Cancer Treatment Reviews 97 (2021) 102187

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevier.com/locate/ctrv

Anti-tumour Treatment

Avelumab first-line maintenance in locally advanced or metastatic urothelial carcinoma: Applying clinical trial findings to clinical practice

Petros Grivas [a,*], Neeraj Agarwal [b], Sumanta Pal [c], Arash Rezazadeh Kalebasty [d], Srikala S. Sridhar [e], Jodi Smith [f,1], Geeta Devgan [g], Cora N. Sternberg [h,2], Joaquim Bellmunt [i,2]

[a] University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA, USA
[b] University of Utah Huntsman Cancer Institute, Salt Lake City, Utah, USA
[c] City of Hope Comprehensive Cancer Center, Duarte, CA, USA
[d] University of California Irvine Medical Center, Orange, CA, USA
[e] Princess Margaret Cancer Centre, Toronto, Ontario, Canada
[f] EMD Serono, Inc., Rockland, MA, USA; an affiliate of Merck KGaA, Darmstadt, Germany
[g] Pfizer, New York, NY, USA
[h] Englander Institute for Precision Medicine, Weill Cornell Medicine, Meyer Cancer Center, New York, New York, USA
[i] Beth Israel Deaconess Medical Center and IMIM-PSMAR Lab, Harvard Medical School, Boston, MA, USA

ARTICLE INFO

Keywords:
Urothelial carcinoma
Bladder cancer
Avelumab
Switch maintenance
Immune checkpoint inhibitor
Immunotherapy

ABSTRACT

Although urothelial carcinoma (UC) is considered a chemotherapy-sensitive tumor, progression-free survival and overall survival (OS) are typically short following standard first-line (1L) platinum-containing chemotherapy in patients with locally advanced or metastatic disease. Immune checkpoint inhibitors (ICIs) have antitumor activity in UC and favorable safety profiles compared with chemotherapy; however, trials of 1L ICI monotherapy or chemotherapy + ICI combinations have not yet shown improved OS vs chemotherapy alone. In addition to direct cytotoxicity, chemotherapy has potential immunogenic effects, providing a rationale for assessing ICIs as switch-maintenance therapy. In the JAVELIN Bladder 100 phase 3 trial, avelumab administered as 1L maintenance with best supportive care (BSC) significantly prolonged OS vs BSC alone in patients with locally advanced or metastatic UC that had not progressed with 1L platinum-containing chemotherapy (median OS, 21.4 vs 14.3 months; hazard ratio, 0.69 [95% CI, 0.56–0.86]; P = 0.001). Efficacy benefits were seen across various subgroups, including recipients of 1L cisplatin- or carboplatin-based chemotherapy, patients with PD-L1+ or PD-L1− tumors, and patients with diverse characteristics. Results from JAVELIN Bladder 100 led to the approval of avelumab as 1L maintenance therapy for patients with locally advanced or metastatic UC that has not progressed with platinum-containing chemotherapy. Avelumab 1L maintenance is also included as a standard of care in treatment guidelines for advanced UC with level 1 evidence. This review summarizes the data that supported these developments and discusses practical considerations for administering avelumab maintenance in clinical practice, including patient selection and treatment management.

Introduction

Urothelial carcinoma (UC) is a common cancer that causes substantial morbidity and mortality. In the US, UC is the sixth most-frequent cancer and was responsible for >80,000 new cases and >17,000 deaths in 2019 [1]. Risk factors include smoking, older age, male sex, exposure to various industrial/organic chemicals, and family history of UC [2,3]. Approximately 5% of patients with UC are initially diagnosed when distant metastases are present [4,5]. Additionally, relapse after radical cystectomy or nephroureterectomy occurs in ≈30–50% of patients, generally resulting in distant metastases [5,6]. In patients who develop distant metastases, 5-year overall survival (OS) rates are < 6% [4].

* Corresponding author at: Department of Medicine, Division of Medical Oncology, University of Washington School of Medicine, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, 1144 Eastlake Ave E, LG-465, Seattle, WA 98109, USA.
E-mail address: pgrivas@uw.edu (P. Grivas).
[1] Affiliation at the time of manuscript preparation.
[2] These authors contributed equally to this work.

https://doi.org/10.1016/j.ctrv.2021.102187
Received 20 January 2021; Received in revised form 12 March 2021; Accepted 15 March 2021
Available online 22 March 2021
0305-7372/© 2021 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Moreover, patients with poor Bajorin risk factors, ie, Eastern Cooperative Oncology Group performance status (ECOG PS) ≥ 2 and/or visceral metastases, have a worse prognosis [7,8]. Patients with locally advanced or metastatic UC (generally termed advanced UC) represent a relatively frail population; US real-world studies show that patients receiving first-line (1L) therapy tend to be elderly (median age, 71–77 years), have compromised PS (ECOG PS ≥ 1 in 58–86% and ≥ 2 in 13–19%), and have a high prevalence of renal impairment (creatinine clearance [CrCl] < 60 mL/min in 49%) [9–13].

Advanced UC usually responds to chemotherapy, and US National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines recommend 1L cisplatin-containing combination chemotherapy for eligible patients [5,14,15]. For cisplatin-ineligible patients, such as those with renal impairment (CrCl or glomerular filtration rate < 50–60 mL/min), poor PS (ECOG PS 2 or Karnofsky PS ≤ 70), hearing loss (grade ≥ 2), peripheral neuropathy (grade ≥ 2), or symptomatic heart failure (New York Heart Association [NYHA] class III/IV), carboplatin + gemcitabine is a recommended option [5,14–17]. Although 1L platinum-containing chemotherapy results in objective responses or stable disease (SD) in approximately 65–75% of patients [18–20], it provides limited long-term benefits, and progression-free survival (PFS; median approximately 6–8 months) and OS (median approximately 9–14 months) are typically short [18–21].

Immune checkpoint inhibitors (ICIs) have antitumor activity against UC. In clinical trials in UC, ICIs were initially assessed as salvage treatment following progression on platinum-containing chemotherapy, and showed favorable efficacy and safety profiles compared with cytotoxic chemotherapy [22–28]. Consequently, PD-L1 inhibitors (atezolizumab, avelumab, and durvalumab) and PD-1 inhibitors (nivolumab or pembrolizumab) received US approval in 2016–17 for the treatment of advanced UC in this setting, followed by approvals in some other countries; however, the accelerated approvals of atezolizumab and durvalumab were withdrawn in 2021 following the failure of confirmatory trials. A retrospective analysis of electronic health records from 117 patients with advanced UC who received 1L chemotherapy followed by any second-line (2L) ICI therapy or 2L chemotherapy found that median OS was longer with 2L ICI therapy (19.2 vs 11.9 months, respectively) [13]. However, patients with progression after 1L platinum-containing chemotherapy have a high symptom burden and often experience rapid deterioration in quality of life and physical function [29,30]. Consequently, only a minority receive 2L (and later) therapy; across four US real-world studies, only 34–39% of patients receiving 1L therapy subsequently received 2L therapy (Fig. 1) [10–12,31].

Pembrolizumab or atezolizumab monotherapy are approved 1L treatment options for the subpopulation of patients with advanced PD-L1+ UC who are cisplatin ineligible, or patients ineligible for platinum-containing chemotherapy (in the US) [5,15]. In KEYNOTE-052 and IMvigor210, the single-arm phase 2 trials that supported their accelerated approvals, median OS with pembrolizumab or atezolizumab in the overall trial populations was 11.3 and 15.9 months, respectively [32–34]. Subsequently, preliminary data from phase 3 trials assessing ICI monotherapy or combination chemoimmunotherapy vs cisplatin- or carboplatin-based chemotherapy alone in advanced UC (IMvigor130 and KEYNOTE-361), which showed shorter OS with ICI monotherapy in the PD-L1− subgroup, resulted in restricted indications to those listed above [35]. Full results from these trials showed that neither pembrolizumab nor atezolizumab monotherapy significantly improved OS in the overall population vs platinum-based chemotherapy [36,37], which was also seen subsequently with durvalumab monotherapy in the phase 3 DANUBE trial [38].

Further treatment options are needed to prolong OS in cisplatin-eligible and cisplatin-ineligible patients with advanced UC. This review summarizes the scientific rationale and clinical data supporting the use of avelumab as 1L maintenance therapy for patients with advanced UC that has not progressed with platinum-containing chemotherapy, followed by discussion of considerations for clinical practice.

Exploiting the complementary effects of chemotherapy and ICIs in advanced UC

In addition to direct cytotoxicity, chemotherapy can have potentially immunogenic effects (Fig. 2). Several chemotherapeutic agents and platinum-based combinations can induce immunogenic cell death, which stimulates immune responses against tumors through release of "danger" signals released from dying cells [39–41]. Cisplatin and gemcitabine also induce other immunogenic effects, including: depletion of immunosuppressive cell types (eg, myeloid-derived suppressor cells and regulatory T cells) [42,43]; enhanced antigen presentation [44–46]; generation of tumor neoantigens [47]; increased tumor infiltration by CD8+ T cells [48]; and increased interferon-γ expression and natural killer (NK) cell activation [49]. Additionally, chemotherapy may upregulate expression of PD-L1 [50–52], a key immune checkpoint.

Potential strategies to leverage the complementary effects of chemotherapy and ICIs are combination or sequential treatment. However, unlike some other tumor types [53–56], phase 3 trials of ICIs in

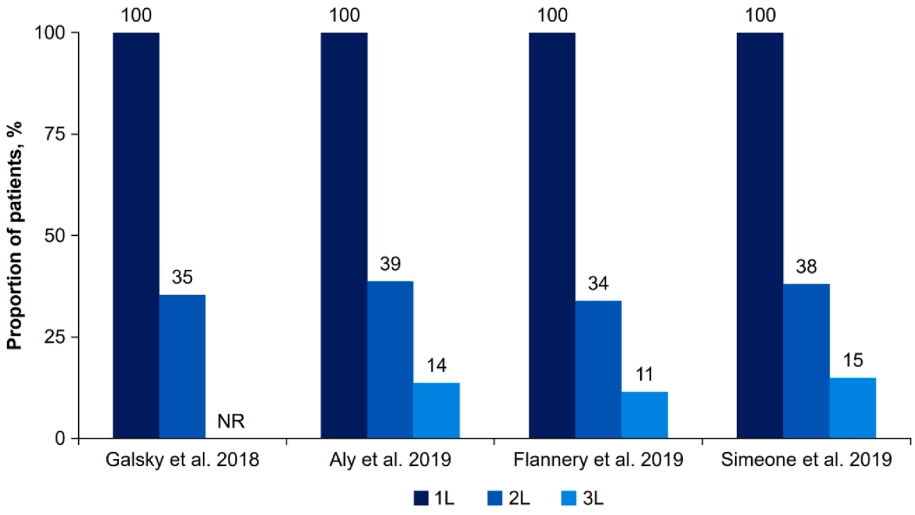

Fig. 1. Patient attrition between first-line therapy and later lines of therapy in real-world studies of patients with metastatic urothelial carcinoma in the US [10–12,31]. 1L, first line; 2L, second line; 3L, third line; NR, not reported.

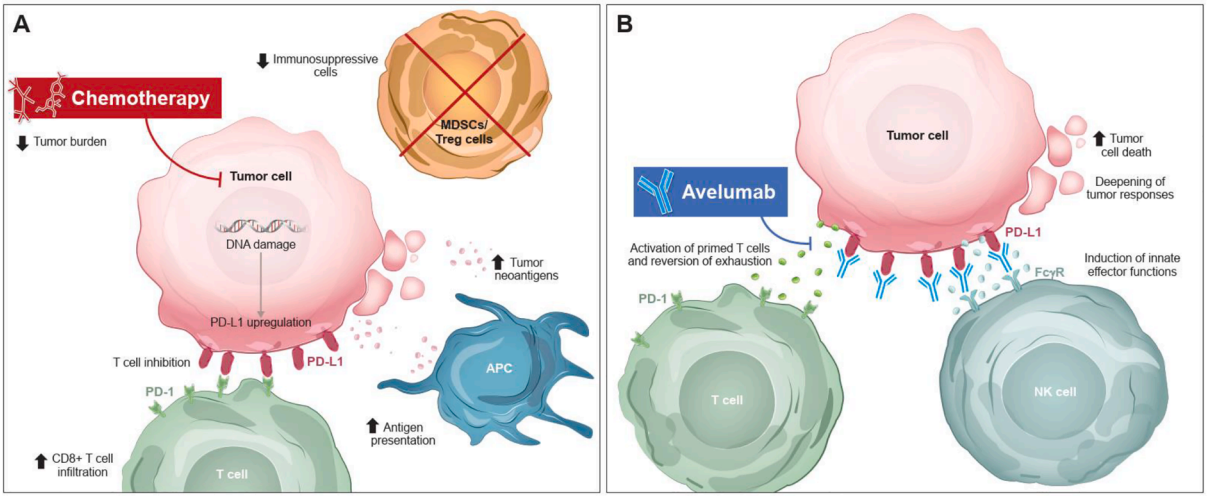

Fig. 2. Rationale for the treatment approach of 1L chemotherapy with avelumab 1L maintenance: potential mechanisms leading to additive antitumor activity between 1L chemotherapy (A) and avelumab 1L maintenance (B) [39–51]. 1L, first-line; APC, antigen-presenting cell; MDSC, myeloid-derived suppressor cell; NK, natural killer; PD-L1, programmed death ligand 1; Treg, regulatory T cell.

combination with 1L chemotherapy in advanced UC have not shown significant improvements in OS. In the IMvigor130 trial of 1L atezolizumab alone or in combination with platinum-containing chemotherapy vs chemotherapy alone, PFS was significantly improved with combination treatment (hazard ratio [HR], 0.82 [95% CI, 0.70–0.96]; P = 0.007), but no significant difference was seen in OS at interim analysis (HR, 0.83 [95% CI, 0.69–1.00]; P = 0.027); this trial is continuing follow-up until its final OS analysis [36]. Exploratory analyses suggested that chemotherapy + atezolizumab may have attenuated OS effects in subgroups defined by biomarkers associated with response to ICIs (high PD-L1 expression and/or tumor mutational burden) [57]. In the final analysis of the KEYNOTE-361 trial of 1L pembrolizumab alone or in combination with platinum-containing chemotherapy vs chemotherapy alone, neither PFS nor OS was significantly improved despite numerical differences [37].

Switch-maintenance therapy is a novel alternative treatment strategy to achieve enhanced antitumor activity in UC using agents with different mechanisms of action. Maintenance treatment can target tumor cell populations persisting after 1L chemotherapy, increasing depth of responses and/or prolonging treatment benefits while avoiding potential cross-resistance, cumulative toxicity, and increased cost [39]. Maintenance therapy following platinum-containing chemotherapy is an established treatment strategy in other tumor types, including pemetrexed in advanced non-small cell lung cancer (NSCLC) and poly(ADP-ribose) polymerase inhibitors in ovarian cancer [58–62]. Previous trials of switch-maintenance therapy in advanced UC using non-immunotherapy approaches (ie, lapatinib, sunitinib, and vinflunine) did not show significantly improved OS, with only vinflunine showing a PFS benefit [63–66]. Administering an ICI in sequence via a 1L maintenance approach may provide treatment benefits that cannot be achieved with combination therapy. Through its direct cytotoxic activity, platinum-containing chemotherapy can control or reduce tumor burden, thereby increasing the opportunity for antitumor activity with ICIs, which appear to be more effective in patients with a smaller tumor burden [67–70]. A switch-maintenance strategy may also enable more patients to receive an ICI within 1L therapy, rather than reserving ICIs for the minority of patients who can receive 2L therapy [10–12,31].

Overall, the cytotoxic and immunogenic effects of chemotherapy, along with the antitumor activity and favorable safety profile of ICIs and the immunogenic nature of UC, provided the rationale for exploring ICIs as 1L maintenance therapy in advanced UC (Fig. 2).

Clinical development of ICI maintenance therapy in UC

Phase 3 trial of avelumab 1L maintenance in UC

Avelumab is an anti–PD-L1 antibody with a wild-type Fc region that has been shown to induce antitumor activity *in vitro* via both adaptive effector cells (T cells) and innate immune effector cells (antibody-dependent cell-mediated cytotoxicity via NK cells) [71–75]. The efficacy and safety of avelumab in UC were first demonstrated in a large phase 1b trial (N = 249) in a poor-risk population in the salvage setting, which showed an objective response rate of 16.5% (95% CI, 12.1–21.8%), median duration of response of 20.5 months (95% CI, 9.7 months to not estimable), and 2-year OS of 20.1% (95% CI, 15.2–25.4%) [76].

JAVELIN Bladder 100 (NCT02603432) was the international, randomized, phase 3 trial that evaluated avelumab as 1L maintenance therapy (Fig. 3). In total, 700 patients with unresectable locally advanced or metastatic (stage IV) UC and no progression (ie, complete response [CR], partial response [PR], or SD) after 4–6 cycles of 1L platinum-containing chemotherapy (cisplatin + gemcitabine or carboplatin + gemcitabine) were enrolled (Table 1). Other key eligibility criteria included age ≥ 18 years, ECOG PS 0–1, and adequate hematologic, hepatic, and renal (CrCl ≥ 30 mL/min) function. Following a treatment-free interval of 4–10 weeks from last dose of 1L chemotherapy, patients were randomly assigned (1:1) to receive either avelumab 1L maintenance (10 mg/kg by intravenous infusion every 2 weeks) + best supportive care (BSC; avelumab arm; n = 350) or BSC alone (control arm; n = 350). Randomization was stratified by best response to chemotherapy (CR or PR vs SD) and site of metastasis (visceral vs nonvisceral) when initiating 1L chemotherapy. The primary endpoint was OS, assessed in two primary populations: all randomized patients (overall population) and patients with PD-L1+ tumors based on the Ventana SP263 assay (51% of patients) [77].

Avelumab 1L maintenance + BSC significantly prolonged OS vs BSC alone at interim analysis, and because prespecified efficacy boundaries were crossed, this became the primary analysis [77]. In the overall population, median OS (measured from randomization, ie, post chemotherapy) was 21.4 months in the avelumab arm vs 14.3 months in the control arm, with an HR of 0.69 (95% CI, 0.56–0.86; P = 0.001), ie, 31% reduction in the risk of death. Avelumab also significantly prolonged OS in the PD-L1+ population; median OS was not reached in the avelumab arm vs 17.1 months in the control arm (HR, 0.56 [95% CI, 0.40–0.79]; P < 0.001; Fig. 4**A**) [77]. Importantly, OS benefits with avelumab 1L maintenance were observed across a range of prespecified

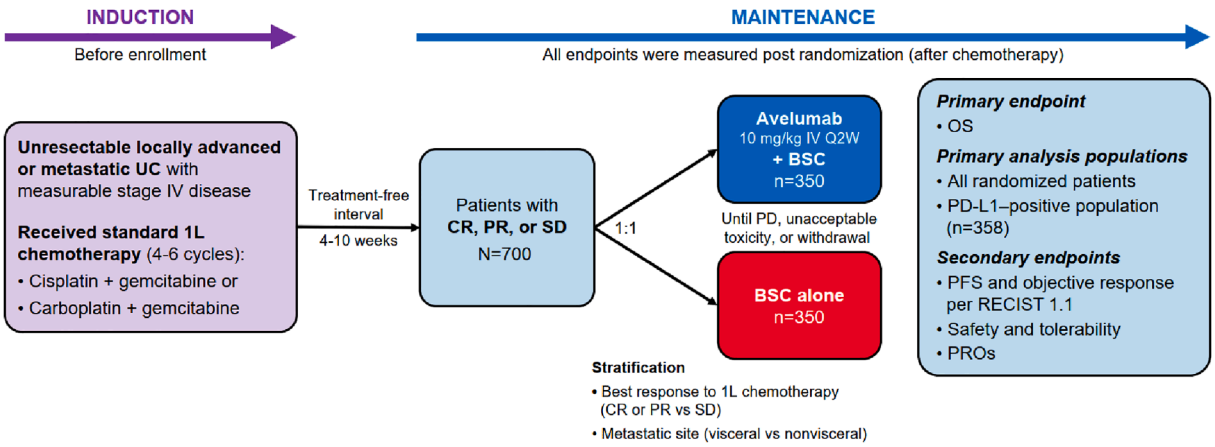

Fig. 3. Design of JAVELIN Bladder 100: an international, randomized, phase 3 trial (NCT02603432) [77]. The trial enrolled patients with unresectable locally advanced or metastatic (stage IV) UC, without disease progression after 4–6 cycles of 1L platinum-containing chemotherapy. Other key inclusion criteria were age ≥18 years, ECOG PS of 0 or 1, and adequate hematologic, hepatic, and renal (creatinine clearance ≥ 30 mL/min) function. Patients who had received adjuvant or neoadjuvant systemic therapy within the preceding 12 months were ineligible. Patients with active autoimmune disease that might have deteriorated during immune checkpoint inhibitor therapy were also ineligible, but patients with type 1 diabetes, vitiligo, psoriasis, or hypo-/hyperthyroid disease not requiring immunosuppressive treatment were eligible. Patients with central nervous system metastases were ineligible if their metastases were symptomatic and required steroids, but were eligible if they had completed their treatment, had recovered from prior radiation or surgery, had discontinued any corticosteroid therapy ≥ 4 weeks previously, and were neurologically stable. BSC (eg, antibiotics, nutritional support, hydration, and pain management) was administered per local practice based on patient needs and clinical judgment [77]. 1L, first-line; BSC, best supportive care; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand 1; PFS, progression-free survival; PR, partial response; PROs, patient-reported outcomes; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; UC, urothelial carcinoma.

Table 1
Safety summary for patients treated with avelumab 1L maintenance in the JAVELIN Bladder 100 trial (N = 344; data cutoff: October 21, 2019) [77]

	Patients, %	
TEAE of any grade (related or unrelated)	98.0	
Grade ≥ 3 TEAE (related or unrelated)	47.4	
Serious TEAE	27.9	
Serious TRAE	9.0	
TEAE leading to death	1.2	
TRAE leading to death	0.3	
irAE of any grade	29.4	
Grade ≥ 3 irAE	7.0	
TEAE leading to avelumab dose reduction	0.3	
TEAE leading to avelumab interruption	40.7	
TEAE leading to avelumab discontinuation	11.9	
TRAE leading to avelumab discontinuation	9.6	
	Any grade	Grade ≥ 3
Any TRAE*	77.3	16.6
Pruritus	13.7	0.3
Hypothyroidism	10.5	0.3
Diarrhea	10.2	0
Infusion-related reaction	10.2	0.9
Asthenia	9.9	0
Fatigue	9.6	0.3
Rash	7.3	0.3
Chills	7.0	0
Nausea	7.0	0.3
Arthralgia	6.7	0.3
Pyrexia	6.7	0
Hyperthyroidism	6.1	0
Dry skin	5.2	0
Increased amylase level	4.4	2.0
Increased lipase level	3.8	2.9

AE, adverse event; irAE, immune-related adverse event; TEAE, treatment-emergent adverse event (adverse event of any cause occurring during study treatment or within 30 days after the last dose of study treatment); TRAE, treatment-related AE.

* Individual TRAEs occurring at any grade in ≥ 5% or grade ≥ 3 in ≥ 2% are listed.

subgroups (Fig. 4**B**) and no significant treatment-by-subgroup interaction was observed for any subgroup variable [77,78].

Among patients who discontinued study therapy following progression (avelumab arm, n = 189; control arm, n = 263), a high proportion of those in the control arm received a subsequent PD-1 or PD-L1 inhibitor (53% vs 9% in the avelumab arm) [77,79]. The prolongation in OS with avelumab 1L maintenance despite frequent use of ICIs as follow-up therapy in the control arm highlights the importance of starting avelumab at the earliest opportunity in patients with disease control from 1L chemotherapy instead of waiting for disease progression and risking clinical deterioration [77].

On the basis of the JAVELIN Bladder 100 results, avelumab was approved for maintenance treatment of patients with locally advanced or metastatic UC that has not progressed with 1L platinum-containing chemotherapy in the US initially [80] followed by several other countries (including the EU [81]). The JAVELIN Bladder 100 treatment approach (1L platinum-containing chemotherapy with avelumab 1L maintenance for patients without disease progression) was added as a preferred or recommended treatment in NCCN and ESMO guidelines, respectively (level 1 evidence) [5,15].

Phase 2 trial of pembrolizumab 1L maintenance in UC

A small randomized phase 2 trial (GU14-182) compared pembrolizumab (anti–PD-1) maintenance with placebo in 107 patients with stage IV UC that had not progressed with 1L platinum-containing chemotherapy. Pembrolizumab maintenance prolonged PFS (primary endpoint; HR, 0.65 [95% CI, not reported]; log-rank P = 0.04) but did not prolong OS (HR, 0.91 [95% CI, 0.52–1.59]; P = 0.7477), which was a secondary endpoint (the study was not adequately powered to detect OS improvement). Although the GU14-182 trial (unlike JAVELIN Bladder 100) had a crossover design and was conducted in the US, only 52% of patients with progression in the placebo arm crossed over to receive pembrolizumab [82], similar to the proportion with post-progression ICI treatment in the control arm of JAVELIN Bladder 100.

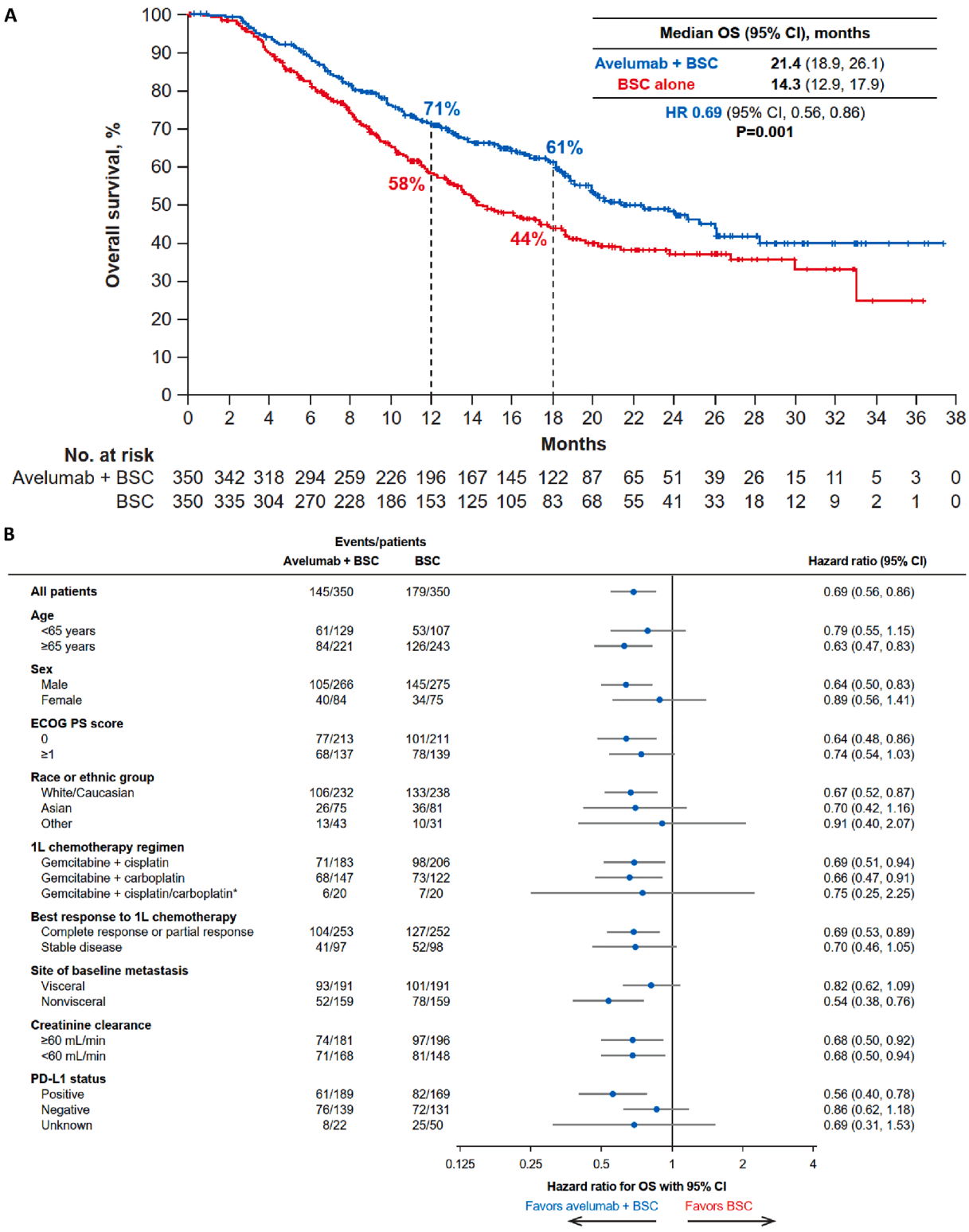

Fig. 4. Prolonged OS with avelumab 1L maintenance in the JAVELIN Bladder 100 trial [77,79]. (A) OS in the overall population. (B) OS in prespecified subgroups. 1L, first-line; BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed death ligand 1. *Includes patients who switched platinum regimens while receiving 1L chemotherapy. From New England Journal of Medicine, Powles T, et al, Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, Volume 383, Pages 1218–1230. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission.

Practical considerations for avelumab maintenance therapy

Data from the JAVELIN Bladder 100 phase 3 trial demonstrate that avelumab 1L maintenance is effective and well tolerated in a range of patients. Trial eligibility criteria, primary and subgroup data, prescribing information, and treatment guidelines provide a framework for administering avelumab maintenance in clinical practice. It should be noted that baseline characteristics of patients entering the trial (except

metastatic site) were recorded after treatment with platinum-containing chemotherapy [77]; thus, several characteristics (eg, ECOG PS, renal function, or measurable disease) may have changed compared with before chemotherapy.

Cisplatin-eligible or cisplatin-ineligible patients

In guidelines for patients with advanced UC, recommendations are tailored according to eligibility for cisplatin-based treatment [5,14–16]. Cisplatin ineligibility is generally defined by the presence of one or more characteristics indicating that cisplatin may not be well tolerated or may worsen existing comorbidity (discussed earlier), although such patients may sometimes still receive cisplatin-based chemotherapy in real-world practice. With respect to these characteristics, JAVELIN Bladder 100 excluded enrollment of patients if they had (post chemotherapy) ECOG PS $\geq$ 2, CrCl $<$ 30 mL/min, congestive heart failure (NYHA class $\geq$ II) or other major cardiac comorbidity, or persisting grade $\geq$ 3 sensory neuropathy [77].

The trial design allowed enrollment of patients who had received 1L combination chemotherapy with either cisplatin + gemcitabine or carboplatin + gemcitabine [77], which are standard regimens in cisplatin-eligible and cisplatin-ineligible populations, respectively [5,14,15]. The chemotherapy regimen was chosen by the treating investigator (cisplatin + gemcitabine was not mandated for all cisplatin-eligible patients), and patients were not categorized as cisplatin eligible or ineligible on trial entry. In the avelumab arm, 1L chemotherapy comprised cisplatin + gemcitabine in 52%, carboplatin + gemcitabine in 42%, and both regimens at different times in 6% [77]. At the time of initiating avelumab, carboplatin-treated patients tended to be less "fit" than cisplatin-treated patients, including a higher median age (71 vs 66 years) and higher prevalence of ECOG PS 1 (49% vs 32%) and renal impairment (CrCl $<$ 60 mL/min; 63% vs 36%) [78]. The improvement in OS with avelumab vs control was similar irrespective of 1L chemotherapy: in the cisplatin + gemcitabine and carboplatin + gemcitabine subgroups, HRs were 0.69 (95% CI, 0.51–0.94) and 0.66 (95% CI, 0.47–0.91), and median OS post chemotherapy with avelumab maintenance was 25.3 and 19.9 months, respectively [77,78]. These data support NCCN and ESMO guideline recommendations for avelumab maintenance treatment in both cisplatin-eligible and -ineligible populations.

Although patients enrolled in the JAVELIN Bladder 100 trial had received only cisplatin + gemcitabine or carboplatin + gemcitabine as 1L chemotherapy, other platinum-containing regimens are used in advanced UC [5,14]. The US and EU labels for avelumab do not specify the combination platinum regimen to be used prior to maintenance [80,81]. Similarly, NCCN guidelines state that avelumab 1L maintenance can also be administered following 1L treatment with dose-dense MVAC, another cisplatin-containing regimen that was not assessed in the trial, and the cisplatin regimen is not specified in ESMO guidelines [5,14]. Choice of 1L platinum-containing chemotherapy prior to avelumab maintenance can therefore be made on an individual patient basis.

Duration of prior chemotherapy

NCCN guidelines recommend a maximum of 6 cycles of 1L platinum-containing chemotherapy for patients with locally advanced or metastatic UC, with re-evaluation after 2–3 cycles [5]. A retrospective study found no difference in OS between patients with metastatic UC who had received 3–5 cycles (median 4) or 6–9 cycles (median 6) of chemotherapy, leading the authors to conclude that 4 cycles of platinum-containing 1L chemotherapy may be adequate in some patients and may avert toxicities [83]. The number of cycles should be an individual patient and provider decision based on benefit-risk considerations of the potential for improved clinical benefit vs toxicity. The approved US/EU labels for avelumab and NCCN guidelines do not make specific recommendations regarding the number of prior cycles before starting avelumab maintenance [5,80,81]. JAVELIN Bladder 100 data support the administration of avelumab in patients with 4–6 prior chemotherapy cycles [15,77], including post hoc analyses showing an OS benefit irrespective of duration/cycles received within this range [84]. No evidence is available to demonstrate the efficacy of avelumab maintenance after more or fewer cycles of 1L induction chemotherapy, and data from prospective or real-world studies are needed to inform clinical judgment.

Response to prior chemotherapy

Nonprogression on 1L chemotherapy is an excellent clinical biomarker for identifying patients who may benefit from avelumab treatment. Avelumab 1L maintenance can be administered to patients with CR, PR, or SD after 1L chemotherapy [5,15,80]. Per standard Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 assessment, SD includes patients in whom the sum of target lesion diameters has increased by <20% (ie, not qualifying as disease progression) [85]. Patients with progression during or following 1L chemotherapy can receive 2L therapy (if fit) [25,76,80]. In the JAVELIN Bladder 100 trial, all patients were stratified according to achievement of objective response or SD with 1L chemotherapy, and in these subgroups, the degree of OS benefit was similar (HRs, 0.69 [95% CI, 0.53–0.89] and 0.70 [95% CI, 0.46–1.05], respectively) [77]. A post hoc analysis further evaluated outcomes in the avelumab and control arms specifically in patients with CR or PR from 1L chemotherapy; in both subgroups, HRs for OS favored avelumab treatment (HRs, 0.81 [0.47–1.38] and 0.62 [95% CI, 0.46–0.83], respectively) and HRs for PFS were similar (HRs, 0.65 [95% CI, 0.45–0.96] and 0.58 [95% CI, 0.44–0.75], respectively), suggesting that patients with CR or PR can benefit from avelumab maintenance [78]. Given that ICIs are associated with durable responses in a proportion of patients, additional follow-up is needed to evaluate whether long-term outcomes diverge further over time.

Older patients

Advanced age is a major risk factor for UC, and the median age in patients receiving 1L chemotherapy in real-world practice is $>$ 70 years [9–13]. In the avelumab arm of JAVELIN Bladder 100, the median age was 68 years, and 63% of patients were aged $\geq$ 65 years. Avelumab 1L maintenance provided an OS benefit in older and younger subgroups ($<$ 65 or $\geq$ 65 years; HRs, 0.79 [95% CI, 0.55–1.15] and 0.63 [95% CI, 0.47–0.83], respectively) [77]. Importantly, the safety profile of avelumab is suitable for older/frailer patients, as discussed in the section on "Safety and tolerability of avelumab." Chronological age (vs biological age) should not influence the decision to use avelumab.

Renal impairment

Renal function declines with age; thus, renal impairment is common in patients with advanced UC. As noted above, the JAVELIN Bladder 100 trial permitted enrollment of patients with CrCl $\geq$ 30 mL/min, and in the avelumab arm, 48% of patients had CrCl $<$ 60 mL/min at study entry. In subgroups with CrCl $\geq$ 60 or $<$ 60 mL/min, HRs for OS with avelumab vs control were 0.68 (95% CI, 0.50–0.92) and 0.68 (95% CI, 0.50–0.94), indicating a similar OS benefit irrespective of renal function [77]. Data in subgroups with greater renal impairment have not yet been reported. However, because monoclonal antibodies are eliminated by intracellular catabolism and not via the kidneys [86], there is no theoretical reason to limit ICI use based on preexisting renal impairment. Furthermore, a real-world study of atezolizumab as salvage treatment in patients with advanced UC found that efficacy and safety in renally impaired patients (CrCl $<$ 30 but $\geq$ 15 mL/min) were generally consistent with the overall population [87], albeit in a different setting.

Bajorin risk groups

Bajorin risk groups are a standard prognostic classification for patients with advanced UC undergoing 1L chemotherapy. The Bajorin risk score (0–2) is calculated according to the presence of two risk factors prior to chemotherapy that predict shorter OS (discussed earlier): visceral metastases and Karnofsky PS $\leq$ 70% (equivalent to ECOG PS $\geq$ 2) [7,8]. The presence of visceral metastases (prior to 1L chemotherapy) was a stratification factor in the JAVELIN Bladder 100 trial, although the study definition classified bone metastases as nonvisceral, in contrast to standard risk classification [7,77]. Overall, 55% of patients had visceral metastases, including 12% and 24% with liver and/or lung lesions, respectively [77,78]. In patients with visceral, liver, or lung metastases, HRs for OS favored avelumab vs control (HRs of 0.82 [95% CI, 0.62–1.09], 0.92 [95% CI, 0.54–1.56], and 0.86 [95% CI, 0.56–1.30], respectively) albeit with a reduced degree of benefit compared with patients with nonvisceral (including bone) metastases or those without liver or lung metastases (HRs of 0.54 [95% CI, 0.38–0.76], 0.65 [95% CI, 0.51–0.83], and 0.63 [95% CI, 0.49–0.82], respectively), reflecting the worse prognosis associated with visceral metastases [77,78]. Patients with ECOG PS 2 after chemotherapy were ineligible for JAVELIN Bladder 100; however, ECOG PS prior to chemotherapy was not collected and patient PS may have changed following achievement of response or SD with 1L chemotherapy. Overall, 61% vs 39% of patients had ECOG PS 0 or $\geq$1 at start of treatment, and in these subgroups, HRs for OS with avelumab vs control were 0.64 (95% CI, 0.48–0.86) vs 0.74 (95% CI, 0.54–1.03), indicating a similar OS benefit with avelumab [77]. Extrapolation of trial data for other ICIs suggests that ECOG PS 2 should not exclude patients in clinical practice from receiving avelumab maintenance [34,88].

PD-L1 status

In the JAVELIN Bladder 100 trial, tumor PD-L1 status was determined using the Ventana SP263 immunohistochemistry assay per manufacturer's instructions, and patients with PD-L1+ or PD-L1− tumors were eligible. Overall, 51% had PD-L1+ tumors, 39% had PD-L1− tumors, and 10% had unknown PD-L1 status. In patients with PD-L1+ tumors, median OS with avelumab vs control was not reached vs 17.1 months, and the HR was 0.56 (95% CI, 0.40–0.79). In patients with PD–L1− tumors, median OS with avelumab vs control was 18.8 vs 13.7 months, with an (unstratified) HR of 0.86 (95% CI, 0.62–1.18). The HR in patients with unknown tumor PD-L1 status was 0.69 (95% CI, 0.31–1.53). The HR for PFS with avelumab vs control was consistent between patients with PD-L1+ or PD-L1− tumors (unstratified, 0.55 [95% CI, 0.42–0.72] vs 0.64 [95% CI, 0.48–0.85], respectively), indicating a broadly similar PFS benefit in both populations [77]. Thus, avelumab can provide an OS and PFS benefit in patients with PD-L1+ or PD-L1− tumors, albeit with a potentially greater magnitude of benefit in patients with PD-L1+ tumors (the trial was not powered to assess PFS/OS in the PD-L1− subgroup). PD-L1 testing is not required when assessing eligibility for avelumab. Analyses of exploratory biomarkers within the trial are ongoing [89]; however, findings are not relevant to routine clinical practice at this time.

Other subgroups

Avelumab can be administered to a wide range of patients, with no contraindications listed in prescribing information [80,81]. In the JAVELIN Bladder 100 trial, patients with various autoimmune diseases not requiring immunosuppressive treatment (type 1 diabetes, vitiligo, psoriasis, and hypo/hyperthyroid disease) or with stable central nervous system metastases were eligible; thus these patients may be considered for treatment. The trial also enrolled a subgroup with UC histological variants (13% of the avelumab arm) and patients with upper tract (30%) or lower tract (70%) tumors [77], although analyses in these subgroups have not yet been reported. Analyses of OS in patients with other characteristics are not yet available from the JAVELIN Bladder 100 trial and might not be informative because of low numbers of patients and events.

Treatment-free interval

Patients enrolled in JAVELIN Bladder 100 received avelumab after a treatment-free interval of 4–10 weeks, which allowed for radiological tumor assessment to confirm trial eligibility and resolution of toxicities related to platinum-containing chemotherapy [77]. The approved label and treatment guidelines do not make specific recommendations regarding the treatment-free interval before starting avelumab maintenance [5,15,80]. It is unknown whether patients with an interval shorter than 4 weeks or longer than 10 weeks after chemotherapy would derive the same OS benefit from avelumab 1L maintenance as trial participants; data from real-world studies may provide insights. Based on the 4–10-week treatment-free interval used in the trial, clinical judgment, patient fitness, and patient preferences can be used to determine the appropriate interval after completing 1L chemotherapy before starting avelumab maintenance. Durations longer than 10 weeks may increase the risk of progression.

Avelumab administration

Other treatment considerations for avelumab maintenance include premedication, dosage, duration of treatment, and subsequent treatment.

Avelumab can be associated with infusion-related reactions, and in JAVELIN Bladder 100, these occurred at any grade in 10% of patients and at grade $\geq$ 3 in 1% [77]. To mitigate the potential for infusion-related reactions, premedication with an oral antihistamine and oral acetaminophen is required before the first 4 doses of avelumab, consistent with the study protocol and prescribing information. Premedication for subsequent doses should be based on clinical judgment and prior infusion-related reactions [80,81].

In the trial, patients received avelumab every 2 weeks by 1-hour intravenous infusion with weight-based dosing of 10 mg/kg [77]. However, this dose has been superseded in all approved indications by a flat dose of avelumab 800 mg every 2 weeks, which provides practical advantages and greater convenience. Flat dosing was approved based on pharmacokinetic and pharmacodynamic analyses showing minimal differences compared with weight-based dosing across various weight ranges [80,90] and thus should be used for maintenance treatment.

Prescribing information states that avelumab 1L maintenance should be administered until disease progression or unacceptable toxicity, consistent with the trial protocol [77,80,81]. No evidence is available to support whether a maximum or fixed duration of avelumab treatment would be beneficial. In the JAVELIN Bladder 100 trial, the median duration of avelumab treatment at data cutoff (October 21, 2019) was 24.9 weeks (range, 2.0–159.9 weeks) [77].

In patients who have progression with avelumab maintenance, next-line treatment should be based on treatment guidelines and clinical judgment for each patient. Potential options may include clinical trial participation, erdafitinib (patients whose tumors have a susceptible *FGFR3* or *FGFR2* activating mutation or fusion), enfortumab vedotin, taxane chemotherapy, vinflunine (in Europe), or rechallenge with platinum-containing chemotherapy (patients with prolonged remission after platinum-based chemotherapy and maintenance therapy) [5,91]. In the JAVELIN Bladder 100 trial, 148 patients (42%) discontinued avelumab 1L maintenance and received subsequent anticancer treatment, which included an anti–PD-1/PD-L1 antibody in 22 (6%), a fibroblast growth factor receptor inhibitor in 9 (3%), and other drug therapies in 140 (40%; some patients received > 1 category of agent) [77].

Safety and tolerability of avelumab

The safety profile of avelumab administered as 1L maintenance treatment (Table 1) was consistent with previous experience with avelumab monotherapy [77,92]. In the JAVELIN Bladder 100 trial, rates of grade ≥ 3 treatment-related adverse events (TRAEs) were 17% in avelumab-treated patients vs 0% in the BSC alone arm, and the most common grade ≥ 3 TRAEs with avelumab were increased lipase (2.9%) and increased amylase (2.0%) levels. The rate of immune-related AEs (irAEs) of any grade with avelumab was 29%, including grade 3 events in 7%, and 9% of all avelumab-treated patients received high-dose corticosteroids (≥40 mg total daily prednisone or equivalent) [77]. Approaches for managing irAEs with avelumab are the same as for other ICIs, and several organizations have published detailed guidance [80,93–96]. In total, 12% and 10% of patients discontinued avelumab because of AEs (any cause) and TRAEs, respectively [77].

The tolerability of avelumab is supported by patient-reported outcome (PRO) data from JAVELIN Bladder 100, which was a secondary trial endpoint. Results from descriptive analyses and mixed models of validated PRO instruments were similar in patients in the avelumab and control arms. Furthermore, median time to deterioration in the NCCN Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18 (NFBISI-18) disease-related symptoms–physical subscale was similar between arms. Thus, avelumab 1L maintenance prolonged OS with no detrimental effect on clinically relevant PROs [97].

Discussion

Avelumab 1L maintenance is a new standard of care that significantly improves OS in patients with advanced UC that has not progressed on 1L platinum-containing chemotherapy. Response or SD with 1L chemotherapy was found to be an excellent clinical biomarker associated with survival benefit from avelumab maintenance. The median OS with avelumab 1L maintenance of 21.4 months was measured from the start of avelumab, not start of chemotherapy, and is the longest OS reported in a phase 3 trial in the 1L UC setting. Improved OS has not been reported to date with 1L ICI monotherapy or combination approaches. Thus, the total OS benefit seen with the JAVELIN Bladder 100 approach (from start of 1L platinum-containing chemotherapy and including avelumab maintenance) represents a major advance in this patient group (Fig. 5) [27,28,32,33,36–38,77]. By administering avelumab as part of 1L treatment, the JAVELIN Bladder 100 approach enables a larger proportion of patients to obtain an OS benefit from ICI therapy, including patients who cannot receive 2L therapy because of clinical deterioration. OS was significantly improved with avelumab despite subsequent PD-1/PD-L1 inhibitor therapy in more than half of patients with disease progression in the control arm, supporting a maintenance approach vs 2L treatment [77]. Outcomes were improved in various subgroups, including cisplatin-eligible or -ineligible patients, poor-prognosis subgroups, and patients with CR, PR, or SD from 1L chemotherapy, with no requirement for PD-L1 testing to determine eligibility. Because of its large clinical trial program across various tumors and US approval since 2017, there is extensive experience with administering avelumab in clinical practice [92], providing reassurance about its long-term safety profile.

Several questions remain regarding avelumab 1L maintenance that may be answered through future studies. This includes the relative benefits after alternative cisplatin-containing combination regimens, such as dose-dense MVAC or others [98,99], compared with cisplatin + gemcitabine as 1L regimen; optimal treatment-free interval between 1L chemotherapy and avelumab maintenance; and the most effective options for next-line therapy. Real-world studies may provide insights in patient populations that were ineligible for participation in the JAVELIN Bladder 100 trial.

Irrespective of these questions, level 1 evidence supports the use of avelumab as a standard of care for 1L maintenance treatment of advanced UC that has not progressed with platinum-containing chemotherapy. Avelumab 1L maintenance has been approved in multiple countries, including the US, EU, Canada, Japan, Australia, Brazil, and Israel, and wider global availability may be expected depending on local approval and reimbursement discussions. In the authors' opinion, the avelumab maintenance regimen can be easily incorporated into standard clinical practice for a wide range of patients with this challenging disease.

CRediT authorship contribution statement

Petros Grivas: Conceptualization, Writing - original draft, Writing - review & editing. **Neeraj Agarwal:** Conceptualization, Writing - original draft, Writing - review & editing. **Sumanta Pal:** Conceptualization, Writing - original draft, Writing - review & editing. **Arash Rezazadeh Kalebasty:** Conceptualization, Writing - original draft, Writing - review & editing. **Srikala S. Sridhar:** Conceptualization, Writing - original draft, Writing - review & editing. **Jodi Smith:** Conceptualization, Writing - original draft, Writing - review & editing. **Geeta Devgan:** Conceptualization, Writing - original draft, Writing - review & editing. **Cora N. Sternberg:** Conceptualization, Writing - original draft, Writing - review & editing. **Joaquim Bellmunt:** Conceptualization, Writing - original draft, Writing - review & editing.

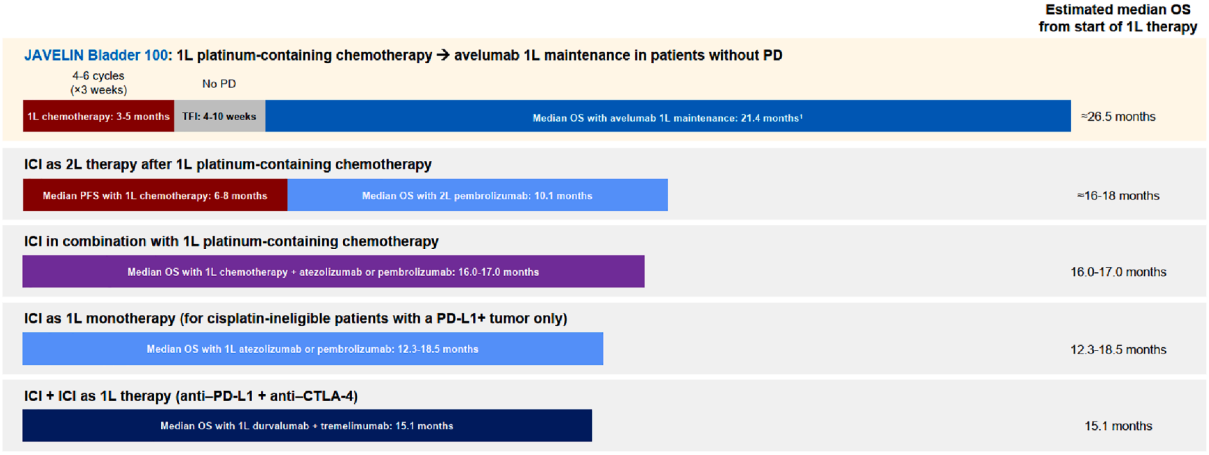

Fig. 5. Survival estimates with approved and nonapproved ICI treatment strategies in patients with locally advanced or metastatic urothelial carcinoma [27,28,32,33,36–38,77]. 1L, first-line; 2L, second-line; CTLA-4, cytotoxic T-lymphocyte–associated protein-4; ICI, immune checkpoint inhibitor; OS, overall survival; PD, progressive disease; TFI, treatment-free interval.

Declaration of Competing Interests

Petros Grivas (in the last 3 years) has provided consulting or advisory services for AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Dyania Health, Driver, EMD Serono, Exelixis, Foundation Medicine, Genentech/Roche, Genzyme, GSK, Heron Therapeutics, Immunomedics, Infinity Pharmaceuticals, Janssen, Merck & Co., Mirati Therapeutics, Pfizer, QED Therapeutics, and Seattle Genetics; and has received research funding from Bavarian Nordic, Bristol Myers Squibb, Clovis Oncology, Debiopharm, GSK, Immunomedics, Kure It Cancer Research, Merck & Co., Mirati Therapeutics, Pfizer, and QED Therapeutics.

Neeraj Agarwal has provided consulting or advisory services for Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Exelixis, Foundation Medicine, Janssen, Lilly, Medivation/Astellas, Merck & Co., Nektar, Novartis, Pfizer, and Pharmacyclics; and has received research funding from Active Biotech, Amgen, AstraZeneca, Bavarian Nordic, Bayer, BN ImmunoTherapeutics, Bristol Myers Squibb, Calithera Biosciences, Celldex, Eisai, Exelixis, Genentech, GSK, Immunomedics, Janssen, Merck & Co., Newlink Genetics, Novartis, Pfizer, Prometheus, Rexahn, Sanofi, Takeda, and TRACON.

Sumanta Pal has provided consulting or advisory services for Astellas, Aveo, Bristol Myers Squibb, Eisai, Exelixis, Genentech, Ipsen, Myriad Pharmaceuticals, Novartis, and Pfizer.

Arash Rezazadeh Kalebasty has provided consulting or advisory services for Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Eisai, EMD Serono, Exelixis, Genentech, Janssen, Medivation, Merck & Co., Novartis, Pfizer, Roche, and Sanofi.

Srikala S. Sridhar has provided consulting or advisory services for Astellas, AstraZeneca, Bristol Myers Squibb, EMD Serono, Merck & Co., Pfizer, and Roche; and has received research funding from Bayer, Janssen, and Pfizer.

Jodi Smith was an employee of EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, at the time of manuscript preparation, and is now an employee of Mirati Therapeutics.

Geeta Devgan is an employee of Pfizer.

Cora N. Sternberg has provided consulting or advisory services to Astellas, AstraZeneca, Bayer, EMD Serono, Incyte, Medscape, Merck & Co., Pfizer, Roche, Sanofi, and UroToday; and has received research funding from Aragon, Array BioPharma, AstraZeneca, Aveo, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Clovis Oncology, Eisai, Exelixis, Genzyme, GSK, Incyte, Janssen, Lilly, Medivation, Merck & Co., Millennium, Myovant Sciences, Nektar, Pfizer, Roche, Sanofi.

Joaquim Bellmunt has provided consulting or advisory services to Astellas, AstraZeneca, Bristol Myers Squibb, Genentech, Merck & Co., Novartis, Pfizer, and Pierre Fabre; has received research funding from EMD Serono, Millennium, Pfizer, and Sanofi; has received honoraria from UpToDate; has received travel, accommodations, or expenses from Ipsen, Merck & Co., and Pfizer; and owns stock in Rainier.

Acknowledgements

Medical writing support for this review was provided by ClinicalThinking, funded by EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, and Pfizer, as part of an alliance between Merck KGaA and Pfizer.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34. https://doi.org/10.3322/caac.21551.

[2] Richters A, Aben KKH, Kiemeney L. The global burden of urinary bladder cancer: an update. World J Urol 2020;38:1895–904. https://doi.org/10.1007/s00345-019-02984-4.

[3] American Cancer Society. Bladder cancer risk factors. https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html.

[4] National Cancer Institute. SEER Cancer Stat Facts: Bladder Cancer. Bethesda, MD. https://seer.cancer.gov/statfacts/html/urinb.html.

[5] National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. Bladder cancer. V1.2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.

[6] Krabbe LM, Eminaga O, Shariat SF, Hutchinson RC, Lotan Y, Sagalowsky AI, et al. Postoperative nomogram for relapse-free survival in patients with high grade upper tract urothelial carcinoma. J Urol 2017;197:580–9. https://doi.org/10.1016/j.juro.2016.09.078.

[7] Bajorin DF, Dodd PM, Mazumdar M, Fazzari M, McCaffrey JA, Scher HI, et al. Long-term survival in metastatic transitional-cell carcinoma and prognostic factors predicting outcome of therapy. J Clin Oncol 1999;17:3173–81. https://doi.org/10.1200/jco.1999.17.10.3173.

[8] Ma C, Bandukwala S, Burman D, Bryson J, Seccareccia D, Banerjee S, et al. Interconversion of three measures of performance status: an empirical analysis. Eur J Cancer 2010;46:3175–83. https://doi.org/10.1016/j.ejca.2010.06.126.

[9] Fisher MD, Shenolikar R, Miller PJ, Fenton M, Walker MS. Treatment patterns and outcomes in stage IV bladder cancer in a community oncology setting: 2008–2015. Clin Genitourin Cancer 2018;16:e1171–9. https://doi.org/10.1016/j.clgc.2018.07.025.

[10] Flannery K, Boyd M, Black-Shinn J, Robert N, Kamat AM. Outcomes in patients with metastatic bladder cancer in the USA: a retrospective electronic medical record study. Future Oncol 2019;15:1323–34. https://doi.org/10.2217/fon-2018-0654.

[11] Aly A, Johnson C, Yang S, Botteman MF, Rao S, Hussain A. Overall survival, costs, and healthcare resource use by line of therapy in Medicare patients with newly diagnosed metastatic urothelial carcinoma. J Med Econ 2019;22:662–70. https://doi.org/10.1080/13696998.2019.1591424.

[12] Simeone JC, Nordstrom BL, Patel K, Mann H, Klein AB, Horne L. Treatment patterns and overall survival in metastatic urothelial carcinoma in a real-world. US setting. Cancer Epidemiol 2019;60:121–7. https://doi.org/10.1016/j.canep.2019.03.013.

[13] Doshi GK, Bhanegaonkar A, Kearney M, Bharmal M, Cislo P, Kim R, et al. Treatment sequencing patterns in patients with metastatic urothelial cancer treated in the community practice setting in the United States: SPEAR-Bladder (Study informing treatment Pathway dEcision in bladder cAnceR). Clinicoecon Outcomes Res 2020;12:645–56. https://doi.org/10.2147/CEOR.S264942.

[14] Bellmunt J, Orsola A, Leow JJ, Wiegel T, De Santis M, Horwich A, et al. Bladder cancer: ESMO Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25(Suppl 3):iii40–8. https://doi.org/10.1093/annonc/mdu223.

[15] European Society for Medical Oncology. eUpdate – bladder cancer treatment recommendations (July 16, 2020). https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations4.

[16] Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. Treatment of patients with metastatic urothelial cancer "unfit" for cisplatin-based chemotherapy. J Clin Oncol 2011;29:2432–8. https://doi.org/10.1200/jco.2011.34.8433.

[17] Koshkin VS, Barata PC, Rybicki LA, Zahoor H, Almassi N, Redden AM, et al. Feasibility of cisplatin-based neoadjuvant chemotherapy in muscle-invasive bladder cancer patients with diminished renal function. Clin Genitourin Cancer 2018;16:e879–92. https://doi.org/10.1016/j.clgc.2018.02.002.

[18] von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ, et al. Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18:3068–77. https://doi.org/10.1200/JCO.2000.18.17.3068.

[19] Dogliotti L, Carteni G, Siena S, Bertetto O, Martoni A, Bono A, et al. Gemcitabine plus cisplatin versus gemcitabine plus carboplatin as first-line chemotherapy in advanced transitional cell carcinoma of the urothelium: results of a randomized phase 2 trial. Eur Urol 2007;52:134–41. https://doi.org/10.1016/j.eururo.2006.12.029.

[20] De Santis M, Bellmunt J, Mead G, Kerst JM, Leahy M, Maroto P, et al. Randomized phase II/III trial assessing gemcitabine/carboplatin and methotrexate/carboplatin/vinblastine in patients with advanced urothelial cancer who are unfit for cisplatin-based chemotherapy: EORTC study 30986. J Clin Oncol 2012;30:191–9. https://doi.org/10.1200/JCO.2011.37.3571.

[21] von der Maase H, Sengelov L, Roberts JT, Ricci S, Dogliotti L, Oliver T, et al. Long-term survival results of a randomized trial comparing gemcitabine plus cisplatin, with methotrexate, vinblastine, doxorubicin, plus cisplatin in patients with bladder cancer. J Clin Oncol 2005;23:4602–8. https://doi.org/10.1200/JCO.2005.07.757.

[22] Plimack ER, Bellmunt J, Gupta S, Berger R, Chow LQ, Juco J, et al. Safety and activity of pembrolizumab in patients with locally advanced or metastatic urothelial cancer (KEYNOTE-012): a non-randomised, open-label, phase 1b study. Lancet Oncol 2017;18:212–20. https://doi.org/10.1016/S1470-2045(17)30007-4.

[23] Sharma P, Retz M, Siefker-Radtke A, Baron A, Necchi A, Bedke J, et al. Nivolumab in metastatic urothelial carcinoma after platinum therapy (CheckMate 275): a multicentre, single-arm, phase 2 trial. Lancet Oncol 2017;18:312–22. https://doi.org/10.1016/S1470-2045(17)30065-7.

[24] Rosenberg JE, Hoffman-Censits J, Powles T, van der Heijden MS, Balar AV, Necchi A, et al. Atezolizumab in patients with locally advanced and metastatic urothelial carcinoma who have progressed following treatment with platinum-based chemotherapy: a single-arm, multicentre, phase 2 trial. Lancet 2016;387:1909–20. https://doi.org/10.1016/s0140-6736(16)00561-4.

[25] Patel MR, Ellerton J, Infante JR, Agrawal M, Gordon M, Aljumaily R, et al. Avelumab in metastatic urothelial carcinoma after platinum failure (JAVELIN Solid Tumor): pooled results from two expansion cohorts of an open-label, phase 1 trial. Lancet Oncol 2018;19:51–64. https://doi.org/10.1016/S1470-2045(17)30900-2.

[26] Powles T, O'Donnell PH, Massard C, Arkenau HT, Friedlander TW, Hoimes CJ, et al. Efficacy and safety of durvalumab in locally advanced or metastatic urothelial carcinoma: updated results from a phase 1/2 open-label study. JAMA Oncol 2017;3:e172411. https://doi.org/10.1001/jamaoncol.2017.2411.
[27] Bellmunt J, de Wit R, Vaughn DJ, Fradet Y, Lee JL, Fong L, et al. Pembrolizumab as second-line therapy for advanced urothelial carcinoma. N Engl J Med 2017;376:1015–26. https://doi.org/10.1056/NEJMoa1613683.
[28] Fradet Y, Bellmunt J, Vaughn DJ, Lee JL, Fong L, Vogelzang NJ, et al. Randomized phase III KEYNOTE-045 trial of pembrolizumab versus paclitaxel, docetaxel, or vinflunine in recurrent advanced urothelial cancer: results of > 2 years of follow-up. Ann Oncol 2019;30:970–6. https://doi.org/10.1093/annonc/mdz127.
[29] Taarnhoj GA, Johansen C, Pappot H. Quality of life in bladder cancer patients receiving medical oncological treatment; a systematic review of the literature. Health Qual Life Outcomes 2019;17:20. https://doi.org/10.1186/s12955-018-1077-6.
[30] Vaughn DJ, Bellmunt J, Fradet Y, Lee JL, Fong L, Vogelzang NJ, et al. Health-related quality-of-life analysis from KEYNOTE-045: a phase III study of pembrolizumab versus chemotherapy for previously treated advanced urothelial cancer. J Clin Oncol 2018;36:1579–87. https://doi.org/10.1200/jco.2017.76.9562.
[31] Galsky MD, Pal SK, Lin SW, Ogale S, Zivkovic M, Simpson J, et al. Real-world effectiveness of chemotherapy in elderly patients with metastatic bladder cancer in the United States. Bladder Cancer 2018;4:227–38. https://doi.org/10.3233/blc-170149.
[32] Balar AV, Galsky MD, Rosenberg JE, Powles T, Petrylak DP, Bellmunt J, et al. Atezolizumab as first-line treatment in cisplatin-ineligible patients with locally advanced and metastatic urothelial carcinoma: a single-arm, multicentre, phase 2 trial. Lancet 2017;389:67–76. https://doi.org/10.1016/s0140-6736(16)32455-2.
[33] Vuky J, Balar AV, Castellano D, O'Donnell PH, Grivas P, Bellmunt J, et al. Long-term outcomes in KEYNOTE-052: phase II study investigating first-line pembrolizumab in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer. J Clin Oncol 2020;38:2658–66. https://doi.org/10.1200/JCO.19.01213.
[34] Grivas P, Plimack ER, Balar AV, Castellano D, O'Donnell PH, Bellmunt J, et al. Pembrolizumab as first-line therapy in cisplatin-ineligible advanced urothelial cancer (KEYNOTE-052): outcomes in older patients by age and performance status. Eur Urol Oncol 2020;3:351–9. https://doi.org/10.1016/j.euo.2020.02.009.
[35] Suzman DL, Agrawal S, Ning YM, Maher VE, Fernandes LL, Karuri S, et al. FDA approval summary: atezolizumab or pembrolizumab for the treatment of patients with advanced urothelial carcinoma ineligible for cisplatin-containing chemotherapy. Oncologist 2019;24:563–9. https://doi.org/10.1634/theoncologist.2018-0084.
[36] Galsky MD, Arija JAA, Bamias A, Davis ID, De Santis M, Kikuchi E, et al. Atezolizumab with or without chemotherapy in metastatic urothelial cancer (IMvigor130): a multicentre, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1547–57. https://doi.org/10.1016/S0140-6736(20)30230-0.
[37] Alva A, Csőszi T, Ozguroglu M, Matsubara N, Geczi L, Cheng SY, et al. Pembrolizumab (P) combined with chemotherapy (C) vs C alone as first-line (1L) therapy for advanced urothelial carcinoma (UC): KEYNOTE-361. Ann Oncol 2020;31:S1142–215. https://doi.org/10.1016/j.annonc.2020.08.2252.
[38] Powles T, van der Heijden MS, Castellano D, Galsky MD, Loriot Y, Petrylak DP, et al. Durvalumab alone and durvalumab plus tremelimumab versus chemotherapy in previously untreated patients with unresectable, locally advanced or metastatic urothelial carcinoma (DANUBE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2020;21:1574–88. https://doi.org/10.1016/S1470-2045(20)30541-6.
[39] Grivas P, Monk BJ, Petrylak D, Reck M, Foley G, Guenther S, et al. Immune checkpoint inhibitors as switch or continuation maintenance therapy in solid tumors: rationale and current state. Target Oncol 2019;14:505–25. https://doi.org/10.1007/s11523-019-00665-1.
[40] de Biasi AR, Villena-Vargas J, Adusumilli PS. Cisplatin-induced antitumor immunomodulation: a review of preclinical and clinical evidence. Clin Cancer Res 2014;20:5384–91. https://doi.org/10.1158/1078-0432.CCR-14-1298.
[41] Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted anticancer agents. Cancer Cell 2015;28:690–714. https://doi.org/10.1016/j.ccell.2015.10.012.
[42] Chen C, Chen Z, Chen D, Zhang B, Wang Z, Le H. Suppressive effects of gemcitabine plus cisplatin chemotherapy on regulatory T cells in nonsmall-cell lung cancer. J Int Med Res 2015;43:180–7. https://doi.org/10.1177/0300060514561504.
[43] Eriksson E, Wenthe J, Irenaeus S, Loskog A, Ullenhag G. Gemcitabine reduces MDSCs, Tregs and TGFβ-1 while restoring the Teff/Treg ratio in patients with pancreatic cancer. J Transl Med 2016;14:282. https://doi.org/10.1186/s12967-016-1037-z.
[44] Beyranvand Nejad E, van der Sluis TC, van Duikeren S, Yagita H, Janssen GM, van Veelen PA, et al. Tumor eradication by cisplatin is sustained by CD80/86-mediated costimulation of CD8+ T cells. Cancer Res 2016;76:6017–29. https://doi.org/10.1158/0008-5472.Can-16-0881.
[45] Wan S, Pestka S, Jubin RG, Lyu YL, Tsai YC, Liu LF. Chemotherapeutics and radiation stimulate MHC class I expression through elevated interferon-beta signaling in breast cancer cells. PLoS ONE 2012;7:e32542. https://doi.org/10.1371/journal.pone.0032542.
[46] McDonnell AM, Lesterhuis WJ, Khong A, Nowak AK, Lake RA, Currie AJ, et al. Tumor-infiltrating dendritic cells exhibit defective cross-presentation of tumor antigens, but is reversed by chemotherapy. Eur J Immunol 2015;45:49–59. https://doi.org/10.1002/eji.201444722.
[47] Grimaldi A, Cammarata I, Martire C, Focaccetti C, Piconese S, Buccilli M, et al. Combination of chemotherapy and PD-1 blockade induces T cell responses to tumor non-mutated neoantigens. Commun Biol 2020;3:85. https://doi.org/10.1038/s42003-020-0811-x.
[48] Fridlender ZG, Sun J, Singhal S, Kapoor V, Cheng G, Suzuki E, et al. Chemotherapy delivered after viral immunogene therapy augments antitumor efficacy via multiple immune-mediated mechanisms. Mol Ther 2010;18:1947–59. https://doi.org/10.1038/mt.2010.159.
[49] Zhang X, Wang D, Li Z, Jiao D, Jin L, Cong J, et al. Low-dose gemcitabine treatment enhances immunogenicity and natural killer cell-driven tumor immunity in lung cancer. Front Immunol 2020;11:331. https://doi.org/10.3389/fimmu.2020.00331.
[50] Fournel L, Wu Z, Stadler N, Damotte D, Lococo F, Boulle G, et al. Cisplatin increases PD-L1 expression and optimizes immune check-point blockade in non-small cell lung cancer. Cancer Lett 2019;464:5–14. https://doi.org/10.1016/j.canlet.2019.08.005.
[51] Tsai TF, Lin JF, Lin YC, Chou KY, Chen HE, Ho CY, et al. Cisplatin contributes to programmed death-ligand 1 expression in bladder cancer through ERK1/2-AP-1 signaling pathway. Biosci Rep 2019;39:BSR20190362. https://doi.org/10.1042/bsr20190362.
[52] Grivas P, Emamekhoo H, Elson P, McKenney J, Zargar H, Magi-Galluzzi C, et al. PD1, PDL1, PDL2 tumor tissue (TT) expression as predictors of response to neoadjuvant chemotherapy (NAC) and outcome in bladder cancer (BC). J Clin Oncol 2016;34:e16023. https://doi.org/10.1200/JCO.2016.34.15_suppl.e16023.
[53] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med 2018;378:2078–92. https://doi.org/10.1056/NEJMoa1801005.
[54] Paz-Ares L, Luft A, Vicente D, Tafreshi A, Gümüş M, Mazières J, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. N Engl J Med 2018;379:2040–51. https://doi.org/10.1056/NEJMoa1810865.
[55] West H, McCleod M, Hussein M, Morabito A, Rittmeyer A, Conter HJ, et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:924–37. https://doi.org/10.1016/s1470-2045(19)30167-6.
[56] Burtness B, Harrington KJ, Greil R, Soulieres D, Tahara M, de Castro G, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet 2019;394:1915–28. https://doi.org/10.1016/s0140-6736(19)32591-7.
[57] Galsky MD, Banchereau R, Hamidi HR, Leng N, Harris W, O'Donnell PH, et al. Tumor, immune, and stromal characteristics associated with clinical outcomes with atezolizumab (atezo) + platinum-based chemotherapy (PBC) or atezo monotherapy (mono) versus PBC in metastatic urothelial cancer (mUC) from the phase III IMvigor130 study. J Clin Oncol 2020;38:5011. https://doi.org/10.1200/JCO.2020.38.15_suppl.5011.
[58] Ciuleanu T, Brodowicz T, Zielinski C, Kim JH, Krzakowski M, Laack E, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432–40. https://doi.org/10.1016/S0140-6736(09)61497-5.
[59] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. N Engl J Med 2016;375:2154–64. https://doi.org/10.1056/NEJMoa1611310.
[60] Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2017;390:1949–61. https://doi.org/10.1016/S0140-6736(17)32440-6.
[61] Poveda A, Floquet A, Ledermann JA, Asher R, Penson RT, Oza AM, et al. Final overall survival (OS) results from SOLO2/ENGOT-ov21: A phase III trial assessing maintenance olaparib in patients (pts) with platinum-sensitive, relapsed ovarian cancer and a BRCA mutation. J Clin Oncol 2020;38:6002. https://doi.org/10.1200/JCO.2020.38.15_suppl.6002. abstract.
[62] Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, et al. Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2017;18:1274–84. https://doi.org/10.1016/s1470-2045(17)30469-2.
[63] Powles T, Huddart RA, Elliott T, Sarker SJ, Ackerman C, Jones R, et al. Phase III, double-blind, randomized trial that compared maintenance lapatinib versus placebo after first-line chemotherapy in patients with human epidermal growth factor receptor 1/2-positive metastatic bladder cancer. J Clin Oncol 2017;35:48–55. https://doi.org/10.1200/JCO.2015.66.3468.
[64] Grivas PD, Daignault S, Tagawa ST, Nanus DM, Stadler WM, Dreicer R, et al. Double-blind, randomized, phase 2 trial of maintenance sunitinib versus placebo after response to chemotherapy in patients with advanced urothelial carcinoma. Cancer 2014;120:692–701. https://doi.org/10.1002/cncr.28477.
[65] García-Donas J, Font A, Pérez-Valderrama B, Virizuela JA, Climent MÁ, Hernando-Polo S, et al. Maintenance therapy with vinflunine plus best supportive care versus best supportive care alone in patients with advanced urothelial carcinoma with a response after first-line chemotherapy (MAJA; SOGUG 2011/02): a multicentre, randomised, controlled, open-label, phase 2 trial. Lancet Oncol 2017;18:672–81. https://doi.org/10.1016/s1470-2045(17)30242-5.
[66] Bellmunt Molins J, Garcia-Donas Jimenez J, Valderrama BP, Virizuela Echaburu JA, Hernando-Polo S, Climent Duran MA, et al. Final overall survival analysis of the SOGUG phase 2 MAJA study: Maintenance vinflunine versus best

supportive care after first-line chemotherapy in advanced urothelial carcinoma. Clin Genitourin Cancer 2020;18:452–60. https://doi.org/10.1016/j.clgc.2020.05.004.
[67] Zheng Y, Narwal R, Jin C, Baverel PG, Jin X, Gupta A, et al. Population modeling of tumor kinetics and overall survival to identify prognostic and predictive biomarkers of efficacy for durvalumab in patients with urothelial carcinoma. Clin Pharmacol Ther 2018;103:643–52. https://doi.org/10.1002/cpt.986.
[68] Joseph RW, Elassaiss-Schaap J, Kefford R, Hwu WJ, Wolchok JD, Joshua AM, et al. Baseline tumor size is an independent prognostic factor for overall survival in patients with melanoma treated with pembrolizumab. Clin Cancer Res 2018;24:4960–7. https://doi.org/10.1158/1078-0432.CCR-17-2386.
[69] Katsurada M, Nagano T, Tachihara M, Kiriu T, Furukawa K, Koyama K, et al. Baseline tumor size as a predictive and prognostic factor of immune checkpoint inhibitor therapy for non-small cell lung cancer. Anticancer Res 2019;39:815–25. https://doi.org/10.21873/anticanres.13180.
[70] Inoue H, Yokota T, Hamauchi S, Onozawa Y, Kawakami T, Shirasu H, et al. Pre-treatment tumor size impacts on response to nivolumab in head and neck squamous cell carcinoma. Auris Nasus Larynx 2020;47:650–7. https://doi.org/10.1016/j.anl.2020.01.003.
[71] Collins JM, Gulley JL. Product review: avelumab, an anti-PD-L1 antibody. Hum Vaccin Immunother 2019;15:891–908. https://doi.org/10.1080/21645515.2018.1551671.
[72] Vandeveer AJ, Fallon JK, Tighe R, Sabzevari H, Schlom J, Greiner JW. Systemic immunotherapy of non-muscle invasive mouse bladder cancer with avelumab, an anti-PD-L1 immune checkpoint inhibitor. Cancer Immunol Res 2016;4:452–62. https://doi.org/10.1158/2326-6066.CIR-15-0176.
[73] Grenga I, Donahue RN, Lepone LM, Richards J, Schlom J. A fully human IgG1 anti-PD-L1 MAb in an in vitro assay enhances antigen-specific T-cell responses. Clin Transl Immunology 2016;5:e83. https://doi.org/10.1038/cti.2016.27.
[74] Boyerinas B, Jochems C, Fantini M, Heery CR, Gulley JL, Tsang KY, et al. Antibody-dependent cellular cytotoxicity activity of a novel anti-PD-L1 antibody avelumab (MSB0010718C) on human tumor cells. Cancer Immunol Res 2015;3:1148–57. https://doi.org/10.1158/2326-6066.CIR-15-0059.
[75] Julia EP, Amante A, Pampena MB, Mordoh J, Levy EM. Avelumab, an IgG1 anti-PD-L1 immune checkpoint inhibitor, triggers NK cell-mediated cytotoxicity and cytokine production against triple negative breast cancer cells. Front Immunol 2018;9:2140. https://doi.org/10.3389/fimmu.2018.02140.
[76] Apolo AB, Ellerton JA, Infante JR, Agrawal M, Gordon MS, Aljumaily R, et al. Avelumab as second-line therapy for metastatic, platinum-treated urothelial carcinoma in the phase Ib JAVELIN Solid Tumor study: 2-year updated efficacy and safety analysis. J Immunother Cancer 2020;8:e001246. https://doi.org/10.1136/jitc-2020-001246.
[77] Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma. N Engl J Med 2020;383:1218–30. https://doi.org/10.1056/NEJMoa2002788.
[78] Grivas P, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone with 1L chemotherapy (CTx) for advanced urothelial carcinoma (UC): Subgroup analyses from JAVELIN Bladder 100. Ann Oncol 2020;31:S550 (abstract 704MO). https://doi.org/10.1016/j.annonc.2020.08.776.
[79] Powles T, Park SH, Voog E, Caserta C, Valderrama B, Gurney H, et al. Maintenance avelumab+ best supportive care (BSC) versus BSC alone after platinum-based first-line (1L) chemotherapy in advanced urothelial carcinoma (UC): JAVELIN Bladder 100 phase III interim analysis. J Clin Oncol 2020;38:abstract LBA1.. https://doi.org/10.1200/JCO.2020.38.18_suppl.LBA1.
[80] Bavencio (avelumab) Prescribing information. EMD Serono; 2020.
[81] Bavencio (avelumab) Summary of product characteristics. Merck KGaA, Darmstadt, Germany; 2021.
[82] Galsky MD, Mortazavi A, Milowsky MI, George S, Gupta S, Fleming MT, et al. Randomized double-blind phase II study of maintenance pembrolizumab versus placebo after first-line chemotherapy in patients with metastatic urothelial cancer. J Clin Oncol 2020;38:1797–806. https://doi.org/10.1200/JCO.19.03091.
[83] Sonpavde GP, Mariani L, Lo Vullo S, Raggi D, Giannatempo P, Bamias A, et al. Impact of the number of cycles of platinum based first line chemotherapy for advanced urothelial carcinoma. J Urol 2018;200:1207–14. https://doi.org/10.1016/j.juro.2018.07.035.
[84] Loriot Y, Powles T, Ángel M, Durán C, Sridhar SS, Bellmunt J, et al. Avelumab (Ave) first-line (1L) maintenance plus best supportive care (BSC) versus BSC alone for advanced urothelial carcinoma (UC): JAVELIN Bladder 100 subgroup analysis based on duration and cycles of 1L chemotherapy. J Clin Oncol 2021;39:438. https://doi.org/10.1200/JCO.2021.39.6_suppl.438. abstract.
[85] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47. https://doi.org/10.1016/j.ejca.2008.10.026.
[86] Ryman JT, Meibohm B. Pharmacokinetics of monoclonal antibodies. CPT Pharmacometrics Syst Pharmacol 2017;6:576–88. https://doi.org/10.1002/psp4.12224.
[87] Sternberg CN, Loriot Y, James N, Choy E, Castellano D, Lopez-Rios F, et al. Primary results from SAUL, a multinational single-arm safety study of atezolizumab therapy for locally advanced or metastatic urothelial or nonurothelial carcinoma of the urinary tract. Eur Urol 2019;76:73–81. https://doi.org/10.1016/j.eururo.2019.03.015.
[88] Khaki AR, Li A, Diamantopoulos LN, Bilen MA, Santos V, Esther J, et al. Impact of performance status on treatment outcomes: a real-world study of advanced urothelial cancer treated with immune checkpoint inhibitors. Cancer 2020;126:1208–16. https://doi.org/10.1002/cncr.32645.
[89] Sridhar S, Powles TB, Loriot Y, Bellmunt J, Sternberg CN, Petrylak DP, et al. Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC): Association between clinical outcomes and exploratory biomarkers. Ann Oncol 2020;31:S552–3. Abstract 699O. https://doi.org/10.1016/j.annonc.2020.08.771.
[90] Novakovic AM, Wilkins JJ, Dai H, Wade JR, Neuteboom B, Brar S, et al. Changing body weight-based dosing to a flat dose for avelumab in metastatic Merkel cell and advanced urothelial carcinoma. Clin Pharmacol Ther 2020;107:588–96. https://doi.org/10.1002/cpt.1645.
[91] European Society for Medical Oncology. eUpdate – bladder cancer treatment recommendations (December 16, 2019). https://www.esmo.org/guidelines/genitourinary-cancers/bladder-cancer/eupdate-bladder-cancer-treatment-recommendations3.
[92] Kelly K, Infante JR, Taylor MH, Patel MR, Wong DJ, Iannotti N, et al. Safety profile of avelumab in patients with advanced solid tumors: a pooled analysis of data from the phase 1 JAVELIN Solid Tumor and phase 2 JAVELIN Merkel 200 clinical trials. Cancer 2018;124:2010–7. https://doi.org/10.1002/cncr.31293.
[93] Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29:iv264–6. https://doi.org/10.1093/annonc/mdx225.
[94] Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 2018;36:1714–68. https://doi.org/10.1200/JCO.2017.77.6385.
[95] Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. Management of immunotherapy-related toxicities (v1.2019). J Natl Compr Canc Netw 2019;17:255–89. https://doi.org/10.6004/jnccn.2019.0013.
[96] Puzanov I, Diab A, Abdallah K, Bingham 3rd CO, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95. https://doi.org/10.1186/s40425-017-0300-z.
[97] Powles TB, Kopyltsov E, Su P-J, Parnis FX, Park SH, Yamamoto Y, et al. Patient-reported outcomes (PROs) from JAVELIN Bladder 100: Avelumab first-line (1L) maintenance + best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma (UC). Ann Oncol 2020;31:S550. Abstract 745P. https://doi.org/10.1016/j.annonc.2020.08.817.
[98] Sternberg CN, de Mulder P, Schornagel JH, Theodore C, Fossa SD, van Oosterom AT, et al. Seven year update of an EORTC phase III trial of high-dose intensity M-VAC chemotherapy and G-CSF versus classic M-VAC in advanced urothelial tract tumours. Eur J Cancer 2006;42:50–4. https://doi.org/10.1016/j.ejca.2005.08.032.
[99] Bellmunt J, von der Maase H, Mead GM, Skoneczna I, De Santis M, Daugaard G, et al. Randomized phase III study comparing paclitaxel/cisplatin/gemcitabine and gemcitabine/cisplatin in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy: EORTC Intergroup Study 30987. J Clin Oncol 2012;30:1107–13. https://doi.org/10.1200/JCO.2011.38.6979.