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Immune checkpoint inhibitors in genitourinary malignancies

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ABSTRACT

Although immune-mediated therapies have been used in genitourinary (GU) malignancies for decades, recent advances with monoclonal antibody checkpoint inhibitors (CPIs) have led to a number of promising treatment options. In renal cell carcinoma (RCC), CPIs have been shown to have benefit over conventional therapies in a number of settings, and they are the standard of care for many patients with metastatic disease. Based on recent data, combinations of CPIs and antiangiogenic therapies are likely to become a new standard approach in RCC. In urothelial carcinoma, CPIs have been shown to have a role in the second-line treatment of metastatic disease, and a number of clinical trials are actively investigating CPIs for other indications. In other GU malignancies, such as prostate cancer, results to date have been less promising. Immunotherapies continue to be an area of active study for all GU disease sites, with several clinical trials ongoing. In this review, we summarize the current evidence for CPI use in RCC, urothelial carcinoma, prostate cancer, testicular germ-cell tumours, and penile carcinoma. Ongoing clinical trials of interest are highlighted, as are the challenges that clinicians and patients will potentially face as immune CPIs become a prominent feature in the treatment of GU cancers.

Key Words Genitourinary malignancies, renal cell carcinoma, urothelial carcinoma, bladder cancer, prostate cancer, testicular germ-cell tumour, penile cancer, checkpoint inhibitors, immunotherapy, immuno-oncology

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BACKGROUND

The genitourinary (GU) malignancies constitute a heterogeneous group of diseases affecting the kidney, renal collecting system, bladder, prostate, testes, and penis, with each malignancy having a distinct biology and clinical outcomes. Treatment of those malignancies therefore involves unique approaches with respect to the roles of surgery, radiation, and systemic therapy. Almost all modalities of systemic treatment have been used in the management of GU cancers, including cytotoxic chemotherapy, antiangiogenic therapies, and hormonal treatments. Immune-based treatments have also previously been used with some benefit in GU malignancies—for example, cytokine treatments for advanced renal cell carcinoma (RCC) and intravesicular instillation of bacillus Calmette–Guérin (BCG) for treatment of non-muscle-invasive (NMI) bladder cancer. However, those older therapies are not discussed in this article.

The advent of more sophisticated immunotherapies in the form of immune checkpoint inhibitors (CPIs)—monoclonal antibodies targeting specific regulatory immune factors—has dramatically changed the landscape of cancer treatment. The most prominent of the monoclonal antibodies currently in use target the CTLA-4 and PD-1 or PD-L1 pathways (Table I). Those therapies have been evaluated in numerous clinical trials in GU oncology, with new data changing the treatment of GU malignancies at a rapid pace. In the present review, we summarize the current evidence for the use of CPIs in GU malignancies and highlight the approaches being evaluated in ongoing clinical trials.

TREATMENTS BY CANCER SITE

Renal Cell Carcinoma

Immune checkpoint inhibitors have a well-established role in metastatic RCC (mRCC), but use in the curative-intent setting is investigational to date.

Adjuvant Treatment of Resected RCC

Currently, no systemic therapy modality for the adjuvant treatment of RCC after nephrectomy is widely accepted. A number of phase III trials assessing the role of CPI treatment in the adjuvant setting are ongoing, but to date, that approach is considered experimental only. Ongoing trials are assessing atezolizumab (see NCT03024996 at https://ClinicalTrials.gov/), nivolumab (NCT03055013), combination ipilimumab–nivolumab (NCT03138512), and pembrolizumab (NCT03142334).

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TABLE I Immune checkpoint inhibitors of interest in genitourinary malignancies

Drug	Target
Atezolizumab	PD-L1
Avelumab	PD-L1
Durvalumab	PD-L1
Ipilimumab	CTLA-4
Nivolumab	PD-1
Pembrolizumab	PD-1
Tremelimumab	CTLA-4

Metastatic RCC

Overall, mRCC has a poor prognosis, with 5-year survival being 12% in patients with distant metastases[1]. However, prognosis can vary widely. Clinical prediction models, such as the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) model, use prognostic factors to risk-stratify patients and could guide the choice of appropriate treatment options[2]. The IMDC model has also been used for patient selection and stratification in clinical trials. Recent prediction models also incorporate gene expression in individual tumours, and those models might have a more prominent role in the future. Before the recent trials in immuno-oncology, antiangiogenic tyrosine kinase inhibitors (TKIs) targeting the vascular endothelial growth factor (VEGF) pathway had been the mainstay of treatment in mRCC. A number of positive trials involving CPIs have resulted in Health Canada approvals in this setting.

Second-Line or Later Treatment: After activity had been established in phase I and II trials[3,4], the first phase III assessment of a CPI in RCC involved nivolumab in a randomized clinical trial for patients who had progressed on at least 1 prior anti-VEGF TKI therapy. The CheckMate 025 trial randomized 821 patients with advanced clear-cell RCC to treatment with either nivolumab or the oral mTOR (mechanistic target of rapamycin) inhibitor everolimus[5]. After a minimum follow-up of 14 months, median overall survival (OS), the primary endpoint, favoured nivolumab: 25.0 months compared with 19.6 months for everolimus [hazard ratio (HR): 0.73; 98.5% confidence interval (CI): 0.57 to 0.93]. Importantly, the OS benefit appeared to be independent of tumour PD-L1 expression. No difference in progression-free survival (PFS) was observed (HR: 0.88; 95% CI: 0.75 to 1.03). The objective response rate (ORR) strongly favoured nivolumab (25%vs. 5% for the everolimus group), with 4 patients (1% of the nivolumab arm) achieving a complete response (CR). Nivolumab was well tolerated, with 19% of patients experiencing a grade 3 or 4 toxicity, and only 8% requiring treatment discontinuation because of toxicity. The results of that trial firmly established nivolumab as a well-tolerated option after progression on anti-VEGF therapies, with Health Canada having approved it for this indication.

First-Line Treatment: The role of CPIs in the management of patients with previously untreated mRCC is the subject of a number of completed and ongoing trials. Multiple strategies have been applied, including single-agent CPI, combination CPIs, and combinations of a CPI and antiangiogenic treatment. Table II shows the results of four published and presented phase III trials, which are discussed in the remainder of this subsection.

The most established approach involves the combination ipilimumab–nivolumab, which was assessed in the phase III CheckMate 214 trial[6]. In that study, 1096 patients with previously untreated clear-cell mRCC were randomized to receive the anti-VEGF TKI sunitinib or ipilimumab–nivolumab every 3 weeks for 4 cycles, followed by a maintenance phase with single-agent nivolumab. The co-primary endpoints were ORR, PFS, and OS in the subgroup of patients with IMDC intermediate- or poor-risk disease. The same endpoints were assessed secondarily in the intention-to-treat (ITT) population. After a median follow-up of 25.2 months, combination ipilimumab–nivolumab, compared with sunitinib, was found to have a significant OS benefit in the intermediate- and poor-risk group, with a HR of 0.63 (99.8% CI: 0.44 to 0.89). Median OS was not yet reached in the ipilimumab–nivolumab arm; it was 26.0 months in the sunitinib arm. The PFS was numerically greater in the combination group (median: 11.6 months vs. 8.4 months; HR: 0.82), but did not reach statistical significance. The ORR was significantly improved at 42% in the ipilimumab–nivolumab arm compared with 27% in the sunitinib arm ($p < 0.001$), with a CR rate of 9% in the CPI arm (compared with 1% in the sunitinib arm). An update with longer follow-up presented at the 2019 Genitourinary Cancers Symposium showed a CR rate of 11% in the combination arm[10]. In the ITT group (comprising all randomized patients, including 23% of the study population with favourable-risk disease), an OS benefit was observed for ipilimumab–nivolumab compared with sunitinib (HR: 0.68; 99.8% CI: 0.49 to 0.95), although no significant benefit in PFS or ORR was observed. Notably, in an exploratory analysis of the 249 patients with favourable-risk disease, sunitinib appeared to be favoured over ipilimumab–nivolumab, with a trend toward improved OS for sunitinib (HR: 1.45; $p = 0.27$) and significant benefit in PFS (median: 15.3 months for ipilimumab–nivolumab vs. 25.1 months for sunitinib; HR: 2.18; 99.1% CI: 1.29 to 3.68) and ORR (29% for ipilimumab–nivolumab vs. 52% for sunitinib; $p < 0.001$). Interestingly, more patients having favourable-risk disease experienced a CR with ipilimumab–nivolumab (8%) than with sunitinib (4%)[10]. However, toxicity with combination CPIs was notable, with 250 patients experiencing grade 3 or 4 toxicity (46%) and 118 patients (22%) discontinuing therapy because of toxicities. Eight treatment-related deaths were reported in the CPI arm compared with four in the sunitinib arm. Despite those toxicities, quality-of-life data indicated a significant difference in favour of ipilimumab–nivolumab[11]. Those results supported Health Canada's approval for ipilimumab–nivolumab as first-line treatment in intermediate- and poor-risk advanced RCC, and the combination is the preferred option provided that there are no contraindications to CPI therapy. Given the increased risk for serious immune-related adverse effects (irAEs), informed consent and patient education, with close follow-up, are essential.

Combining a CPI with an anti-VEGF agent is an approach assessed in a number of trials, several of which have been

TABLE II Phase III trials in the first-line treatment of metastatic renal cell carcinoma with immune checkpoint inhibitors

Variable	Motzer *et al.*, 2018[6] (CheckMate 214)	Motzer *et al.*, 2018[7] (IMmotion 151)	Motzer *et al.*, 2019[8] (JAVELIN Renal 101)	Rini *et al.*, 2019[9] (KEYNOTE-426)
Treatment arms				
Investigational	Ipilimumab–nivolumab	Atezolizumab–bevacizumab	Avelumab–axitinib	Pembrolizumab–axitinib
Comparator	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Included in primary analysis				
PD-L1 groups	Any	Any	≥1%	Any
IMDC risk groups	Intermediate and poor risk	Any	Any	Any
Primary outcome	OS, PFS, ORR	OS in ITT, PFS in PD-L1–positive	OS, PFS both in PD-L1–positive	OS, PFS
Median OS (months)				
Investigational	Not estimable	Not estimable	Not estimable	Not estimable
Comparator	26.0	Not estimable	Not estimable	Not estimable
Hazard ratio	0.63	0.81	Not reached	0.53
p Value	<0.001	0.09		<0.0001
Median PFS (months)				
Investigational	11.6	11.2	13.8	15.1
Comparator	8.4	7.7	7.2	11.1
Hazard ratio	0.82	0.74	0.61	0.69
p Value	0.03	0.02	<0.001	<0.001
Objective response rate (%)				
Investigational	42	37	55	59
Comparator	27	33	26	36
Complete responses (%)				
Investigational	9	5	3.4	5.8
Comparator	1	2	1.8	1.9

IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; OS = overall survival; PFS = progression-free survival; ITT = intention-to-treat.

recently presented and published. The combination of the anti-VEGF monoclonal antibody bevacizumab with the anti–PD-L1 agent atezolizumab was compared with sunitinib in the first-line setting in the IMmotion151 trial[7] (915 patients randomized). The co-primary endpoints were OS in the ITT population (which included all patients regardless of PD-L1 status) and PFS in the PD-L1–positive population (≥ 1% expression on tumour-infiltrating immune cells), which constituted 40% of the ITT population. In the PD-L1–positive population, PFS was superior in the combination arm, the median being 11.2 months compared with 7.7 months in the sunitinib arm (HR: 0.74; 95% CI: 0.57 to 0.96). Data for OS were immature at the time of reporting in 2018, and median OS was not reached in either arm in the ITT population (HR: 0.81; 95% CI: 0.63 to 1.03; $p = 0.09$). In the PD-L1–positive cohort, the ORR was 43% in the combination arm (with 9% CRs) compared with 35% in the sunitinib arm (with 4% CRs). The ORR was slightly lower in the larger ITT population (37% for the combination vs. 33% for sunitinib alone). Grade 3 or 4 toxicities occurred in 40% of patients in the bevacizumab–atezolizumab group and in 54% of patients in the sunitinib group. Mature OS data from the trial are awaited before bevacizumab–atezolizumab can be considered a standard treatment option.

Two trials recently published promising data for the combination of the anti-VEGF TKI axitinib and a CPI. The JAVELIN Renal 101 trial compared axitinib–avelumab with sunitinib in 886 patients with treatment-naïve mRCC[8]. The co-primary endpoints were OS and PFS in the subgroup of patients with PD-L1–positive disease (≥ 1% immune cells positive for PD-L1 within the tumour area), who constituted 69% of the total ITT population. At the time of data cut-off, the OS data were immature. However, PFS was significantly improved in the combination arm for both the PD-L1–positive and ITT populations. For the cohort of patients with PD-L1–positive disease, median PFS was 13.8 months compared with 7.2 months in the control arm (HR: 0.61; 95% CI: 0.47 to 0.79); in the ITT population, the median PFS was 13.8 months for patients receiving axitinib–avelumab and 8.4 months for patients receiving sunitinib (HR: 0.69; 95% CI: 0.56 to 0.84). The ORR in the combination arm was 51.4% in the ITT group (with 3.4% CRs) and 25.7% in the control arm. All examined subgroups benefited, including all IMDC risk groups and all PD-L1 cohorts. The toxicity rates were comparable in the two groups, with 71.2% of the patients in the combination arm and 71.5% in the sunitinib arm experiencing a grade 3 or 4 toxicity, although the rate of treatment discontinuation favoured avelumab–axitinib (7.6% vs. 13.4% in the sunitinib arm).

In an investigation of pembrolizumab–axitinib, the second trial, KEYNOTE-4269, randomized 861 previously untreated patients to either the combination or to sunitinib, regardless of PD-L1 status. The dual primary endpoints were OS and PFS for the ITT population. At the first interim

analysis, both endpoints favoured the combination arm. A statistically significant improvement in OS was observed in the axitinib–pembrolizumab arm (HR: 0.53; 95% CI: 0.38 to 0.74; $p < 0.0001$). Median OS was not yet reached in either arm. The PFS was also significantly longer in the axitinib–pembrolizumab arm (median: 15.1 months vs. 11.1 months in the sunitinib arm; HR: 0.69; 95% CI: 0.57 to 0.84). All examined subgroups, including the IMDC risk groups and PD-L1 groups, appeared to benefit from combination treatment. The ORR was 59% in the combination therapy arm (with 5.8% CRs) and 35.7% in the sunitinib arm (with 1.9% CRs). Grade 3 or greater toxicity was observed in 75.8% of the patients in the experimental arm and in 70.6% of those in the sunitinib arm. In the combination arm, 10.7% of patients had to discontinue therapy because of toxicity. The most common toxicities in both groups were diarrhea and hypertension. Notably, the rate of grade 3 or 4 hepatic transaminitis was higher than anticipated in the combination arm, and further analysis is required to characterize that observation.

With promising results emerging from the foregoing trials, a number of questions remain. Given that all of the first-line trials used sunitinib as a control, it is not clear which of the regimens should be preferentially used. Choice is especially an issue in the intermediate- and poor-risk IMDC groups, for which no data comparing ipilimumab–nivolumab, the current standard of care, with CPI–axitinib combinations are available. Further, in the case of CPIs combined with anti-VEGF, the ideal second-line treatment upon progression is not clear. In both JAVELIN Renal 101 and KEYNOTE-426, the most common subsequent therapy after combination CPI–anti-VEGF treatment was cabozantinib, an oral TKI targeting MET and AXL in addition to VEGF, which is known to have activity in both the first and subsequent lines[12,13]. Retrospective data indicate that TKIs do in fact have activity after a CPI[14], lending support to that approach, but further randomized data will be required to determine the agents to use and their sequencing.

The role of single-agent CPI therapy in treatment-naïve patients remains undefined, with no phase III data available. A large phase II trial of single-agent pembrolizumab in 110 previously untreated patients with advanced clear-cell RCC resulted in an ORR of 38.2% with 3 CRs (2.7% of the cohort)[15]. Median PFS was 8.7 months in the cohort, and median OS was not yet reached. A first-line phase II trial of single-agent nivolumab, with salvage treatment with combination ipilimumab–nivolumab (NCT03117309 at https://ClinicalTrials.gov/) is ongoing and might provide important insights into the question of combination therapy sequencing. However, outside a clinical trial setting, there is no role for first-line single-agent CPI treatment in mRCC at this time.

A number of phase III trials using CPIs are ongoing in the first-line setting, including a trial comparing nivolumab–cabozantinib with sunitinib (NCT03141177), and a 3-arm trial of combination lenvatinib–pembrolizumab compared with lenvatinib–everolimus and with sunitinib alone (NCT02811861). Both studies will use PFS in all-comers as the primary outcome. Another phase III trial is investigating combination nivolumab–bempegaldesleukin (a CD122 agonist) in comparison with either sunitinib or cabozantinib (NCT03729245).

Urothelial Carcinoma

Urothelial carcinoma, also called transitional-cell carcinoma, most commonly affects the bladder and, less frequently, the ureters, renal pelvis, and urethra. Within the bladder, urothelial carcinoma is broadly grouped into NMI bladder cancer, muscle-invasive (MI) bladder cancer, and metastatic disease. Immunotherapy with CPIs is being actively investigated in all three realms, with published data from phase III trials currently available only in the metastatic setting.

Non-MI Bladder Cancer

The standard treatment for most cases of NMI bladder cancer is complete transurethral resection of the bladder tumour, usually followed by intravesicular BCG and close surveillance. Cystectomy is generally reserved for refractory or high-risk cases. Currently, CPIs do not have a role in the management of NMI bladder cancer, but are the subject of ongoing clinical trials. Preliminary results from KEYNOTE-057, a single-arm, phase II trial of pembrolizumab, demonstrated activity in patients with high-risk BCG-unresponsive NMI bladder cancer[16]. In a cohort of 101 patients who were not candidates for, or who refused, cystectomy, 36.5% attained a CR at 3 months with pembrolizumab. A phase III study of the treatment, KEYNOTE-676 (NCT03711032 at https://ClinicalTrials.gov/), is ongoing, as are phase III studies of atezolizumab (NCT03799835) and durvalumab (NCT03528694) combined with BCG.

MI Bladder Cancer

Ideally, MI bladder cancer is treated with radical cystectomy. Cisplatin-based neoadjuvant chemotherapy before cystectomy was shown to have a 5% absolute survival advantage over surgery alone[17]. Bladder-conserving treatment with multimodality therapy (maximal transurethral resection followed by chemoradiation) is considered an acceptable alternative in selected patients[18].

Immunotherapy is being actively investigated as neoadjuvant or adjuvant therapy in patients undergoing cystectomy and bladder-conserving approaches. To date, only early-phase trials of neoadjuvant CPI therapy have reported results. In an Italian phase II single-arm trial (50 patients), 3 cycles of pembrolizumab given before radical cystectomy yielded a pathologic CR (pCR) rate of 42%[19]. Patients with immune and tumour cells highly expressing PD-L1 (≥ 10%) as determined by the combined positive score seemed to derive more benefit (pCR rate of 54.3% vs. 13.3% in the <10% group). In another single-arm phase II trial, patients with MI bladder cancer were administered 2 cycles of atezolizumab before cystectomy[20]. In 68 evaluable patients, the pCR rate was 29% (95% CI: 19% to 42%). Again, tumour expression of PD-L1 appeared to affect treatment efficacy: a pCR was attained by 40% of patients with PD-L1–positive disease and by 16% of those with PD-L1–negative disease.

Although those results are promising, results from ongoing phase III trials are awaited. The NIAGARA trial is comparing standard neoadjuvant chemotherapy with durvalumab plus neoadjuvant chemotherapy, followed by durvalumab monotherapy after radical cystectomy (NCT03732677 at https://ClinicalTrials.gov/). Trials investigating CPIs in the adjuvant setting include those comparing

atezolizumab (NCT2450331), nivolumab (NCT02632409), and pembrolizumab (NCT03244384) with observation or placebo. Additional ongoing trials are studying the role of CPIs in curative-intent, bladder-sparing treatment of MI bladder cancer, with one trial comparing chemoradiation plus atezolizumab with conventional chemoradiation alone (NCT03775265). Finally, another ongoing phase III trial (NCT03661320) is comparing standard neoadjuvant chemotherapy with two experimental treatments given in addition to neoadjuvant chemotherapy: nivolumab monotherapy and nivolumab–BMS-986205 (a novel immunomodulator targeting IDO1), both given before and after radical cystectomy.

Metastatic Urothelial Cancer

Immunotherapy has been studied in a number of clinical trials in metastatic urothelial carcinoma, with the most extensive data being available in the second-line setting after progression on standard-of-care platinum-based combination chemotherapy. Table III summarizes published results in the second-line setting.

Second-Line Treatment: Pembrolizumab was compared with second-line chemotherapy in the phase III KEYNOTE-045 randomized trial[26]. Patients who had progressed after or within 12 months of receiving a platinum-based regimen (n = 542) were assigned to receive pembrolizumab or investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine). The co-primary endpoints were OS and PFS. Results after a median follow-up of 14.1 months showed a significant OS benefit for pembrolizumab over chemotherapy (HR: 0.73; 95% CI: 0.59 to 0.91), with median OS values of 10.3 months and 7.4 months respectively. No benefit for PFS was observed (HR: 0.98; 95% CI: 0.81 to 1.19). The ORR analysis favoured the pembrolizumab group (21%; 95% CI: 16.4% to 26.5%) over the chemotherapy group (11.4%; 95% CI: 7.9% to 15.8%). Median duration of response was not yet reached in the pembrolizumab arm. The OS benefit was observed in all examined subgroups, including the cohort with a PD-L1 combined positive score less than 1%. Toxicities were as expected for single-agent pembrolizumab, with 15% of the group experiencing a grade 3 or greater toxicity, and 5.6% requiring treatment discontinuation because of toxicity. In contrast, 49.4% of patients in the chemotherapy arm experienced grade 3 or greater adverse effects, with 11.0% requiring toxicity-related treatment discontinuation. Based on those results, pembrolizumab was approved by Health Canada in the second-line setting.

Another phase III trial, IMvigor211, assessed the role of atezolizumab in the second line, after promising results emerged from a large single-arm phase II trial in 310 patients. The demonstrated ORR of 15% (CR rate: 5%)[21] led to conditional approval by Health Canada. In IMvigor211, 931 patients with metastatic urothelial carcinoma who progressed on or within 12 months of platinum-based chemotherapy were then randomized to receive atezolizumab or investigator's choice of chemotherapy (paclitaxel, docetaxel, or vinflunine)[22]. The primary endpoint of OS was assessed in a hierarchical fashion: first in the population

TABLE III Key trials in the second-line treatment of advanced or metastatic urothelial carcinoma

Variable	Phase III trials		Phase I and II trials			
	Bellmunt *et al.*, 2017[20] (KEYNOTE-045)	**Powles *et al.*, 2018[21] (IMvigor 211)**	**Sharma *et al.*, 2016[22] (CheckMate 032)**	**Sharma *et al.*, 2017[23] (CheckMate 275)**	**Powles *et al.*, 2017[24]**	**Patel *et al.*, 2018[25] (JAVELIN Solid Tumor)**
Treatment arms						
Investigational	Pembrolizumab	Atezolizumab	Nivolumab	Nivolumab	Durvalumab	Avelumab
Comparator	Chemotherapy[a]	Chemotherapy[a]				
Study phase	III	III	I/II	II	I/II	I
Primary outcome	OS, PFS	OS (in PD-L1 ≥ 5%)	Objective response rate	Objective response rate	Safety, objective response rate	Objective response rate
Median OS (months)						
Investigational	10.3	11.1	9.7	8.7	18.2	6.5
Comparator	7.4	10.6				
Hazard ratio	0.73	0.87[b]				
p Value	0.002	0.41				
Median PFS (months)						
Investigational	2.1	2.4	2.8	2.0	1.5	1.7
Comparator	3.3	4.2				
Hazard ratio	0.98	1.01				
p Value	0.42	Not reported				
Objective response rate (%)						
Investigational	21	23	24	20	18	17
Comparator	11	22				

[a] Investigator's choice (docetaxel, paclitaxel, vinflunine).
[b] In the PD-L1 ≥5% group (primary outcome of the trial).
OS = overall survival; PFS = progression free survival.

with 5% or greater PD-L1 expression on tumour-infiltrating immune cells (denoted IC 2/3), then in patients with 1% or greater PD-L1 expression on tumour-infiltrating immune cells (IC 1/2/3), and then in the ITT population. The results demonstrated no significant difference in OS for the population with 5% or greater PD-L1 expression on tumour-infiltrating immune cells, with the median OS being 11.1 months in the atezolizumab arm and 10.6 months in the chemotherapy arm (HR: 0.87; 95% CI: 0.61 to 1.21), thereby not meeting the primary endpoint of the study. The ORR in the IC 2/3 population did not differ significantly for atezolizumab (23%; 95% CI: 15.6% to 31.9%) and chemotherapy (21.6%; 95% CI: 14.5% to 30.2%). No difference in PFS was noted between the arms (HR: 1.01; 95% CI: 0.75 to 1.34). Exploratory analyses in the ITT population revealed similar trends. Safety data indicated that atezolizumab was better tolerated, with a lower rate of grade 3 or 4 toxicities (20% vs. 43%) and an adverse effect–related treatment discontinuation rate of 3% compared with 15% in the chemotherapy group. The lack of an observed OS benefit calls into question the role of atezolizumab in the second-line setting.

Nivolumab[23,24], durvalumab[25], and avelumab[27] have been studied in single-arm phase I or II trials, the results of which are summarized in Table III. Based on those early-phase studies, durvalumab and avelumab both received conditional approval from Health Canada in that setting.

First-Line Treatment: Standard first-line therapy for metastatic urothelial carcinoma involves cisplatin-based combination chemotherapy, which has been shown to have a survival advantage[28]. However, patient factors such as performance status, renal dysfunction, neuropathy, hearing loss, or congestive heart failure can render 30%–50% of patients unsuitable for cisplatin-based treatment[29]. Thus, CPIs might have a role not only in improving outcomes in cisplatin-eligible patients, but also in providing effective options for cisplatin-ineligible patients.

In the first-line setting, 2 CPIs have been evaluated in phase II trials[30,31]. Atezolizumab was assessed in a single-arm study of 119 cisplatin-ineligible patients. After a median follow-up of 17 months, the ORR was 23% (95% CI: 16% to 31%) with 11 CRs (9%). Median OS was 15.9 months (95% CI: 10.4 months to not yet reached). Pembrolizumab was also investigated as first-line therapy in a single-arm phase II trial involving 374 platinum-ineligible patients. The ORR in that trial was found to be 24% (95% CI: 20% to 29%), with 6% CRs. Based on those data, atezolizumab and pembrolizumab were both granted accelerated approval in 2017 by the U.S. Food and Drug Administration for cisplatin-ineligible patients. No similar approval has been granted by Health Canada to date.

Phase III trials of the foregoing agents are underway. IMvigor130 is assessing atezolizumab both as monotherapy and in combination with chemotherapy, with a comparator of chemotherapy alone (see Table IV for details). Similarly, KEYNOTE-361 is randomizing patients to pembrolizumab alone, pembrolizumab combined with chemotherapy, or chemotherapy alone. Notably, in June 2018, the U.S. Food and Drug Administration issued a warning after early results from both trials indicated worse outcomes in the CPI monotherapy arms for the low-expression PD-L1 cohort[32]. Further results are pending, although both trials have stopped enrolling patients with tumours of low PD-L1 status to their respective monotherapy arms, and CPI monotherapy should not be used in such patients in that setting until mature results are available. Table IV summarizes the ongoing trials of CPIs in the first-line setting.

TABLE IV Upcoming trials of checkpoint inhibitor therapy in the first-line treatment of metastatic urothelial carcinoma

ClinicalTrials.gov ID (study name)	Treatment arms	Study phase	Platinum eligible or ineligible?
NCT02516241	Durvalumab Durvalumab–tremelimumab Cisplatin or carboplatin–gemcitabine	III	Both
NCT02807636 (IMvigor130)	Atezolizumab Atezolizumab–cisplatin or carboplatin–gemcitabine Cisplatin or carboplatin–gemcitabine	III	Both
NCT02853305 (KEYNOTE-361)	Pembrolizumab Pembrolizumab–cisplatin or carboplatin–gemcitabine Cisplatin or carboplatin–gemcitabine	III	Both
NCT03036098 (CheckMate 901)	Ipilimumab–nivolumab Nivolumab–cisplatin–gemcitabine[a] Cisplatin or carboplatin–gemcitabine	III	Both[a]
NCT03133390	Atezolizumab Atezolizumab–bevacizumab	II	Ineligible
NCT03361865 (KEYNOTE-672)	Pembrolizumab Pembrolizumab–epacadostat	III	Ineligible
NCT03240016	Pembrolizumab–nab-paclitaxel	II	Ineligible

[a] Only cisplatin-eligible patients are randomized to the nivolumab–cisplatin–gemcitabine arm.

Prostate Cancer

Immune CPIs have not shown a consistent benefit in clinical trials to date, and they currently have no defined role in the treatment of prostate cancer. Two phase III clinical trials of ipilimumab in the setting of metastatic castrate-resistant prostate cancer (mCRPC) have been reported[33,34]. The CA184-043 trial randomized 799 patients with mCRPC and at least 1 bone metastasis progressing after docetaxel to receive either placebo or ipilimumab after receipt of bone-directed radiotherapy. The primary outcome, OS, was not significantly different in the two groups (HR: 0.85; 95% CI: 0.72 to 1.00; $p = 0.53$). Median OS was 11.2 months in the ipilimumab arm and 10.0 months in the control arm. Grades 3–4 toxicities occurred in 59% of patients in the ipilimumab arm and in 41% in the placebo arm. In another phase III trial, CA184-095, involving 602 patients with mCRPC who had received no prior chemotherapy treatment, ipilimumab was not found to be superior to placebo in terms of OS (HR: 1.11; 95.87% CI: 0.88 to 1.39). A higher serum prostate-specific antigen response rate was observed in the CPI arm (23% vs. 8% with placebo). Grade 3 or 4 toxicity occurred at a rate of 40% in the patients treated with ipilimumab and at a rate of 6% in the patients receiving placebo.

In the phase II KEYNOTE-199 trial, in which 253 patients with mCRPC previously treated with docetaxel were enrolled, pembrolizumab was shown to have only minor activity[35]. The ORR in patients with measurable disease was 5% (95% CI: 2% to 8%), and the disease control rate for all patients was 26%.

Despite existing data indicating a low level of activity for CPIs in prostate cancer, considerable interest remains, possibly as a result of case reports of long-term responders to ipilimumab[36] and the potential for combining CPIs with other treatment modalities (such as chemotherapy or hormonal therapy). Additional clinical trials are ongoing, including the IMbassador250 phase III trial of atezolizumab–enzalutamide compared with enzalutamide alone in mCRPC, and three planned phase III trials with pembrolizumab combined with docetaxel, enzalutamide, or olaparib. Further data are needed before CPIs become standard therapy in prostate cancer.

Testicular Germ-Cell Tumours

Testicular germ cell tumours (GCTs) are among the most highly curable solid tumours. About 80% of patients with metastatic disease will be cured with first-line or salvage chemotherapy[37]. However, those treatments fail about 15%–20% of patients, a subgroup that is thus in need of additional treatment options. Recent trials using targeted therapies in such patients have yielded disappointing results[38–41]. Although GCTs have been shown to express PD-L1[42], and a number of case studies and series have described activity for CPIs in those tumours[43–45], early-phase trials have been disappointing to date. A phase II trial of pembrolizumab in 12 patients with platinum-refractory disease produced zero responses[46]. A dual-arm phase II trial in 18 chemotherapy-refractory patients with GCT resulted in 0 of 9 patients responding to single-agent durvalumab; 2 of 9 (22%) responded to durvalumab–tremelimumab[47]. Ongoing clinical trials include a phase II trial of avelumab (NCT03403777 at https://ClinicalTrials.gov/) and basket trials of combination ipilimumab–nivolumab therapy (NCT02834013), single-agent nivolumab (NCT02832167), and atezolizumab (NCT02458638). Another phase II trial of ipilimumab–nivolumab in rare GU malignancies is enrolling patients with refractory GCT in addition to other tumour types such as penile carcinoma (NCT03333616). Until more definitive data become available, CPI therapy in GCT remains an experimental approach.

Penile Cancer

To date, no data are available about the use of CPIs in squamous-cell carcinoma of the penis. However, penile cancers have been shown to have high rates of PD-L1 expression[48], and the known benefit of CPIs in squamous-cell carcinoma of the head and neck[49,50] and lung[51–53] indicate that CPIs might plausibly have activity in penile squamous-cell carcinoma. In addition to the phase II ipilimumab–nivolumab trial already mentioned (NCT03333616), a trial of pembrolizumab in advanced penile cancer is underway (NCT02837042).

SUMMARY

Immune CPIs have demonstrated positive results in GU clinical trials and in the clinic. Those treatments have changed the standard of care in kidney and bladder cancer, and many patients worldwide are benefiting from them today. For other indications, more data and novel approaches will be needed to incorporate CPIs into the standard of care. Several trials in a number of different clinical settings are moving toward combined-modality therapy, with CPIs being used in tandem with other treatments such as chemotherapy and targeted therapies. The treatment of GU malignancies has changed profoundly as a result of CPI therapies and is certain to evolve further over time.

A number of questions still remain. It is not always clear how best to sequence treatments, because CPIs, particularly when combined with other treatment modalities, move into the first-line setting in metastatic disease. The role of predictive biomarkers in patient selection for treatment requires further study, because no predictive biomarkers are currently available for any of the GU malignancies. Similarly, predicting the patients that are at high risk for serious irAEs continues to be a challenge, especially with the more-toxic regimens such as ipilimumab–nivolumab.

In many cases, CPIs are improving clinical outcomes for patients with GU cancer, but costs and resources are an important issue to consider. Immune CPI therapies are inherently expensive and burden a limited health care system because of frequent visits with treating oncologists and nursing staff while on treatment, infusion visits (every 2–4 weeks, depending on the regimen), and unscheduled visits to assess for emergent toxicities. Additionally, irAEs can prompt emergency room visits, admission to inpatient units, and occasionally, expensive immunosuppressive treatments. Active efforts to educate patients, families, and their health care providers (including primary care providers, emergency room physicians, and internal medicine subspecialists) about irAEs is crucial to curtailing morbidity and mortality from the treatments, but again, additional resources are required. In Canada, the challenges of

providing treatments that require access by patients to such supports and resources is complicated by Canada's vast geographic span; patients in rural and remote areas distant from large cancer centres might be underserved or placed at higher risk for complications from adverse effects unless local safeguards are in place. The financial implications of combining CPIs with costly treatments such as anti-VEGF TKIs must also be considered, and the cost-effectiveness of such combined approaches is not yet clear. Given all those considerations, oncologists and health care systems must adapt to accommodate the additional challenges that CPI therapies will introduce as they become more ubiquitous in the clinic.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: LW has served on advisory boards for Pfizer, Merck, Novartis, Bristol–Myers Squibb, Ipsen, and Astellas (no personal financial compensation); she is also participating in or has participated in research with Pfizer, Roche, AstraZeneca, Bristol–Myers Squibb, Merck, Novartis, and Ipsen (financial compensation to her institution). MT has no conflicts of interest to disclose.

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