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From Clinical Trials to Real-life Clinical Practice: The Role of Immunotherapy with PD-1/PD-L1 Inhibitors in Advanced Urothelial Carcinoma

Syed A. Hussain [a,*], *Alison Birtle* [b], *Simon Crabb* [c], *Robert Huddart* [d], *Diane Small* [e], *Maxwell Summerhayes* [e], *Robert Jones* [f], *Andrew Protheroe* [g]

[a] *Institute of Translational & Stratified Medicine, Plymouth University, Peninsula Schools of Medicine and Dentistry, Plymouth, UK;* [b] *Lancashire Teaching Hospitals NHS Trust, Preston, UK;* [c] *Southampton Experimental Cancer Medicine Centre, University of Southampton, Southampton, UK;* [d] *Royal Marsden NHS Foundation Trust, London, UK;* [e] *Roche Products Ltd., Welwyn Garden City, UK;* [f] *Institute of Cancer Sciences, University of Glasgow, Glasgow, UK;* [g] *Oxford Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, UK*

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Abstract

Context: A number of PD-1/PD-L1 inhibitors have recently been approved for use in patients with locally advanced or metastatic urothelial carcinoma (UC) on the basis of results from several clinical trials.
Objective: To review the evidence from these trials and consider what it means for the use of these drugs in first-line and post-platinum settings in real-life clinical practice.
Evidence acquisition: PubMed was searched for full reports of clinical trials of single-agent PD-1/PD-L1 inhibitors in advanced UC. Twelve publications were included.
Evidence synthesis: Responses to PD-1/PD-L1 inhibitors appear to be durable but are only achieved in 17–26% of patients. These drugs offer different toxicity and efficacy profiles to standard chemotherapy regimens. This should be considered when choosing a treatment strategy for each patient.
Conclusions: PD-1/PD-L1 inhibitors represent a major step forward in the management of advanced UC, although several questions remain regarding their optimal use in routine clinical practice. A validated predictive biomarker of response is yet to be defined, and this is perhaps the most significant unmet need for currently available drugs.
Patient summary: We reviewed the results from clinical trials that investigated how well certain types of anticancer drugs called PD-1/PD-L1 inhibitors worked in patients with bladder cancer. We found that more research is required to identify (1) the factors that might predict which patients with bladder cancer will respond to PD-1/PD-L1 inhibitors and (2) the optimum duration of treatment with these drugs.

* Corresponding author. Institute of Translational & Stratified Medicine, Plymouth University, Peninsula Schools of Medicine and Dentistry, Davy Road, Plymouth Science Park, Plymouth PL6 8BX, UK. Tel.: +44 1752 764260.
E-mail address: syed.hussain@plymouth.ac.uk (S.A. Hussain).

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1. Introduction

Immunotherapy is not a novel concept in the treatment of urothelial carcinoma (UC). For decades, intravesical instillation of the attenuated mycobacterium bacillus Calmette-Guérin has been used to prevent disease recurrence or progression in non–muscle-invasive bladder cancer following transurethral resection of the tumour [1]. Now an exciting and rapidly evolving modern era of immunotherapy has begun in the advanced (locally advanced or metastatic) UC setting with the approval of several monoclonal antibody treatments. The mechanism underlying the antitumour activity of these drugs is inhibition of immune checkpoints, such as the PD-1/PD-L1 pathway (Fig. 1), and they offer new treatment possibilities for patients who have historically had few options available to them.

The standard first-line treatment of advanced UC remains cisplatin-based chemotherapy, such as methotrexate, vinblastine, doxorubicin and cisplatin (MVAC), or gemcitabine–cisplatin (GC) [2]. These treatments have confirmed activity in bladder cancer, but are associated with clinically significant toxicities, including myelosuppression, ototoxicity, neurotoxicity, and nephrotoxicity [3–5]. In a phase 3 randomised trial comparing these regimens, objective response rates (ORRs) were comparable in the GC and MVAC groups (49.4% vs 45.7%, respectively), with approximately 12% of patients in each group achieving a complete response (CR) [5]. Median overall survival (OS) was 14.0 and 15.2 mo, respectively, and median progression-free survival (PFS) was approximately 8 mo in each treatment arm [6]. Frequent thrombocytopenia and neutropenia were reported for both treatments [5]. Common grade 3/4 nonhaematological toxicities included nausea, vomiting, alopecia, infection, and mucositis [5]. Of the two regimens, GC was associated with lower rates of toxicity-related mortality, neutropenic sepsis, and grade 3/4 mucositis, making it the preferred first-line treatment [5]. Most UC patients who respond to first-line cisplatin-based chemotherapy are likely to experience disease progression within a disappointingly short period of time [7]. Until recently, the only treatment option approved for patients failing first-line chemotherapy was vinflunine (in Europe only), which was associated with a modest improvement in PFS versus best supportive care alone [8]. Other chemotherapy regimens have shown activity in patients with UC who have progressed on platinum-based chemotherapy, but these have not been tested in randomised phase 3 trials [9], resulting in a lack of consensus on the standard of care in this setting.

UC is a disease that mostly affects older people, who often have pre-existing comorbidities and/or renal impairment. Many of these patients are considered “unfit for cisplatin-based treatment” [10] and, until now, would commonly be offered carboplatin-based chemotherapy, such as gemcitabine–carboplatin (GemCarbo) or methotrexate, carboplatin, and vinblastine (M-CAVI). In the EORTC 30986 trial that compared these two regimens in cisplatin-ineligible patients, the ORR was higher with GemCarbo than with M-CAVI (41.2% vs 30.3%), but median OS (9.3 vs 8.1 mo) and PFS (5.8 vs 4.2 mo) were similar [11]. Severe acute toxicities were more common in patients receiving M-CAVI, particularly in those with poor renal function [11].

There are five PD-1/PD-L1 inhibitors—atezolizumab, pembrolizumab, nivolumab, durvalumab, and avelumab—now approved in the USA for use in patients with advanced UC who have progressed during or within 12 mo of receiving platinum-based chemotherapy [12–16]. Atezolizumab, pembrolizumab, and nivolumab are also approved for relapsed UC in Europe [17–19]. The licences for atezolizumab and pembrolizumab were recently extended to include first-line treatment in cisplatin-ineligible patients [12,14,18,19]. PD-1/PD-L1 inhibitors are effective in only a proportion of patients with advanced UC, but responses appear to be durable for these patients [20–26]. In clinical trials, treatment was continued for either a fixed duration or until disease progression, unacceptable toxicity, or study completion. In clinical practice, the optimal treatment duration for anti-PD-1/PD-L1 drugs in UC is unknown, and patients generally continue to receive these treatments until loss of clinical benefit or unacceptable toxicity.

Here we summarise current clinical evidence for PD-1/PD-L1 inhibitors in the treatment of advanced UC. Importantly, we consider what this evidence means for real-life clinical practice in terms of selecting patients with UC for immunotherapy and when, or if, treatment with these agents can be stopped.

2. Evidence acquisition

A PubMed search of the literature was performed for original research reports using the terms “bladder cancer”, “urothelial carcinoma”, “urothelial cancer”, “transitional cell carcinoma”, “immunotherapy”, “atezolizumab”, “avelumab”, “durvalumab”, “nivolumab”, “pembrolizumab”, “checkpoint inhibitor”, “PD-1”, and “PD-L1”. The search was restricted to articles in English published since 2007 and limited to fully published reports of prospective clinical trials. An additional search was carried out to identify trials of chemotherapy regimens used in cisplatin-ineligible patients in the first-line setting for comparison with safety data from immunotherapy trials. Additional terms for this search included “cisplatin-ineligible”, “unfit”, “carboplatin”, “first-line”, and “untreated”. Prospective multicentre trials published in the past 10 yr were included, as well as other relevant peer-reviewed publications known to the authors.

3. Evidence synthesis

A flowchart of the search strategy is shown in Supplementary Figure 1. The search identified reports for 12 trials of PD-1/PD-L1 inhibitors in advanced UC, which are summarised below.

3.1. PD-1/PD-L1 inhibitors in the post-platinum setting

Atezolizumab was granted accelerated approval in the USA on the basis of results from IMvigor210, a two-cohort,

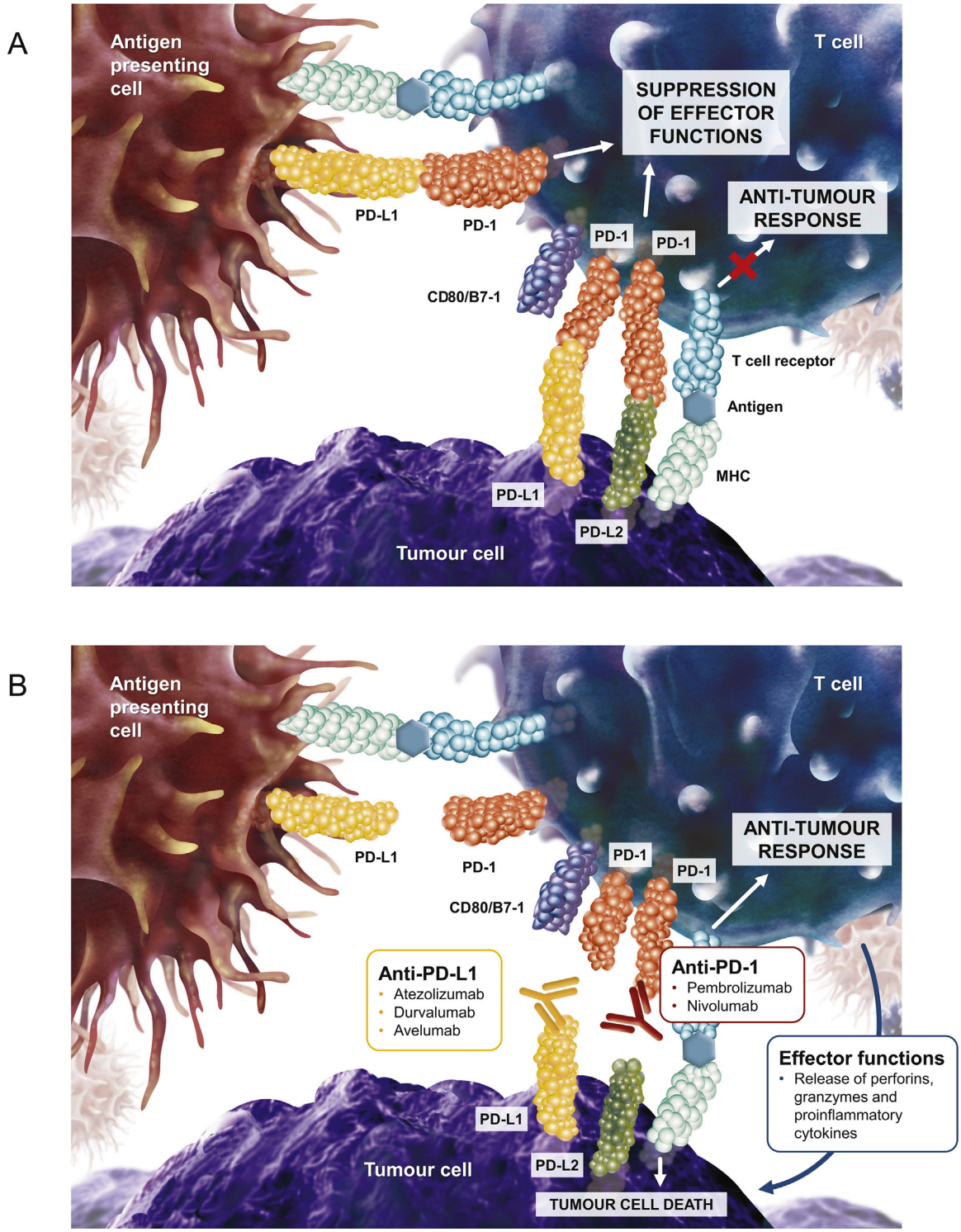

Fig. 1 – PD-1/PD-L1 inhibitors prevent the suppression of antitumour T-cell effector functions. The PD-1/PD-L1 interaction is a component of a complex and incompletely understood mechanism for control of immune surveillance that is corrupted by some tumours. (A) Binding of PD-L1 to PD-1 results in downstream suppression of normal T-cell effector functions [43]. Tumours expressing PD-L1 use this pathway to evade the antitumour activity of T cells within the tumour microenvironment and prevent the activation and migration of tumour-infiltrating lymphocytes to the tumour site [43]. (B) By preventing this suppression, PD-1/PD-L1 inhibitors effectively kick start the immune response against the cancer cells. As PD-L1 binds PD-1 and B7-1, and PD-1 is bound by PD-L1 or PD-L2, PD-1 and PD-L1 inhibitors have different interactions, which may or may not matter clinically. MHC = major histocompatibility complex.

multicentre, phase 2 trial in patients with advanced UC. This was followed by the confirmatory phase 3 trial IMvigor211, which involved 931 patients randomly assigned to receive atezolizumab or the investigators' choice of vinflunine, docetaxel, or paclitaxel [27]. IMvigor211 did not meet its primary endpoint of OS, which was first evaluated in patients with PD-L1 expression on ≥5% of immune cells (IC2/3 population; $n = 234$) in accordance with the prespecified hierarchical testing procedure. In this population, the median OS was 11.1 and 10.6 mo in the atezolizumab and chemotherapy arms, respectively (hazard ratio [HR] 0.87, 95% confidence interval [CI] 0.63–1.21; $p = 0.41$). Exploratory analysis demonstrated a significant difference in OS in the intent-to-treat (ITT) population for patients treated with atezolizumab compared with chemotherapy (HR 0.85, 95% CI 0.73–0.99; $p = 0.038$; Table 1) [27,28]. In the IC2/3 population, ORRs were similar between atezolizumab and chemotherapy (23.0% vs 21.6%), but the median duration of response was longer in the atezolizumab arm (15.9 vs 8.3 mo; HR 0.57, 95% CI 0.26–1.26). Responses to atezolizumab were durable regardless of PD-L1 status, and PD-L1 expression appeared to be prognostic rather than predictive of response [28]. In the ITT population, treatment-related adverse events (AEs) of any grade and of grade 3/4 and AEs that led to treatment discontinuation were more common with chemotherapy than with atezolizumab (Table 2). AEs of special interest of any grade occurred in 139 (30.3%) and 98 patients (22.1%) in the atezolizumab and chemotherapy groups, respectively. Grade 3/4 AEs of special interest occurred in 37 (8.1%) and 13 patients (2.9%), respectively. Overall, results from IMvigor211 were consistent with those from earlier studies of atezolizumab (Table 1) [25,29]. The previous phase 2 trial, IMvigor210 (cohort 2), enrolled 310 patients who had experienced progression after platinum-based therapy. These patients were treated with atezolizumab, which resulted in an ORR of 15% (Table 1) [25]. PD-L1 expression on tumour-infiltrating immune cells was associated with an increased response to atezolizumab, with an ORR of 26% in the IC2/3 population and 18% for those with expression on ≥1% of immune cells (IC1/2/3), similar to that seen in the phase 3 study [27]. Of the 121 patients who were treated beyond RECIST v1.1-defined disease progression, 20 (16.5%) went on to experience a reduction in the target lesion of at least 30% from baseline [25]. Further post hoc analysis of postprogression outcomes in this trial confirmed a prolonged clinical benefit in patients who continued treatment beyond progression [30]. The safety profile of atezolizumab was similar to that observed in IMvigor211. The incidence of immune-mediated AEs is summarised in Table 3 [25]. Exploratory biomarker analyses suggested associations between the response to atezolizumab treatment and The Cancer Genome Atlas (TCGA) gene expression subtype, tumour mutational burden, and CD8 infiltration [25].

The other phase 3 trial of a PD-1/PD-L1 inhibitor completed in the post-platinum setting in advanced UC tested the PD-1 inhibitor pembrolizumab [14]. KEYNOTE 045, like IMvigor211, randomised patients ($n = 542$) to receive pembrolizumab or the investigators' choice of single-agent chemotherapy [22]. Median OS was significantly better among patients treated with pembrolizumab compared with those treated with chemotherapy in the ITT population (Table 1; HR 0.73, 95% CI 0.59–0.91; $p = 0.002$) [22]. This benefit was evident regardless of PD-L1 expression and in all subgroups examined. There was no significant difference in PFS between treatment groups (HR 0.98, 95% CI 0.81–1.19; $p = 0.42$). ORR was significantly higher in the pembrolizumab than in the chemotherapy group ($p = 0.001$), and responses in the pembrolizumab group were durable (Table 1). Overall, treatment-related AEs of any grade and grade ≥3 were more common in the chemotherapy arm (Table 2). Immune-mediated AEs were observed in 45 patients (16.9%) in the pembrolizumab arm (Table 3) and 19 (7.5%) in the chemotherapy arm. These results support previous observations in the UC cohort of the KEYNOTE 012 phase 1b study (Table 1) [31].

Nivolumab is a PD-1 inhibitor that was approved for patients with advanced UC who failed to respond to previous platinum-based chemotherapy on the basis of results from the phase 2 CheckMate 275 trial ($n = 265$; Table 1) [26]. Favourable ORR outcomes were observed for all treated patients and across all PD-L1 subgroups when compared with the historical control of single-drug chemotherapy [26]. Responses were ongoing at the time of analysis in 40 of the 52 patients who achieved a response, including four patients who had stopped nivolumab and had not received subsequent treatment [26]. Responses to nivolumab were observed across all predefined patient subgroups [26]. Seventy patients (26.4%) were treated beyond disease progression. Of these, 24 (34.3%) went on to experience a nonconventional clinical benefit [26]. Treatment-related AEs occurred in 174 patients (64.4%), the majority of which were grade 1/2 [26], and were similar to those described for atezolizumab and pembrolizumab (Table 2). Most immune-mediated AEs resolved with steroid treatment (Table 3); however, some endocrine-associated AEs required ongoing hormone replacement therapy [26]. Exploratory biomarker analyses suggested that markers of pre-existing immunity might be associated with a response to nivolumab [26]. Similar observations were made in CheckMate 032, an earlier phase 1/2 trial (Table 1) [32].

Although not yet approved in Europe, the PD-L1 inhibitor durvalumab has been granted accelerated approval in the USA for patients with advanced UC who have experienced progression on platinum-containing chemotherapy. Approval was based on the results from an ongoing phase 1/2 study that involved 191 patients who had experienced progression on or within 1 yr of receiving platinum-based chemotherapy, with the exception of nine treatment-naïve patients [24]. Patients received durvalumab for up to 1 yr. Responses were achieved in 34 patients (17.8%) and were observed in all subgroups examined. Responses appeared durable, with 26 patients (76.5%) experiencing an ongoing response at the time of analysis, including six patients who stopped treatment after completing 12 mo of durvalumab [24]. ORR was 28% among patients classified as PD-L1-high (≥25% of either tumour or immune cells) compared with 5%

Table 1 – Clinical trials of PD-1/PD-L1 inhibitors in the postplatinum treatment of advanced urothelial carcinoma[a]

Trial	Treatment received/median duration	*n*	Response		Median time to response	Median duration of response	Median OS, mo (95% CI)	12-mo OS, % (95% CI)	Median PFS, mo[b] (95% CI)	12-mo PFS, % (95% CI)
			ORR, % (95% CI)	BR (%)[a]						
NCT01375842 [29]; phase 1 expansion study; minimum FU 6 wk; PEs, safety and tolerability	Atezolizumab 15 mg/kg Q3W/ 65 d (range 1–259)	65	IHC 2/3: 43 (26–63) IHC 0/1: 11 (4–26)	IHC 2/3: CR 7	NRP	IHC 2/3: NR (range 0.1+ to 30.3+ wk) IHC 0/1: NR (range 0.1+ to 6.0+ wk)	NRP	NRP	NRP	NRP
IMvigor210 Cohort 2 [25]; single-arm phase 2; MFU 11.7 mo; PE, ORR	Atezolizumab 1200 mg Q3W/12 wk (range 0–66)	310	15 (11–19)	CR 5 PR 10 SD 19 PD 51 NE 15	2.1 mo (95% CI 2.0–2.2)	NR	7.9 (6.6–9.3)	36 (30–41)	2.1 (2.1–2.1)	NRP
IMvigor211 [27]; randomised phase 3; MFU 17.8 mo; PE, OS tested hierarchically in pre-specified populations	Atezolizumab 1200 mg Q3W/ 2.8 mo (range 0–24)	467	13 (11–17)	CR 3 PR 10 SD 20 PD 52 NE 15	NRP	21.7 mo (95% CI 13.0–21.7)	8.6 (7.8–9.6)	39.2 (34.8–43.7)	2.1 (2.1–2.2)	NRP
	Chemotherapy Q3W/ vinflunine 2.1 mo (range 0–15); paclitaxel 2.1 mo (range 0–23); docetaxel 1.6 mo (range 0–10)	464	13 (11–17)	CR 3 PR 10 SD 35 PD 32 NE 19	NRP	7.4 mo (95% CI 6.1–10.3)	8.0 (7.2–8.6)	32.4 (28.0–36.8)	4.0 (3.4–4.2)	NRP
KEYNOTE 012 [31]; multicohort phase 1b; MFU 13 mo; PEs, safety and ORR	Pembrolizumab 10 mg/kg Q2W/71 d (range 1–708)	27	26 (11–46)	CR 11 PR 15 SD 15 PD 52 NE 7	2 mo (range 2–13)	10 mo (range 4–22+)	13 (5–20)	50 (29–70)	2 (2–4)	15 (5–31)
KEYNOTE 045 [22]; randomised phase 3; MFU 14.1 mo; PEs, OS and PFS	Pembrolizumab 200 mg Q3W/3.5 mo (range <0.1–20)	270	21 (16–27)	CR 7 PR 14 SD 17 PD 48.5 NE 13	2.1 mo (range 1.4–6.3)	NR (range 1.6+ to 15.6+ mo)	10.3 (8.0–11.8)	43.9 (37.8–49.9)	2.1 (2.0–2.2)	16.8 (12.3–22.0)
	Chemotherapy Q3W/ 1.5 mo (range <0.1–14.2)	272	11 (8–16)	CR 3 PR 8 SD 33.5 PD 33 NE 22	2.1 mo (range 1.7–4.9)	4.3 mo (range 1.4+ to 15.4+)	7.4 (6.1–8.3)	30.7 (25.0–36.7)	3.3 (2.3–3.5)	6.2 (3.3–10.2)
CheckMate 032 [32]; single-arm phase 1/ 2; MFU 15.2 mo; PE, ORR	Nivolumab 3 mg/kg Q2W/8.5 doses (range 1–46)	78	24 (15–35)	CR 6 PR 18 SD 28 PD 38 NE 9	1.5 mo (IQR 1.2–4.1)	9.4 mo (IQR 5.7–12.5)	9.7 (7.3–16.2)	46 (34–56)	2.8 (1.5–5.9)	21 (12–31)

Table 1 (*Continued*)

Trial	Treatment received/median duration	*n*	Response		Median time to response	Median duration of response	Median OS, mo (95% CI)	12-mo OS, % (95% CI)	Median PFS, mo[b] (95% CI)	12-mo PFS, % (95% CI)
			ORR, % (95% CI)	BR (%)[a]						
CheckMate 275 [26]; single-arm phase 2; MFU 7.0 mo; PE, ORR	Nivolumab 3 mg/kg Q2W/NRP	265	20 (15–25)	CR 2 PR 17 SD 23 PD 39 NE 18	1.9 mo (IQR 1.8–2.0)	NR (IQR 7.4 mo–NR)	8.74 (6.05–NR)	NRP	2.0 (1.9–2.6)	NRP
Study 1108 [24]; single-arm phase 1/2; MFU 5.8 mo, PEs, safety and ORR	Durvalumab 10 mg/kg Q2W/2.8 mo (range 0.4–12.5)	191	18 (13–24)	CR 4 PR 14 NE 17	1.4 mo (range 1.2–7.2)	NR (range 0.9+ to 19.9+ mo)	18.2 (8.1–NE)	55 (44–65)	1.5 (1.4–1.9)	16 (10–23)
JAVELIN Solid Tumor: initial cohort [33]; expansion cohort phase 1b; MFU 16.5 mo; PEs, safety and tolerability	Avelumab 10 mg/kg Q2W/14.1 wk (IQR 6.0–35.1)	44	18 (8–33)	CR 11 PR 7 SD 34 PD 34 NE 14	13.0 wk (IQR 8.8–38.6)	NR (95% CI 12.1 wk–NE)	13.7 (8.5–NE)	54.3 (37.9–68.1)	11.6 wk (6.1–17.4)	19.1 (8.5–32.8) at 48 wk
JAVELIN Solid Tumor: pooled analysis [23]; expansion cohort phase 1b; MFU 9.9 mo; PE, ORR	Avelumab 10 mg/kg Q2W /12.0 wk (IQR 6.0–19.7)	249[c]	17 (11–24)	CR 6 PR 11 SD 23 PD 42 NE 18	11.4 wk (IQR 5.9–17.4)	NR (95% CI 42.1 wk–NE)	6.5 (4.8–9.5)	53 (45–60) at 6 mo	6.6 wk (6.1–11.4)	24 (18–31) at 24 wk

+ = ongoing response at data cutoff; BR = best response; CI = confidence interval; CR = complete response; IHC = immunohistochemistry; IQR = interquartile range; MFU = median follow-up; NE = not estimable; NR = not reached; NRP = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PE = primary endpoint; PFS = progression-free survival; PR = partial response; Q2W = every 2 wk; Q3W = every 3 wk; SD = stable disease.

[a] Some percentages do not add up to 100 because of rounding.

[b] Unless otherwise indicated.

[c] *n* = 161 postplatinum patients with >6 mo of FU follow-up included in the efficacy analysis.

Table 2 – Treatment-related AE data from trials of PD-1/PD-L1 inhibitors in patients with advanced urothelial carcinoma who experienced progression on platinum-based chemotherapy

	IMvigor211 [27]		KEYNOTE 045 [22]		CheckMate 275 [26]	Study 1108 [24]	JAVELIN Solid Tumor [23]
	Atezolizumab	Chemotherapy	Pembrolizumab	Chemotherapy	Nivolumab	Durvalumab	Avelumab
Patients (*n*)	459	443	266	255	270	191	249
Any grade AE, *n* (%)	319 (69.5)	395 (89.2)	162 (60.9)	230 (90.2)	174 (64.4)	116 (60.7)	166 (66.7)
Most common	Fatigue: 71 (15.5) ↓ appetite: 56 (12.2) Pruritus: 55 (12.0) Asthenia: 51 (11.1) Diarrhoea: 50 (10.9)	Constipation: 145 (32.7) Alopecia: 120 (27.1) Nausea: 117 (26.4) Fatigue: 116 (26.2)	Pruritus: 52 (19.5) Fatigue: 37 (13.9) Nausea: 29 (10.9) Diarrhoea: 24 (9.0)	Alopecia: 96 (37.6) Fatigue: 71 (27.8) Anaemia: 63 (24.7) Nausea: 62 (24.3) Constipation: 52 (20.4)	Fatigue: 45 (16.7) Pruritus: 25 (9.3) Diarrhoea: 24 (8.9) ↓ appetite: 22 (8.1)	Fatigue: 37 (19.4) ↓ appetite: 18 (9.4) Diarrhoea: 16 (8.4) Rash: 14 (7.3)	Infusion-related reaction: 73 (29.3) Fatigue: 40 (16.1) Rash: 37 (14.9) Diarrhoea: 15 (6.0)
Grade 3/4, *n* (%)	91 (19.8)	189 (42.7)	36 (13.5)[a]	122 (47.8)[a]	48 (17.8)	13 (6.8)	20 (8.0)
Most common	Anaemia: 9 (2.0) Asthenia: 8 (1.7) Fatigue: 7 (1.5)	Neutropenia: 49 (11.1) ↓ NC: 26 (5.9) Febrile neutropenia: 25 (5.6) Anaemia: 21 (4.7)	Pneumonitis: 5 (1.9) Colitis: 3 (1.1) Fatigue: 3 (1.1) Diarrhoea: 3 (1.1)	Neutropenia: 34 (13.3) ↓ NC: 31 (12.2) Anaemia: 20 (7.8) Fatigue: 11 (4.3)	Fatigue: 5 (1.9) Diarrhoea: 5 (1.9) Asthenia: 4 (1.5) Rash: 3 (1.1)	↑ AST: 3 (1.6) ↑ ALT: 2 (1.0) ↑ GGT: 2 (1) Hypertension: 2 (1.0)	Fatigue: 4 (1.6) Asthenia: 2 (0.8) Elevated lipase: 2 (0.8) Hypophosphataemia: 2 (0.8)
Serious AE, *n* (%)	72 (15.7)	110 (24.8)	Not reported	Not reported	Not reported	9 (4.7)	19 (7.6)
AE leading to discontinuation, *n* (%)	16 (3.5)	63 (14.2)	15 (5.6)	28 (11.0)	13 (4.8)	3 (1.6)	14 (5.6)
AE leading to death, *n* (%)	4 (0.9) General physical health deterioration; respiratory failure; intestinal perforation; toxic epidermal necrolysis	9 (2.0) Cardiorespiratory arrest; death (2)[b]; respiratory tract infection; sepsis; pneumonia (2); septic shock; toxic shock syndrome	4 (1.5) Pneumonitis; urinary tract obstruction; malignant neoplasm progression; unspecified	4 (1.6) Sepsis (2); septic shock; unspecified	3 (1.1) Pneumonitis; acute respiratory failure; cardiovascular failure	2 (1.0) Autoimmune hepatitis; pneumonitis	1 (0.4) Pneumonitis

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyltransferase; NC = neutrophil count.

[a] Grade 3/4 data for KEYNOTE 045 were calculated by subtracting grade 5 data from the data in Table 2 in [22].

[b] Annotated under general disorders and administration site conditions.

Table 3 – Immune-mediated adverse events (any grade) reported in at least two patients in clinical trials of PD-1/PD-L1 inhibitors in advanced urothelial carcinoma

	Patients, *n* (%)							
	Atezolizumab		Pembrolizumab		Nivolumab		Durvalumab	Avelumab
	IMvigor210 cohort 1 [21] (*n* = 119)	IMvigor210 cohort 2 [25] (*n* = 310)	KEYNOTE 052 [20] (*n* = 370)	KEYNOTE 045 [22] (*n* = 266)	CheckMate 032 [32] (*n* = 78)[a]	CheckMate 275 [26] (*n* = 270)[b]	Study 1108 [44] (*n* = 191)[b]	JAVELIN Solid Tumor [23] (*n* = 249)[b]
Overall	14 (11.8)	23 (7.4)	63 (17.0)	45 (16.9)	–	–	22 (11.5)	34 (13.7)
Skin-related	–	–	–	–	–	47 (17.4)	–	–
Rash	4 (3.4)	2 (0.6)			7 (9)	–	2 (1.0)	12 (4.8)
Severe skin reaction	–	–	–	2 (0.8)	–	–	–	–
Endocrine-related	–	–	–	–	–	39 (14.4)	–	–
Hypothyroidism	1 (0.8)	–	24 (6.5)	17 (6.4)	–	–	10 (5.2)	9 (3.6)
Hyperthyroidism	–	–	9 (2.4)	10 (3.8)	3 (4)	–	2 (1.0)	2 (0.8)
Thyroiditis	–	–	2 (0.5)	2 (0.8)	–	–	–	–
Hypothyroidism/thyroiditis	–	–		–	7 (9)	–	–	–
Adrenal insufficiency	–	–	5 (1.4)	1 (0.4)	0	–	1 (0.5)	–
Type 1 diabetes	–	–	3 (0.8)	–	0	–	–	–
Diabetic ketoacidosis	–	–	2 (0.5)	–	–	–	–	–
Gastrointestinal-related	–	–	–	–	–	25 (9.3)	–	–
Diarrhoea	1 (0.8)	–	–		–	–	4 (2.1)	1 (0.4)
Colitis	1 (0.8)	–	8 (2.2)	6 (2.3)	–	–	1 (0.5)	–
Diarrhoea/colitis	–	–	–	–	2 (3)	–	–	–
Pulmonary-related	–	–	–	–	–	10 (3.7)	–	–
Pneumonitis	–	2 (0.6)	7 (1.9)	11 (4.1)	2 (3)	–	1 (0.5)	3 (1.2)
Dyspnoea	–	2 (0.6)	–	–	–	–	–	–
Hepatic-related	–	–	–	–	–	10 (3.7)	–	–
Hepatitis	–	–	–	–	3 (4)	–	–	–
Increased ALT	2 (1.7)	2 (0.6)	–	–	–	–	–	1 (0.4)
Increased AST	1 (0.8)	2 (0.6)	–	–	–	–	–	2 (0.8)
Increased blood bilirubin	2 (1.7)	–	–	–	–	–	–	–
Renal-related	–	0	–	–	–	3 (1.1)	–	–
Nephritis	–	–	–	2 (0.8)	1 (1)	–	–	–
Other	–	–	–	–	–	–	–	–
Rhabdomyolysis	2 (1.7)	–	–	–	–	–	–	–
Infusion reaction	–	–	–	2 (0.8)	–	–	–	–

– = not reported; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[a] Includes only patients who received immune-modulating medication for treatment of the event, with the exception of endocrine events.

[b] Treatment-related events.

among patients classified as PD-L1-low (<25% of both tumour and immune cells). The incidence of treatment-related AEs and immune-mediated AEs is summarised in Tables 2 and 3, respectively [24].

The JAVELIN Solid Tumor study is a phase 1 trial evaluating avelumab in patients with a range of tumour types. A pooled analysis of two cohorts of patients with advanced UC (n = 249) who received at least one dose of avelumab was recently reported [23]. This included 161 patients with platinum-refractory disease with a minimum of 6-mo follow-up who were included in the efficacy analyses [23]. After median follow-up of 9.9 mo, the response rates to avelumab were comparable to those seen with other PD-1/PD-L1 inhibitors (Table 1). At data cutoff, responses were ongoing in 81.4% of patients, including eight of the nine patients who achieved CR. Responses were seen in patients with poor prognostic factors, including heavily pretreated patients and those with visceral metastases. ORR was 24% among PD-L1-positive patients (≥5% tumour cells) versus 13% among PD-L1-low/negative patients. PFS was also prolonged in patients with higher PD-L1 expression [23]. These findings support earlier results from the initial cohort of 44 patients (Table 1) [33]. Treatment-related AEs occurred at a similar rate as for other PD-1/PD-L1 inhibitors (Table 2). However, 29% of patients in the JAVELIN Solid Tumor trial experienced an infusion-related reaction (all grade 1/2), which may be a higher rate than that observed with other drugs in the class [23]. AEs that were potentially immune-mediated occurred in 34 patients (13.7%; Table 3).

3.2. PD-1/PD-L1 inhibitors in the frontline setting in cisplatin-ineligible patients

Approximately half of patients with advanced UC who are considered for systemic therapy are deemed unfit for cisplatin-based chemotherapy because of renal impairment, comorbidities, and/or a poor performance status [2]. Until recently, these patients would have been offered carboplatin-based chemotherapy, which has poor efficacy with regard to OS but reasonable ORRs in this setting, or best supportive care. Now patients also have the option of pembrolizumab or atezolizumab. These immunotherapies were approved for use as first-line treatment in cisplatin-ineligible patients following results from two multicentre, single-arm, phase 2 trials in this patient population (Table 4) [20,21]. It has not yet been established that either of these options provides a survival advantage over carboplatin-based chemotherapy or best supportive care in cisplatin-ineligible patients in randomised head-to-head comparisons, although the single-arm phase 2 data for atezolizumab are encouraging, with median OS of almost 16 mo (see below). Ongoing prospective randomised studies are addressing this question.

IMvigor210 (cohort 1) included 119 previously untreated patients with advanced UC who received atezolizumab [21]. An objective response to atezolizumab was achieved in 23% of patients, with median OS of 15.9 mo (Table 4). As seen in the post-platinum setting, responses to atezolizumab were durable, with 19 of 27 responses ongoing at the time of analysis. In 11 patients who stopped treatment after achieving CR or PR, six had an ongoing response, four had progressive disease, and one had died by the data cutoff date. ORRs in all PD-L1 subgroups were comparable to those observed in the overall population, and included a response rate of 21% in patients negative for PD-L1 expression on tumour-infiltrating immune cells [21]. Exploratory biomarker analyses suggested a potential predictive role for tumour mutational burden and TCGA molecular subtype in the response to atezolizumab, in agreement with findings in the postplatinum setting [25]. Similarly, the incidence of treatment-related AEs in the first-line setting was also comparable to that observed in patients who had previously experienced progression on platinum-based chemotherapy (Table 5).

Results from KEYNOTE 052, a phase 2 trial of pembrolizumab in cisplatin-ineligible patients, led to approval of pembrolizumab in the frontline setting in this group. Response rates to pembrolizumab were similar to those observed for atezolizumab in this patient population (Table 4). Responses appeared to be durable, with 83.1% of responses ongoing at the time of data cutoff. In contrast to atezolizumab, high PD-L1 expression (≥10% on both tumour and immune cells) enriched the response to pembrolizumab, but responses were still seen in those with low PD-L1 expression (<1%). Pembrolizumab exhibited activity regardless of age, performance status, and the presence of metastases [20]. OS data were considered immature at the time of publication, as median follow-up for patients in KEYNOTE 052 was 5 mo [20]. However, after median follow-up of 9.5 mo, the median OS was calculated as 11.0 mo (95% CI 10.0–13.6) [18]. Toxicity data were comparable to those observed for atezolizumab in the first-line setting (Table 5) [20].

3.3. What these data mean for clinical practice

In the postplatinum setting there are high-level phase 3 data supporting the use of pembrolizumab in the treatment of advanced UC [22]. Atezolizumab did not meet its primary endpoint in the confirmatory phase 3 trial, but did induce durable responses with a safety profile distinct from single-agent chemotherapy [27]. Clinical trial data for other PD-1/PD-L1 inhibitors suggest that nivolumab, avelumab, and durvalumab can also induce long-lasting responses in some patients, which has led to accelerated approval of these drugs in some countries while confirmatory phase 3 trials are performed [22–26]. Patients who have been excluded from clinical trials include those with predominantly non-urothelial histology, autoimmune disease, significant organ dysfunction, or symptomatic brain metastases, so evidence supporting the use of immune checkpoint inhibitors in these populations is lacking. Response rates in clinical trials in the post-platinum setting range from 13% to 26%, and although this does not capture patients who achieve stable disease who still appear to benefit from immunotherapy to some extent [21], it does suggest that these treatments are not effective in a substantial proportion of patients [22–26]. There is

Table 4 – Clinical trials of PD-1/PD-L1 inhibitors in the first-line treatment of advanced urothelial carcinoma in cisplatin-ineligible patients[a]

Trial	Treatment received/median duration	*n*	Response		Median time to response (mo)	MRD, mo (95% CI)	Median OS, mo (95% CI)	OS, % (95% CI)		Median PFS, mo (95% CI)	6-mo PFS, % (95% CI)
			ORR, % (95% CI)	BR (%)				6 mo	12 mo		
IMvigor210 Cohort 1 [21] Single-arm phase 2; MFU 17.2 mo; PE ORR	Atezolizumab 1200 mg Q3W/15 wk (range 0–102)	119	23 (16–31)	CR 9 PR 13 SD 24 PD 36 NE 18	2.1 (range 1.8–10.5)	NE (14.1–NE)	15.9 (10.4–NE)	NRP	57 (48–66)	2.7 (2.1–4.2)	NRP
KEYNOTE 052 [20] Single-arm phase 2; MFU 5 mo, PE ORR	Pembrolizumab 200 mg Q3W/3 mo (range 0.03–16)	370	24 (20–29)	CR 5 PR 19 SD 23 PD 42 NE 11	2 (95% CI 2.0–2.1)	NR (9–NR)	11.0 (10.0–13.6) [at 9.5-mo FU]	67 (62–73)	NRP	2 (2–3)	30 (25–35)

BR = best response; CI = confidence interval; CR = complete response; CTCAE = Common Terminology Criteria for Adverse Events; MFU = median follow-up; MRD = median response duration; NE = not estimable; NR = not reached; NRP = not reported; ORR = objective response rate; OS = overall survival; PD = progressive disease; PE = primary endpoint; PFS = progression-free survival; PR, partial response; Q3W, every 3 wk; SD, stable disease; WHO = World Health Organisation.

[a] Defined as a patient meeting at least one of the following criteria: WHO or Eastern Cooperative Oncology Group performance status of 2, or Karnofsky performance status of 60–70%; creatinine clearance <60 ml/min; CTCAE grade ≥2 hearing loss; CTCAE grade ≥2 peripheral neuropathy; or New York Heart Association class III heart failure [10].

currently no way of identifying patients who will or will not benefit from treatment with a PD-1/PD-L1 inhibitor. Unlike other tumour types [34], PD-L1 expression has not demonstrated utility as a predictor of response to immunotherapy in UC. Subgroup analyses of clinical trials in UC have also failed to identify clinical characteristics that predict better outcomes for immunotherapy compared with chemotherapy, or vice versa. Thus, none of the evidence generated to date is strong enough to support refusing PD-1/PD-L1 inhibitor treatment on the basis of such markers. Owing to the clear benefits seen in patients who do respond to immunotherapy and the lack of better alternatives, treatment with a PD-1/PD-L1 inhibitor should be considered for all eligible patients who have experienced disease progression on or soon after platinum-based chemotherapy.

In the frontline setting, single-arm trials have shown that pembrolizumab and atezolizumab are active in patients who are not eligible for cisplatin-based treatment [20,21]. However, there is currently no direct evidence to indicate that their efficacy is better than existing standards of care. ORRs are higher for carboplatin-based chemotherapy than immunotherapy (30–40% vs 23–24%), but median OS is shorter (8.1–9.3 vs 11.0–15.9 mo) [11,20,21]. To what extent these differences are due to patient selection is unclear. In current practice, the decision to opt for one treatment strategy over the other may come down to clinical judgement, taking into account factors such as speed of disease and treatment toxicity. Haematological toxicities are commonly associated with chemotherapy regimens (Table 5), particularly affecting those with renal impairment [11]. Although severe, these AEs are manageable and generally resolve quickly. The incidence and severity of treatment-related AEs are lower with immune checkpoint inhibitors than with chemotherapy (Table 5). However, immune-related AEs associated with PD-1/PD-L1 inhibitors can occur across a variety of organs (Table 3) and may have long-term effects that require prolonged treatment [26]. Management of these toxicities requires early involvement of the relevant clinical teams and potentially the use of corticosteroids or hormone replacement therapies [35]. Thus, immunotherapy and chemotherapy offer different toxicity and efficacy profiles in cisplatin-ineligible patients in the first-line setting. These issues should be discussed with patients who are suitable for either treatment, so that the patient can make an informed decision. Ideally, such patients should be entered into ongoing clinical trials to improve the evidence base for making these decisions. Another consideration in this decision-making is the lack of published data supporting the use of chemotherapy after failure of first-line immunotherapy, in contrast to the availability of high-level evidence for the use of immunotherapy after unsuccessful carboplatin-based treatment. The optimal sequencing of these treatments in this setting, and whether combining immunotherapy with carboplatin-based chemotherapy is more effective than either agent alone remain unclear. Ongoing clinical trials, such as IMvigor130, KEYNOTE 361, and DANUBE, should shed some light on this issue [36–38].

Table 5 – Toxicity data from trials of PD-1/PD-L1 inhibitors and chemotherapy as first-line treatment for advanced urothelial carcinoma in cisplatin-ineligible patients[a]

Trial	Treatment arm(s)	Cisplatin ineligibility criteria, *n* (%)	Safety data, *n* (%)
IMvigor210 cohort 1 [21] Phase 2	Atezolizumab (*n* = 119)	Renal impairment:[b] 83 (69.7) Hearing loss: 17 (14.3) Peripheral neuropathy: 7 (5.9) ECOG PS 2: 24 (20.2) Renal impairment and ECOG PS 2: 8 (6.7)	Any grade TRAEs, 79 (66.4); most common: fatigue, 36 (30.3); diarrhoea, 14 (11.8); pruritus, 13 (10.9) Grade ≥3 TRAEs, 20 (16.8); most common: fatigue, 4 (3.4); ↑ ALT 4 (3.4); ↑ AST 3 (2.5) TRAEs leading to discontinuation, 9 (7.6); TRAEs leading to death, 1 (0.8)
KEYNOTE 052 [20] Phase 2	Pembrolizumab (*n* = 370)	Renal impairment: 182 (49.2) ECOG PS 2: 120 (32.4) Renal impairment and ECOG PS 2: 35 (9.5) Other:[c] 33 (8.9)	Any grade TRAEs, 229 (61.9); most common: fatigue, 62 (16.8); pruritus, 52 (14.1); rash, 36 (9.7) Grade ≥3 TRAEs, 58 (28.8); most common: fatigue, 8 (2.2); ↑ ALP, 5 (1.4); colitis, 4 (1.1); muscle weakness, 4 (1.1) Serious TRAEs, 36 (9.7); TRAEs leading to discontinuation, 19 (5.1); TRAEs leading to death, 1 (0.3)
EORTC 30986 [45] Phase 2	GemCarbo (*n* = 88) vs M-CAVI (*n* = 87)	Renal impairment only: 52 (59.1) vs 51 (58.6) WHO PS 2 only: 12 (13.6) vs 14 (16.1) Renal impairment and WHO PS 2: 24 (27.3) vs 22 (25.3)	Serious acute toxicity:[d] 12 (13.6) vs 20 (23.0) Mucositis (grade 3): 1 (1.1) vs 5 (5.7) Thrombocytopenia (grade 4 with bleeding): 3 (3.4) vs 0 Neutropenic fever (grade 3/4): 5 (5.7) vs 12 (13.8) Renal toxicity (grade 3/4): 3 (3.4) vs 2 (2.3) TRAE leading to death: 2 (2.3) vs 4 (4.6)
EORTC 30986 [11] Phase 2/3	GemCarbo (*n* = 119)[e] vs M-CAVI (*n* = 119)[e]	Renal impairment: 66 (55.5) vs 65 (54.6) WHO PS 2: 21 (17.6) vs 21 (17.6) Renal impairment and WHO PS 2: 32 (26.9) vs 33 (27.7)	Serious acute toxicity:[d] 11 (9.3) vs 25 (21.2) Grade 3/4 toxicities: leukopenia, 53 (44.9) vs 55 (46.6); thrombocytopenia, 57 (48.3) vs 23 (19.5); neutropenia, 62 (52.5) vs 75 (63.6); infection, 14 (11.9) vs 15 (12.7) TRAEs leading to death, 2 (1.7) vs 4 (3.4)
Hussain et al. [46] Phase 1/2	Split-dose GC (n = 32)	Renal impairment: 19 (59.4)	Grade 3/4 toxicities: thrombocytopenia, 15 (46.9); neutropenia, 11 (34.4); anaemia, 4 (12.5); nausea, 2 (6.3); AE leading to death, 3 (9.4)
JASINT1 [47] Phase 2	Vinflunine–gemcitabine (*n* = 34) vs vinflunine–carboplatin (*n* = 35)	Renal impairment: 34 (100.0) vs 35 (100.0)	Haematological toxicities of any grade: neutropenia, 28 (82.4) vs 30 (85.7); anaemia, 33 (97.1) vs 34 (100.0); thrombocytopenia, 24 (70.6) vs 22 (62.9) Haematological toxicities grade 3/4: neutropenia, 13 (38.2) vs 23 (65.7); anaemia, 9 (26.5) vs 9 (25.7); thrombocytopenia, 2 (5.9) vs 7 (20.0) Nonhaematological toxicities of any grade: asthenia/fatigue, 20 (58.8) vs 15 (42.9); nausea, 12 (35.3) vs 16 (45.7); constipation, 10 (29.4) vs 14 (40.0) Nonhaematological toxicities grade 3/4: asthenia/fatigue, 8 (23.5) vs 7 (20.0); infection, 4 (11.8) vs 1 (2.9); constipation, 1 (2.9) vs 2 (5.7) No toxic deaths reported
Siefker-Radtke et al. [48] Phase 2	Gemcitabine, paclitaxel, and doxorubicin (*n* = 39)	Renal impairment: 39 (100.0)	Haematological toxicities: neutropenia grade 3/4, 13 (33.3); thrombocytopenia grade 3, 6 (15.4); neutropenic fever, 4 (10.3) Nonhaematological toxicities grade 3/4: fatigue, 4 (10.3); mucositis, 4 (10.3) No dose reductions for nephrotoxicity and no treatment-related deaths

Table 5 (*Continued*)

Trial	Treatment arm(s)	Cisplatin ineligibility criteria, *n* (%)	Safety data, *n* (%)
GETUG V01 [49] Phase 2	Gemcitabine (*n* = 22)[f] vs gemcitabine and oxaliplatin (n = 22)	Renal impairment only: 14 (63.6) vs 12 (54.5) ECOG PS 2 only: 3 (13.6) vs 4 (18.2) Renal impairment and ECOG PS 2: 5 (22.7) vs 6 (27.3)	Haematological toxicities: neutropenia grade 3/4: 13 (61.9) vs 7 (31.8); thrombocytopenia grade 3/4: 4 (19.0) vs 5 (22.7); anaemia grade 2/3: 20 (95.2) vs 18 (81.8) Nonhaematological toxicities: nausea grade 2/3: 4 (19.0) vs 10 (45.5); vomiting grade 2/3: 2 (9.5) vs 4 (18.2); diarrhoea grade 1/2: 8 (38.1) vs 9 (40.9); mucositis grade 1/2: 4 (19.0) vs 4 (18.2); peripheral neuropathy grade 1–3: 1 (4.8) vs 15 (68.2); asthenia any grade: 20 (95.2) vs 19 (86.4) TRAE leading to discontinuation: 1 (4.8) vs 2 (9.1) TRAE leading to death: 0 vs 1 (4.5)
Calabro et al. [50] Phase 2	Gemcitabine and paclitaxel (*n* = 54)	WHO PS 2: 7 (13.0) Some patients had compromised renal function (median creatine clearance was 62 ml/min, range 41–112)	Haematological toxicities grade 3/4: neutropenia, 10 (18.5); anaemia, 6 (11.1); thrombocytopenia, 3 (5.6), leukopenia, 3 (5.6) Nonhaematological toxicities grade 3/4: neurotoxicity, 6 (11.1); diarrhoea 4 (7.4)

AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; GemCarbo = gemcitabine and carboplatin; M-CAVI = methotrexate, carboplatin, and vinblastine; PS = performance status; TRAE = treatment-related AE; WHO = World Health Organisation.

[a] Defined as a patient meeting at least one of the following criteria: WHO or ECOG PS of 2, or Karnofsky PS of 60–70%; creatinine clearance <60 ml/min; CTCAE grade ≥2 hearing loss; CTCAE grade ≥2 peripheral neuropathy; or New York Heart Association class III heart failure [10].

[b] Defined as glomerular filtration rate or creatine clearance >30 to <60 ml/min.

[c] Includes New York Heart Association class III heart failure, grade ≥2 peripheral neuropathy, and grade ≥2 hearing loss.

[d] Defined as the occurrence of any of the following events, either directly or at least possibly related to treatment administration: mucositis grade 3 or 4, thrombocytopenia grade 4 associated with bleeding, neutropenic fever grade 3 or 4, renal toxicity grade 3 or 4, and death.

[e] *n* = 118 in the safety population.

[f] *n* = 21 in the safety population.

An important unresolved question regarding the use of immunotherapy in UC is whether treatment can be safely stopped without impacting clinical outcomes. Most trials of PD-1/PD-L1 inhibitors in advanced UC to date have continued treatment until disease progression, unacceptable toxicity, or study completion, and there is a lack of clinical evidence and follow-up data on the optimal treatment duration. Ongoing responses were observed in study 1108, in which patients stopped durvalumab after completing 12 mo of treatment [24], and in other trials in patients who discontinued immunotherapy after achieving a response [21,22,26]. These reports are anecdotal, and it remains unclear whether this observation can be extrapolated more widely; however, there have been similar observations for other tumour types [39,40]. Only one randomised trial has evaluated the duration of treatment with a PD-1/PD-L1 inhibitor. CheckMate 153 is an ongoing phase 3/4 trial in non–small cell lung cancer that randomised 220 patients who had been treated with nivolumab for 1 yr to either treatment continuation or cessation, regardless of response [41]. Nivolumab continuation significantly improved PFS compared with treatment cessation (HR 0.42, 95% CI 0.25–0.71). Almost half of the patients (43/87) with a response or stable disease at randomisation developed progressive disease after discontinuing nivolumab; OS data are awaited [41]. Owing to the lack of clinical data for UC and conflicting evidence for other tumours, it is not currently possible to say whether stopping immunotherapy in advanced UC either after a set duration or once a response has been achieved is an appropriate treatment approach. In patients with stable disease who are otherwise well, there may be a benefit in continuing treatment with PD-1/PD-L1 inhibitors, as late responses have been reported in UC clinical trials [21,22]. Two patients in IMvigor210 (cohort 1) and three patients in KEYNOTE 045 achieved responses 6 mo after starting immunotherapy treatment [21,22]. The current strategy of treating patients until loss of clinical benefit appears to be the most appropriate course of action in the first-line and post-platinum settings. However, the definition of "clinical benefit" is not clear. In the second-line setting, if a patient exhibits minor disease progression, but is not deteriorating and has no organ dysfunction, it would be tempting to continue treatment to the next assessment point. This approach is supported by data from clinical trials that show a nonconventional benefit in some patients who have been treated beyond progression [25,26,32]. However, if a patient has more significant disease progression, treatment with PD-1/PD-L1 inhibitors should be stopped. In the first-line setting, stopping criteria for immunotherapies should perhaps be stricter due to the availability of alternative subsequent treatments. Although some of the studies described in this review have investigated treatment beyond progression as a surrogate for pseudoprogression, no studies have focused on this phenomenon in UC

and it remains poorly characterised. Thus, owing to the uncertainty around such progression kinetics, patients who develop clinically significant disease on first-line immunotherapy or experience a deterioration in performance status or major organ involvement should be switched to chemotherapy without delay.

4. Conclusions

PD-1/PD-L1 inhibitors represent an important advance in the treatment of advanced UC and significantly improve prognosis for some patients. A number of key questions remain. There is no definitive evidence that anti-PD-1/PD-L1 drugs offer a superior treatment option in the first-line setting in cisplatin-ineligible patients compared with current standards of care. It is uncertain when or if treatment can be stopped without impacting any clinical benefit achieved, and there are no biomarkers that identify patients who will benefit from these drugs. In addition, owing to a lack of head-to-head data, the choice of which PD-1/PD-L1 inhibitor to use first, or whether there is a difference in efficacy between anti-PD-1 and anti-PD-L1 drugs, remains uncertain. However, this is a relatively new research field and it is developing rapidly. Ongoing trials are investigating the use of PD-1/PD-L1 inhibitors as adjuvant and maintenance therapy, in earlier disease stages, and in combination with chemotherapy and/or other immune checkpoint inhibitors, such as the CTLA-4 inhibitors ipilimumab and tremelimumab, or targeted therapies [42]. As these clinical data mature, UC patient populations eligible for immunotherapy treatment may broaden. In the metastatic setting, novel next-generation immunotherapies, such as indoleamine 2,3-dioxygenase inhibitors, are in development, which could further expand the treatment landscape for this difficult-to-treat cancer.

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Appendix A. Supplementary data

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