durvalumab/tremelimumab followed by durvalumab maintenance achieved a 20.8% objective response rate with significant but acceptable toxicity. Durvalumab/tremelimumab is being further investigated in DANUBE (NCT02516241) [51], a randomized phase 3 trial of durvalumab with or without tremelimumab versus standard-of-care cisplatin- or carboplatin-based chemotherapy in the first-line metastatic setting, similar to CheckMate 901. The primary end point is progression-free survival, and results will be stratified by cisplatin eligibility and by PD-L1 status. Durvalumab/tremelimumab is also being evaluated in the

Table 2 Select ongoing and recent clinical trials evaluating novel immune-oncology combination therapies for advanced urothelial carcinoma

Mechanism	Combination	Trial	Phase	Status	Clinical context	Primary end point(s)	ORR (%)
Dual checkpoint blockade	Ipilimumab + nivolumab	CheckMate 032	1/2	Follow-up	2 L Platinum-refractory	ORR	29
		CheckMate 901	3	Accruing	1 L Cisplatin-eligible and ineligible	PFS and OS among cisplatin-ineligible patients	–
	Durvalumab + tremelimumab	NCT02261220	1	Follow-up	2 L Platinum-refractory	Safety and toxicity, ORR	21
		DANUBE	3	Accruing	1 L Cisplatin-eligible and ineligible	OS among combination arm and among PD-L1-high patients in monotherapy arm	–
Cytokine-based therapy	NKTR-214 + (atezolizumab (OR pembrolizumab))	PROPEL	1/2	Accruing	1 L Cisplatin-ineligible, 2 L	Safety and toxicity	
	NKTR + nivolumab (+ ipilimumab)	PIVOT-02	1/2	Accruing	1 L Cisplatin-ineligible, 2 L, 3 L	Safety and toxicity, ORR	60*
Antiangiogenesis	Ramicirumab + pembrolizumab	NCT02443324	1	Follow-up	2 L Platinum-refractory, 3 L	Safety	13
	Bevacizumab + atezolizumab	NCT03133390	2	Accruing	1 L Cisplatin-ineligible	OS	–
	Cabozantinib + nivolumab ± ipilimumab	NCT02496208	1	Accruing	2 L	Safety and toxicity	38**
	Axitinib + avelumab	JAVELIN Medley VEGF	2	Accruing	1 L Cisplatin-ineligible	ORR	–
FGFR targeted therapy	AZD4547 + durvalumab	BISCAY	1	Accruing	2 L	Safety and toxicity	–
	Rogaratinib + atezolizumab	FORT-2	1/2	Accruing	1 L Cisplatin-ineligible	Toxicity, PFS	–
	Vofatamab + pembro	FIERCE-22	1/2	Accruing	2 L	Safety and toxicity, ORR	–
PARP inhibitor	Olaparib + durvalumab	BISCAY	1	Accruing	2 L	Safety and toxicity	–
	Olaparib + durvalumab	BAYOU	2	Accruing	1 L Cisplatin-ineligible	PFS	–
Antibody–drug conjugate	Enfortumab vedotin + (pembrolizumab OR atezolizumab)	EV-103	1	Accruing	1 L Cisplatin-ineligible, 2 L	Safety and toxicity	–

*Preliminary ORR from $n = 10$ 1 L cisplatin-ineligible mUC patients

**Preliminary ORR from $n = 16$ 2 L mUC patients, overall including both with and without ipilimumab

neoadjuvant in cisplatin-ineligible MIBC (NCT02812420 [52], NCT03234153). If ipilimumab or tremelimumab is ultimately incorporated into the standard treatment for urothelial cancer, predictive biomarkers will be critical in identifying patients who may be spared the significant toxicity of CTLA-4 blockade. Data from non-randomized single-arm studies of durvalumab [22] and durvalumab/tremelimumab [50] appear to suggest a benefit to combination therapy. Among patients with low PD-L1 expression, the addition of tremelimumab was associated with a 15% ORR, whereas durvalumab monotherapy achieved only a 5% ORR in a similar cohort in study 1108. However, this association was not observed in CheckMate 032, where PD-L1-low patients achieved a 23.8% ORR with combination ipilimumab/nivolumab and a 25.6% ORR with nivolumab alone.

In addition to CTLA-4, other investigator-initiated trials are examining antibodies targeting novel immune costimulatory molecules. Nivolumab is being tested in combination with the 4-1BB agonist urelumab (NCT02845323) and a novel first-in-class antibody against the inhibitory KIR receptor on natural killer cells (NCT03532451), both in the neoadjuvant cisplatin-ineligible setting.

Cytokine-Based Agonists

NKTR-214 is a pegylated recombinant IL-2 which acts to preferentially activate cytotoxic lymphocytes and natural killer cells over regulatory T cells [53, 54]. In a phase 1 study, NKTR-214 demonstrated safety and preliminary efficacy against a range of metastatic solid tumors [55], and ongoing clinical trials are incorporating NKTR-214 into the treatment of mUC. PROPEL (NCT03138889; Table 2) [56] is a phase 1 trial of atezolizumab in combination with escalating doses of NKTR-214 among patients with platinum-refractor mUC. PIVOT-02 (NCT02983045; Table 2) [57] is a multi-cohort phase 1/2 trial of NKTR-214 in combination with either nivolumab alone or ipilimumab/nivolumab to assess the safety and activity of these combinations across a range of metastatic tumors including first-line immunotherapy-naïve and platinum-refractory mUC. Additionally, an NCI-sponsored trial is investigating atezolizumab in combination with CYT107, a recombinant IL-7, in platinum-refractory and cisplatin-ineligible mUC (NCT03513952).

Anti-Angiogenesis and Tyrosine Kinase Inhibitors

Mounting evidence suggests a strong biologic link between angiogenesis and immunosuppression in the tumor microenvironment [58]. There exists, therefore, considerable interest in combining checkpoint blockade immunotherapy—particularly anti-PD-1/L1 agents—with antiangiogenic agents. The first such trial to report data in urothelial cancer combined a VEGFR-2 antibody, ramucirumab, with the PD-1 antibody pembrolizumab. In a large multi-cohort phase 1 study (NCT02443324; Table 2) [59], investigators found that in platinum-refractory mUC, this combination was well tolerated and demonstrated modest antitumor activity [60]. In addition, a multi-cohort phase 1 study demonstrated the ability of the VEGF-A antibody, bevacizumab, to potentiate PD-1/L1 blockade in metastatic renal cell carcinoma [61], and an investigator-initiated trial is currently testing the combination of atezolizumab with bevacizumab among patients with mUC in the first-line cisplatin ineligible setting (NCT03133390; Table 2). Another investigator-initiated trial is testing pembrolizumab in combination with a novel EphB4-HSA fusion protein which acts to inhibit angiogenesis (NCT02717156).

Cabozantinib is a multi-kinase inhibitor of MET and VEGFR-2 [62] which is being combined with checkpoint inhibitors in UC. The combination of cabozantinib with either nivolumab or ipilimumab/nivolumab was investigated in a multi-cohort phase 1 trial (NCT02496208; Table 2) [63], demonstrating relative safety and antitumor activity, with an ORR 36% across all genitourinary tumor types. In addition, two investigator-initiated trials are underway evaluating cabozantinib in combination with pembrolizumab (NCT03534804) and with atezolizumab (NCT03170960) [64]. Axitinib, a selective inhibitor of VEGF receptors [65], is being tested in combination with avelumab in JAVELIN Medley VEGF, an ongoing phase 2 study in non-small cell lung cancer and mUC in the first-line cisplatin-ineligible setting (NCT03472560; Table 2). Finally, apatinib is a small molecule inhibitor with high affinity for VEGFR-2 and is being investigated in combination with pembrolizumab for the treatment of platinum-refractory mUC (NCT03407976).

Targeted Therapy

Preclinical data suggest that genetically targeted therapies may potentiate the response to immunotherapy via enhanced immune-mediated killing and inhibition of tumor-mediated immunosuppression [66]. BISCAY is phase 1b umbrella study of the PD-L1 antibody durvalumab in combination with any one of several biomarker-directed targeted therapies (NCT02546661; Table 2) [67]. Patients whose tumors harbor an FGFR3 mutation or FGFR fusion will be treated with AZD4547, a fibroblast growth factor receptor inhibitor [68], either as monotherapy or in combination with druvalumab. Two additional ongoing trials are investigating similar combinations. FORT-2 (NCT03473756; Table 2) [69] is an international phase 1/2 trial of the novel FGFR inhibitor, rogaratinib in combination with atezolizumab, and FIERCE-22 (NCT03123055; Table 2) is an international phase 1/2 study of pembrolizumab in combination with the FGFR3 inhibitor, vofatamab (B-701).

BISCAY assigns patients with deficient homologous recombination repair to treatment with durvalumab combined with the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib [70]. The combination of durvalumab/olaparib is also being investigated in two separate phase 2 trials in the first-line cisplatin-ineligible setting for mUC (NCT03459846, BAYOU; Table 2) as well as in the neoadjuvant setting (NCT03534492, NEODURVARIB). Additionally, BISCAY assigns patients with deleterious mutations to cell cycle progression genes (CDKN2a, RB1, etc.) to a WEE1 inhibitor [71] in combination with durvalumab, and still other BISCAY modules combine durvalumab with inhibitors of MTORC1/2 [72], STAT3 [73], and MEK1/2 [74].

Antibody–Drug Conjugates

Enfortumab vedotin is a novel antibody–drug conjugate (ADC) comprised of an antibody to nectin-4 (overexpressed in the majority of UBCs) bound to a cytotoxic microtubule disrupting agent [75], which has demonstrated efficacy in platinum-refractory mUC [76]. Specifically, updated data from the phase I study in 112 patients with mUC treated at the recommended phase 2 dose of 1.25 mg/kg demonstrated an ORR of 40% in the second-line setting, including a 40% ORR in patients with liver metastases [77]. Given the strong antitumor effect observed as monotherapy, enfortumab vedotin is being tested in combination with immunotherapy in both the first-line cisplatin-ineligible and platinum-refractory settings (NCT03288545, EV-103; Table 2) [78]. Of note, the microtubule inhibitor, eribulin mesylate [79], is also being investigated in combination with atezolizumab (NCT03237780) and avelumab (NCT03502681). Notably, bladder cancer has one of the highest rates of HER2 expression of any solid tumor [80], and a novel HER2-based ADC, trastuzumab deruxtecan [81], is currently being investigated in a multi-cohort phase 1 trial of breast and urothelial cancer in combination with nivolumab (NCT03523572).

Novel Immunotherapeutic Modalities

In addition to the transformative success of immune checkpoint inhibitors across a range of solid tumors, other immunotherapeutic modalities have also demonstrated efficacy. In melanoma, talimogene laherparepvec is an FDA-approved oncolytic herpes virus which acts as an in situ vaccine [82] and may enhance the response to systemic checkpoint blockade [83]. STORM is an ongoing phase 1 study of the oncolytic coxsackievirus A21 (CVA21) with pembrolizumab in advanced solid tumors including mUC (NCT02043665) [84]. Preliminary results suggest the combination is well tolerated, and a single partial response was observed among 13 evaluable patients. SPICE (NCT02636036) [85] is an ongoing phase 1 trial with a urothelial carcinoma expansion cohort examining the combination of enadenotucirev, an oncolytic adenovirus, and pembrolizumab.

Vaccination has long been an investigational strategy to generate durable antitumor immune responses. Sipuleucel-T, a dendritic cell-based vaccine, is FDA-approved for the treatment of metastatic castration-resistant prostate cancer [86]. In UC, NEO-PV-01 is a personalized neoantigen-based peptide vaccination platform which demonstrated clinical activity and neoantigen-specific T cell expansion in a phase 1 trial in combination with nivolumab (NCT02897765) [87]. R07198457 is a personalized mRNA-based vaccine designed to stimulate expression of neoantigens by antigen-presenting cells, is being tested in a phase 1 trial in combination with atezolizumab (NCT03289962). An alternative strategy to stimulate neoantigen expression, INO-5401, a plasmid-based technology, acts to increase expression of tumor antigens in situ, and is currently in early clinical development for urothelial cancer in combination with atezolizumab (NCT03502785). Finally, intratumoral poly-ICLC, a TLR3 agonist which acts as an in situ vaccine, is being combined with durvalumab/tremelimumab in an ongoing phase 1/2 clinical trial (NCT02643303) [88].

Cellular immunotherapy has demonstrated clinically significant and durable responses in leukemia and lymphoma [89]; however, efficacy in non-hematologic cancers has been inconsistent. Nevertheless, there is continued interest in treating solid tumors with adoptive cellular therapy including chimeric antigen receptor T cells and tumor-infiltrating lymphocytes (NCT01174121). Future preclinical and clinical work in this area will focus on identifying optimal tumor-specific antigens, enhancing trafficking and epitope spreading, and overcoming the immunosuppressive tumor microenvironment [90].

Conclusions

PD-1/L1 axis blockade has transformed the treatment landscape in mUC, achieving durable responses in a subset of patients with minimal toxicity. Ongoing phase 3 trials will assess the superiority of incorporating of PD-1/L1 antibodies in the first-line setting and provide further insights on the utility of PD-L1 expression as a predictive biomarker. The well-demonstrated efficacy and favorable toxicity profile of immune checkpoint inhibition suggests a potential role in the adjuvant and neoadjuvant settings as well as in bladder-preservation strategies. Future clinical research in immune-oncology for urothelial cancer will undoubtedly emphasize combination therapy. Given the abundance of newly approved and clinical-stage investigational therapeutics, correlative analyses will be critical in prioritizing agents and combinations for testing in biologically rational clinical trials.

Compliance with Ethical Standards

Conflict of Interest Michael Lattanzi has no conflicts of interest.

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- • Of importance
- •• Of major importance

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