

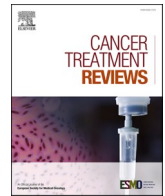
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Individualizing first-line treatment for advanced urothelial carcinoma: A favorable dilemma for patients and physicians

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ABSTRACT

The treatment landscape for patients with advanced urothelial carcinoma (UC) has evolved rapidly in recent years. In current guidelines, combination treatment with enfortumab vedotin plus pembrolizumab is the first-line (1L) standard of care, and other recommended 1L treatment options are platinum-based chemotherapy followed by avelumab as switch-maintenance treatment in patients without progression, or combination treatment with nivolumab, cisplatin, and gemcitabine for cisplatin-eligible patients only. Individual patients differ in terms of their health status, disease characteristics, expected toxicities, and treatment preferences; thus, a “one-size-fits-all” approach to treatment is unlikely to be optimal. The availability of several treatment options creates the potential for individualized treatment. In this review, we discuss factors that may be considered when selecting 1L treatment for patients with advanced UC, including efficacy and safety data from phase 3 trials and real-world studies, quality of life, patient priorities for treatment, patient and disease characteristics, treatment sequencing, biomarkers, and treatment access and cost. Patients and physicians should discuss the benefit-risk balance of all available 1L options to enable shared decision-making. Longer follow-up from clinical trials and additional real-world studies are needed to further inform treatment selection.

Introduction

Bladder cancer is the ninth most common cancer worldwide [1]. Urothelial carcinoma (UC) accounts for > 90% of bladder cancers [2]. UC can also occur in the upper urinary tract, including the ureter and renal pelvis, and upper and lower tract UC share histological characteristics and treatment approaches [3,4]. UC is strongly associated with frailty and older age (median age at diagnosis of bladder cancer is 73 years [5]), creating additional considerations for treatment, eg, a higher likelihood of comorbidities or reduced fitness, and a greater risk of treatment-related toxicity [6]. Real-world data suggest that ≈40% of

patients with advanced UC do not receive systemic treatment [7].

The treatment landscape for advanced UC has evolved rapidly in recent years and several first-line (1L) treatment options are now available, with access varying between countries. Combination treatment with enfortumab vedotin (EV), an antibody-drug conjugate targeted to Nectin-4, plus pembrolizumab, an immune checkpoint inhibitor (ICI), is the 1L standard of care in US and European guidelines [8,9]. Other recommended 1L options are platinum-based (cisplatin- or carboplatin-containing) chemotherapy (PBC) followed by 1L switch-maintenance treatment with avelumab (an ICI) in patients without progression, and combination treatment with nivolumab (an ICI) plus

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cisplatin-gemcitabine followed by nivolumab monotherapy for cisplatin-eligible patients only. ICI monotherapy is an additional 1L option for platinum-ineligible patients or cisplatin-ineligible patients with PD-L1+ tumors in different countries [9–11].

Efficacy outcomes reported in the phase 3 EV-302 trial of EV plus pembrolizumab (EVP), including a doubling in median overall survival (OS) and progression-free survival (PFS), are a major development in the treatment of advanced UC [12]. However, considerations associated with this regimen have been highlighted, including its side-effect profile, indefinite treatment duration with EV, high cost (“financial toxicity”), lack of biomarker selection, and uncertainties about treatment sequencing after progression [13–15]. Patient selection for EVP based on criteria created for cisplatin or carboplatin ineligibility [9,16–18] is unlikely to be appropriate because of the distinct mechanisms of action and toxicity profiles of different treatments; thus, EV-ineligible criteria (EVITA) have been proposed [19]. However, these criteria are not fully evidence based because of limited data to evaluate EVP unsuitability [20,21] and are not included in treatment guidelines.

The availability of multiple treatment options creates the potential

for individualized treatment, ie, selecting the best treatment option for each patient. Because patients differ in terms of their health status, disease characteristics, and personal situation, a “one-size-fits-all” approach to treatment is unlikely to be appropriate. In this review, we discuss factors that might be considered when individualizing 1L treatment for patients with advanced UC (Fig. 1).

Efficacy of 1L treatment options

The status of EVP as the standard-of-care 1L treatment for advanced UC is based on efficacy data from the phase 3 EV-302 trial, which compared EVP vs PBC in platinum-eligible patients with advanced UC (N = 886) [12]. After a median follow-up of 17.2 months, OS, PFS, and objective response rate (ORR) were significantly improved with EVP vs PBC (Fig. 2). Median OS was 31.5 vs 16.1 months (hazard ratio [HR], 0.47 [95% CI, 0.38–0.58]; $p < 0.001$; 1-year OS rate, 78.2% vs 61.4%) and median PFS was 12.5 vs 6.3 months (HR, 0.45 [95% CI, 0.38–0.54]; $p < 0.001$; 1-year PFS rate, 50.7% vs 21.6%), respectively. ORRs were 67.7% vs 44.4%, including complete response (CR) in 29.1% vs 12.5%,

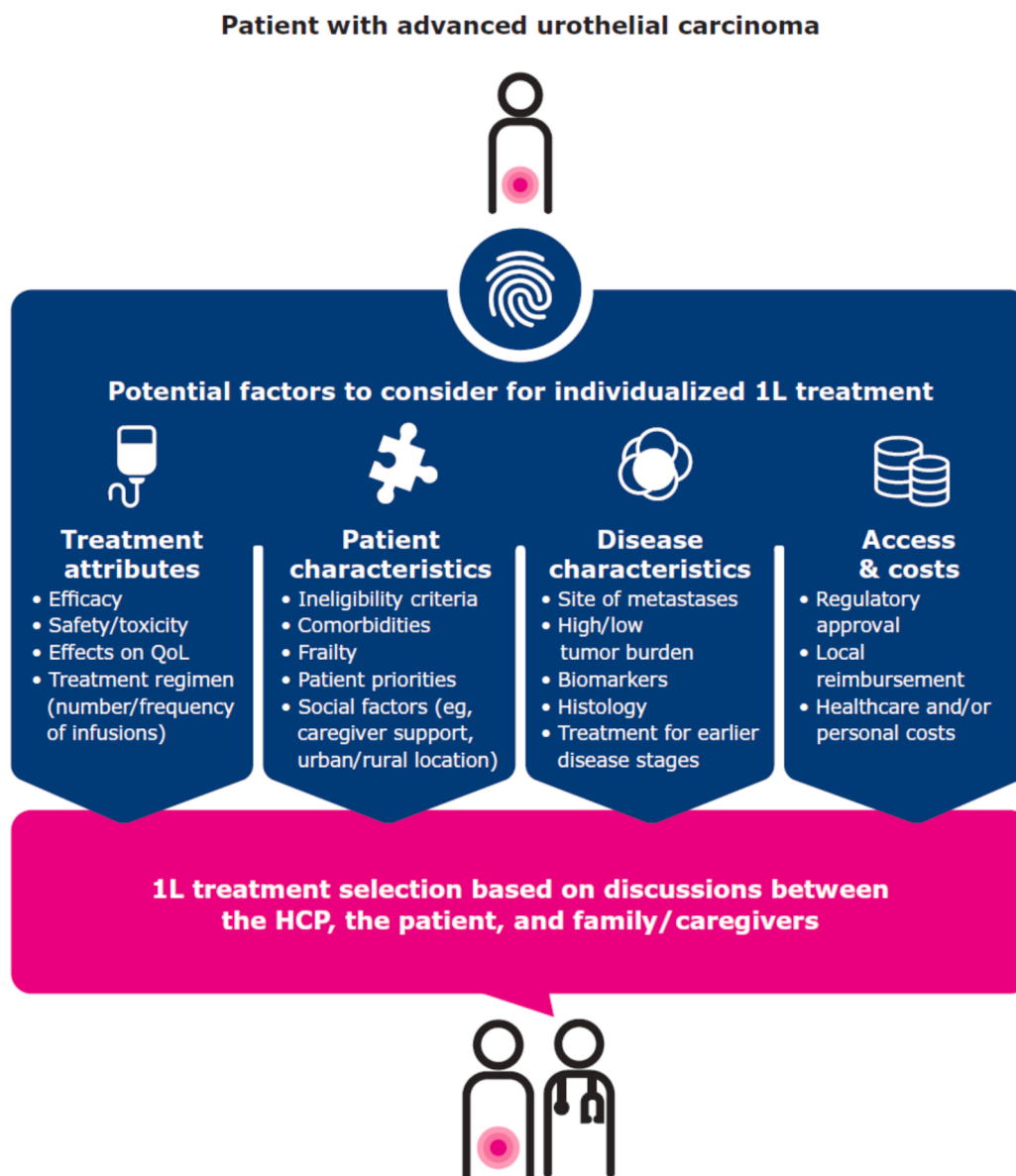


Fig. 1. Overview of factors that may be considered when selecting 1L treatment for patients with advanced urothelial carcinoma. 1L, first line; HCP, healthcare professional; QoL, quality of life.

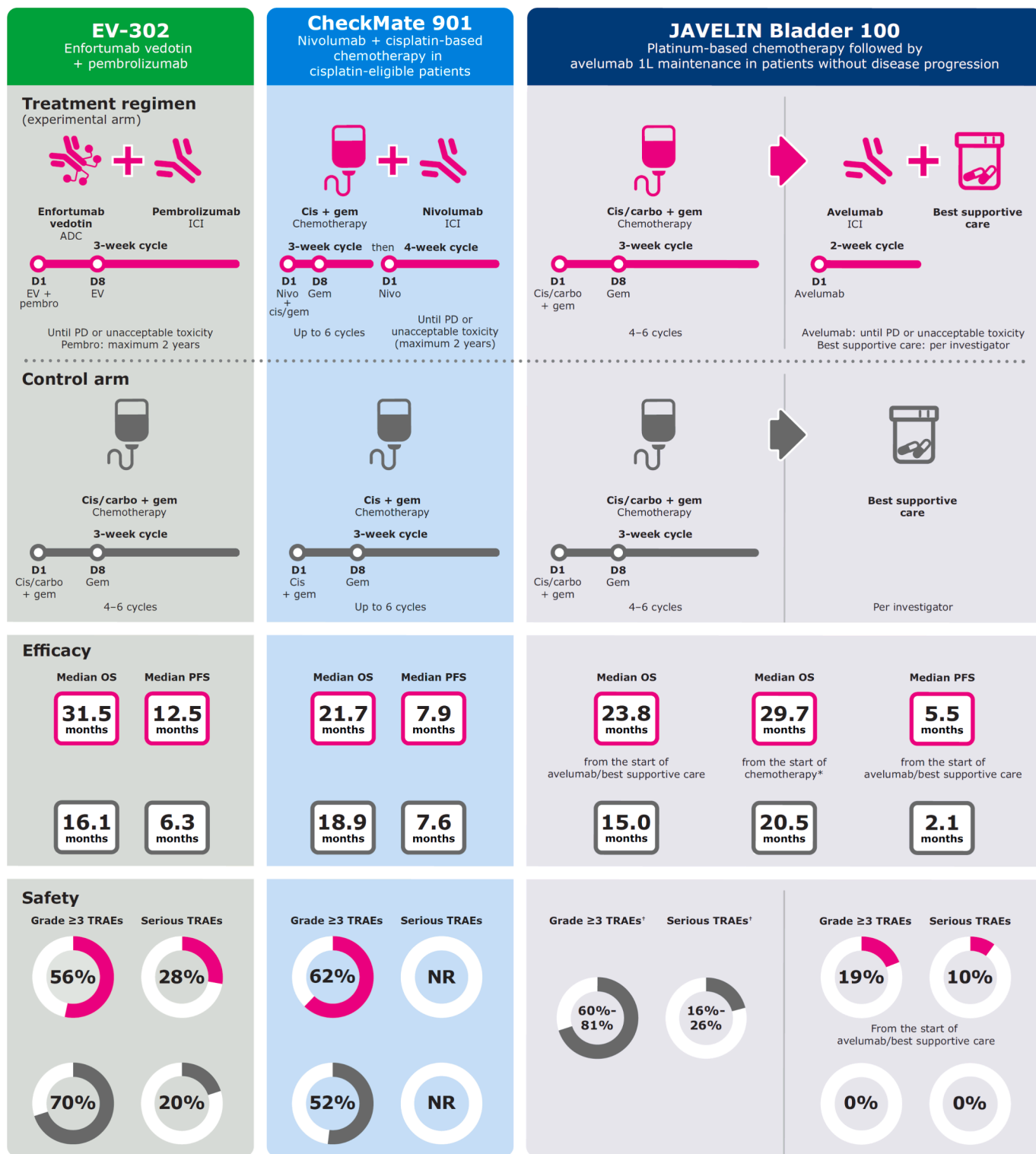


Fig. 2. Summary of treatment regimens and efficacy and safety data from phase 3 trials of recommended 1L treatment options [12,23–28,37]. 1L, first line; ADC, antibody-drug conjugate; carbo, carboplatin; cis, cisplatin; D, day; gem, gemcitabine; ICI, immune checkpoint inhibitor; IRR, infusion-related reaction; nivo, nivolumab; OS, overall survival; pembro, pembrolizumab; PFS, progression-free survival; TRAE, treatment-related adverse event. *Data for OS from the start of chemotherapy in JAVELIN Bladder 100 should be interpreted with caution because the trial enrolled a selected trial population of patients without progression following 1L platinum-based chemotherapy. †Safety of platinum-based chemotherapy was not assessed in JAVELIN Bladder 100 because all patients had completed 1L platinum-based chemotherapy prior to trial enrollment. Safety data shown for platinum-based chemotherapy are based on control arms from recent phase 3 trials [12,23–26].

and median duration of response was not reached vs 7.0 months, respectively. Median time to response was 2.1 months in both arms. In the chemotherapy arm, 30% of patients received avelumab 1L maintenance despite 78% having response or stable disease, reflecting the late protocol amendment explicitly permitting maintenance treatment; outcomes in this subgroup have not been reported [12]. In a real-world study of 101 US patients treated with 1L EVP, the ORR was 54%, and 1-year OS and PFS rates were 67% and 30%, respectively [22], which were lower than rates in clinical trials, reflecting treatment of a more heterogeneous population.

Before EVP was available, PBC was the standard 1L treatment for advanced UC for > 20 years. The efficacy of PBC was confirmed in control arms of recent phase 3 trials in patients who received 1L cisplatin or carboplatin plus gemcitabine (without avelumab maintenance or newer next-line treatments). Median OS and PFS ranged from 12.1–16.1 months and 6.3–7.1 months, and ORRs ranged from 43%–49% [12,23–26]. The phase 3 JAVELIN Bladder 100 trial showed that in patients without progression after 1L PBC (cisplatin or carboplatin plus gemcitabine; N = 700), avelumab 1L maintenance added to best supportive care (BSC) significantly prolonged OS and PFS vs BSC alone [27,28]. Median OS from randomization (start of maintenance/end of chemotherapy) was 23.8 vs 15.0 months (HR, 0.76 [95% CI, 0.63–0.91]; p = 0.0036), and median PFS was 5.5 vs 2.1 months (HR, 0.54 [95% CI, 0.46–0.64]; p < 0.0001), respectively [28]. In a post hoc analysis in this selected population without progression, median OS from start of 1L

PBC in the avelumab and BSC alone arms was 29.7 vs 20.5 months, respectively (HR, 0.77 [95% CI, 0.64–0.92]) [29]. The efficacy of avelumab 1L maintenance observed in JAVELIN Bladder 100 is consistent with real-world data from different countries, which reported median OS from start of avelumab ranging from 21.3–26.2 months [30–36].

In the substudy of the phase 3 CheckMate-901 trial, 1L nivolumab plus cisplatin-gemcitabine followed by nivolumab monotherapy in cisplatin-eligible patients significantly prolonged OS and PFS vs 1L cisplatin-gemcitabine alone (N = 608). Median OS was 21.7 vs 18.9 months (HR, 0.78 [95% CI, 0.63–0.96]; p = 0.02), and median PFS was 7.9 vs 7.6 months (HR, 0.72 [95% CI, 0.59–0.88]; p = 0.001), respectively. ORRs were 57.6% vs 43.1%, including CR in 21.7% vs 11.8%, respectively, and median time to response was 2.1 months in both arms [37]. In the chemotherapy arm, only 20% received ICI maintenance, despite 71% having response or stable disease [38].

The efficacy of ICI monotherapy was assessed in several phase 3 trials that did not show OS benefit. Patients treated with 1L ICI monotherapy had outcomes similar to those treated with carboplatin-based chemotherapy, whereas improvement was seen in exploratory analyses of atezolizumab monotherapy in patients with PD-L1+ tumors [23,25,26]. ICI monotherapy remains an approved 1L option in the US and EU for platinum-ineligible patients or cisplatin-ineligible patients with PD-L1+ tumors, respectively [9–11,39]; however, it is not discussed in detail here.

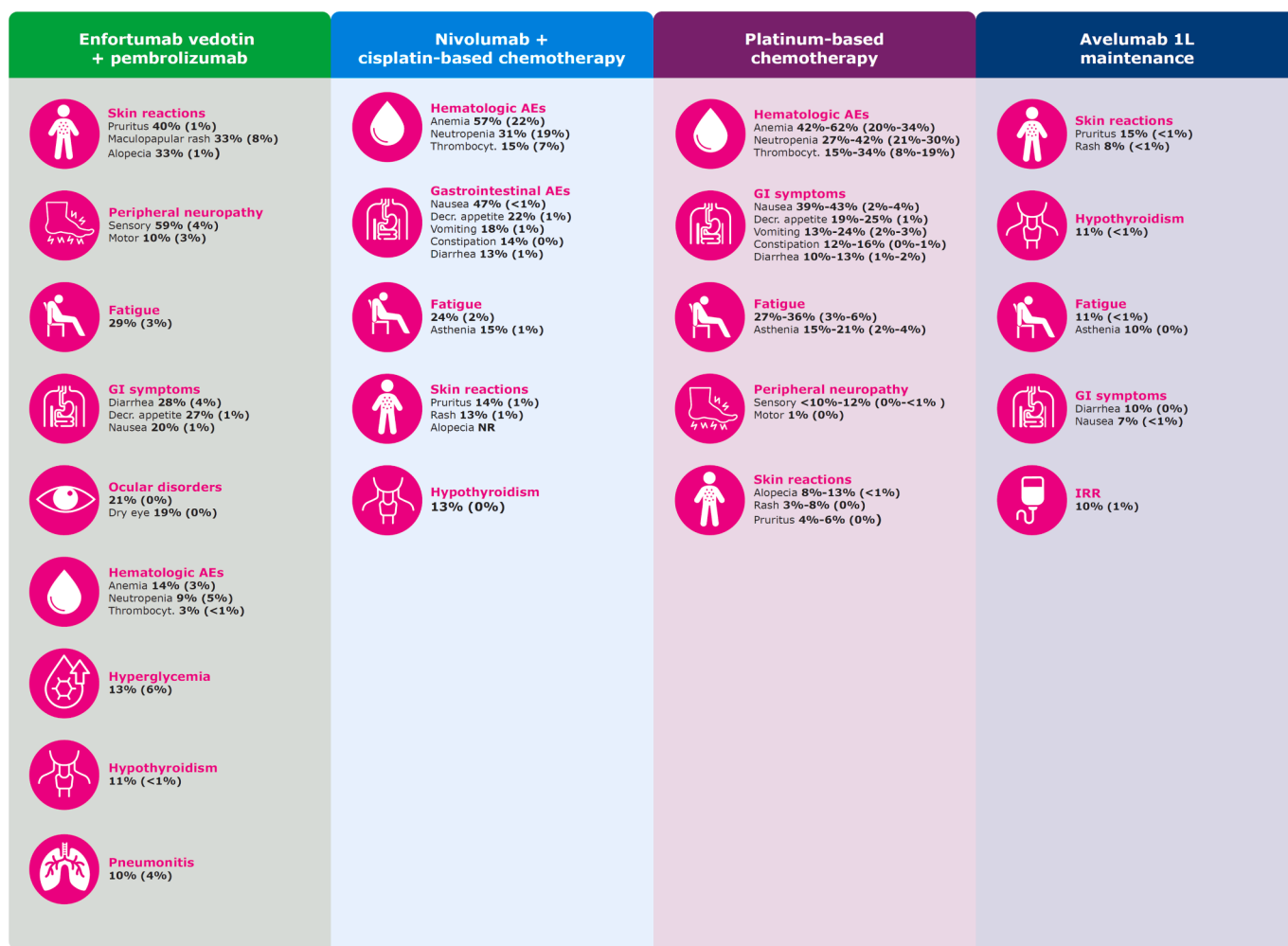


Fig. 3. Summary of the toxicity profiles of recommended 1L treatment options based on the common TRAEs reported in phase 3 trials [12,23–28,37,50]. Percentages shown indicate rates of TRAEs of any grade (grade ≥ 3). For enfortumab vedotin plus pembrolizumab, rates obtained from analyses of adverse events of special interest are reported if available. 1L, first line; AE, adverse event; decr., decreased; GI, gastrointestinal; IRR, infusion-related reaction; thrombocyt., thrombocytopenia; TRAE, treatment-related adverse event.

Safety profiles of 1L treatment options

Although efficacy and survival data are often a priority for physicians, other factors are relevant to treatment decision-making. In particular, patients often prioritize treatment experience over OS, including avoiding adverse events (AEs) and maintaining quality of life [21,40–42]; thus, the distinct toxicity profiles of the different 1L options are an important consideration (Fig. 3).

In EV-302, EVP was administered continuously until progression or unacceptable toxicity (EV on days 1 and 8; pembrolizumab on day 1 for up to 2 years; 21-day cycles) [12]. Median duration of treatment was 7.0 months (9 cycles) for EV and 8.5 months (11 cycles) for pembrolizumab. With EVP, rates of treatment-related AEs (TRAEs) of special interest of any grade (grade ≥ 3) included skin reactions in 67% (15%), peripheral neuropathy in 63% (7%), ocular disorders in 21% (0%), hyperglycemia in 13% (6%), hypothyroidism in 11% (< 1%), and pneumonitis in 10% (4%). Other common TRAEs with EVP of any grade (grade ≥ 3) included alopecia in 33% (0.5%), fatigue in 29% (3%), diarrhea in 28% (4%), and decreased appetite in 27% (1%) [12]. Among patients who had neuropathy with EVP, median time to onset (grade ≥ 2) was 6 months (range, 0.3–25) and 87% had residual neuropathy at last follow-up (grade ≥ 2 in 45%) [43]. Analyses of EV monotherapy have shown that treatment-related peripheral neuropathy is cumulative (exposure related) [44,45]. In the EVP arm of EV-302, grade ≥ 3 TRAEs occurred in 56%, and serious TRAEs occurred in 28%. TRAEs led to discontinuation of any study drug in 35% (EV alone, 30%; pembrolizumab alone, 21%), interruption in 68% (EV alone, 60%; pembrolizumab alone, 50%), and any dose reduction in 41% [12].

The safety profile of PBC (cisplatin or carboplatin plus gemcitabine) was demonstrated in control arms of several recent phase 3 trials [12,23–26]. Patients received up to 6 cycles (cisplatin/carboplatin on day 1, gemcitabine on days 1 and 8; 21-day cycles), consistent with guidelines [9,18,39]. Across these trials, the most common TRAEs of any grade (grade ≥ 3) with PBC were hematologic, including anemia in 42–62% (20–34%), neutropenia in 27–42% (21–30%), and thrombocytopenia in 15–34% (8–19%). Other common TRAEs of any grade (grade ≥ 3) were nausea in 39–43% (2–4%), fatigue in 27–36% (3–6%), decreased appetite in 19–25% (1%), vomiting in 13–24% (2–3%), constipation in 12–16% (0–1%), and diarrhea in 10–13% (1–2%). Peripheral neuropathy occurred in < 10–12% (0–< 1%). Grade ≥ 3 TRAEs occurred in 60–81%, serious TRAEs occurred in 16–26%, and TRAEs led to treatment discontinuation in 17–29% [12,23–26]. Data were not reported separately for cisplatin- vs carboplatin-based chemotherapy; however, TRAEs known to occur more often with cisplatin vs carboplatin include peripheral neuropathy, nephrotoxicity, and ototoxicity [46–48].

In JAVELIN Bladder 100, avelumab 1L maintenance treatment was administered every 2 weeks until progression or unacceptable toxicity in patients without progression after 4–6 cycles of PBC [27,28]. The median duration of avelumab treatment was 5.8 months (median 11.5 infusions) [49]. The most common TRAEs of any grade with avelumab were pruritus (15%), hypothyroidism (11%), fatigue (11%), asthenia (10%), diarrhea (10%), and infusion-related reaction (IRR; 10%). Grade ≥ 3 TRAEs occurred in 19% of patients; the most common were increased lipase (3%), increased amylase (2%), and IRR (1%) [28,50]. Premedication for IRRs involves antihistamine and acetaminophen (paracetamol) before the first 4 infusions of avelumab. Serious TRAEs occurred in 10% and TRAEs led to discontinuation in 12%. In a long-term analysis from JAVELIN Bladder 100, the safety profile of avelumab in the subgroup treated for ≥ 1 year was consistent with the overall population [28].

In CheckMate-901, cisplatin-gemcitabine was administered for up to six 21-day cycles, and nivolumab was administered continuously until progression or unacceptable toxicity (on day 1 of chemotherapy cycles, then every 4 weeks for up to 2 years). Median duration of treatment in the nivolumab plus cisplatin-gemcitabine arm was 7.4 months (vs 3.7

months in the control arm). Common TRAEs were consistent with expectations for combined cisplatin-gemcitabine/ICI treatment. The most common TRAEs of any grade (grade ≥ 3) included hematologic AEs: anemia in 57% (22%), neutropenia in 31% (19%), and thrombocytopenia in 15% (7%); and gastrointestinal AEs: nausea in 47% (< 1%), vomiting in 18% (1%), constipation in 14% (0%), and diarrhea in 13% (1%). Other common TRAEs of any grade (grade ≥ 3) included fatigue in 24% (2%), decreased appetite in 22% (1%), pruritus in 14% (1%), rash in 13% (1%), and hypothyroidism in 13% (0%). Grade ≥ 3 TRAEs occurred in 62% (serious AEs not reported) and TRAEs led to discontinuation in 21%. Peripheral neuropathy data were not reported (< 10% incidence) [37].

Given widespread use of PBC and ICIs, healthcare providers are likely to have extensive experience in preempting, identifying, and managing their associated toxicities. Incorporating new treatment options such as EVP requires a learning curve for managing and preventing new AEs, particularly potentially serious toxicities with unpredictable onset (eg, neurotoxicity, skin toxicity, and hyperglycemia) [15,51,52]. Understanding risk factors, effective monitoring, patient/caregiver education, and early recognition of toxicities is crucial, and further research is needed. For example, a prospective observational study in Germany (P-EVOLUTION) is assessing the incidence and severity of peripheral neuropathy with EVP and treatment regimen adjustments [53].

Quality of life with 1L treatment options

In phase 3 trials, it is important to assess health-related quality of life via patient-reported outcomes (PROs) to ensure that treatment has no significant detrimental effects, and that OS benefits represent “quality survival”.

In the EV-302 trial, PRO analyses showed that both EVP and PBC (up to 6 cycles) had no detrimental impact on quality of life or functioning. Time to pain progression, measured using the Brief Pain Inventory Short Form instrument, was similar with EVP vs PBC (median, 14.2 vs 10.0 months; HR, 0.92; $p = 0.48$). Patients with moderate/severe pain at baseline treated with EVP had a > 2-point improvement in worst pain from week 3–26. Global health status/quality of life score (European Organisation for Research and Treatment of Cancer quality of life questionnaire [EORTC QLQ-C30]) worsened at week 3 with EVP treatment, and from week 1–17 with PBC, before returning to baseline. Time to confirmed deterioration was similar with EVP vs PBC (median, 5.9 vs 3.2 months; HR, 0.98) [12,54]. Studies of long-term quality of life with EVP treatment are needed to assess any impact of persistent TRAEs.

PRO analyses from the JAVELIN Bladder 100 trial showed that adding avelumab to BSC in patients without progression after 1L PBC had no detrimental impact on quality of life, which is particularly important for maintenance treatment [55,56]. PROs were measured using a bladder cancer-specific instrument (National Comprehensive Cancer Network/Functional Assessment of Cancer Therapy Bladder Symptom Index-18) and a general instrument (EuroQol EQ-5D [EQ-5D-5L]). In general, PROs were similar in the avelumab plus BSC and BSC alone arms, with no notable differences observed in disease-related symptoms (physical and emotional) or overall well-being measures. Post hoc analyses suggested a reduction in pain and an increase in being bothered by side effects in the avelumab arm; however, this did not correspond to changes in overall quality of life [55]. In long-term analyses, prolonged avelumab treatment was associated with stable PROs, including in patients treated for ≥ 1 year [56]. Quality of life was also examined in a post hoc analysis of quality-adjusted time without cancer symptoms or toxicity (Q-TWiST), an integrated measure that incorporates efficacy, safety, and PROs. Mean Q-TWiST was 22% longer with avelumab plus BSC vs BSC alone, demonstrating a net benefit of treatment [57].

In CheckMate-901, the addition of nivolumab to cisplatin-gemcitabine had a minimal effect on PROs according to EORTC QLQ-

C30 and EQ-5D-5L instruments, with noninferiority shown up to week 16 in key measures, including physical functioning, global health status, and fatigue [58].

Patient priorities for treatment

Individual patients may have different priorities for treatment, such as maximizing disease reduction or survival or minimizing toxicity and maintaining quality of life. This difference in priorities was shown by a study of treatment-attribute preferences among 151 oncologists and 150 patients with UC. Whereas most oncologists prioritized OS improvement, most patients prioritized treatment experience (ie, fewer grade 3/4 TRAEs and fewer medications) [40]. EVP represents the first instance of indefinite chemotherapy for advanced UC [13], and studies assessing the optimal number of EV cycles are required. Although all recommended 1L regimens require prolonged treatment, continuous ICI treatment is likely to be more tolerable than continuous EV treatment, as shown by treatment durations for EV vs pembrolizumab in the EV-302 trial (median, 7.0 vs 8.5 months, respectively) [12]. It has been discussed that grade ≥ 2 skin toxicities associated with EVP and peripheral neuropathy of any grade associated with EVP or cisplatin may substantially impact patients' and carers' quality of life [13,51,59]. Notably, a study of patient preferences for 1L treatment of advanced UC found that patients were willing to trade a lower probability of response for a reduced risk of TRAEs, including peripheral neuropathy or mild-to-moderate skin reactions, or reduced cancer-related pain [42]. Logistical aspects of treatment should be discussed with patients, including the number/frequency of infusions requiring travel and clinic attendance. Additionally, cultural differences among countries or differences in patient understanding may influence patient priorities for treatment. These various factors highlight the importance of communication between physicians and patients for informed decision-making [41].

Patient characteristics

Patients with various comorbidities may be less suited to receiving specific 1L treatments owing to their different toxicity profiles. Clinical trials of EV excluded patients with preexisting peripheral neuropathy (grade ≥ 2) or uncontrolled diabetes (hemoglobin A_{1c} $\geq 8\%$ or $\geq 7\%$ with diabetes symptoms) [12,60,61], and clinical trials of ICIs excluded patients with active autoimmune disease or conditions requiring systemic treatment with corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications [12,27,37], thus close monitoring is required when treating these patients. In an article discussing suitability for EVP based on trial exclusion criteria and toxicity data, authors proposed EV-ineligible criteria (EVITA), suggesting that patients may not be optimal candidates for EVP if they meet ≥ 2 of the following: hemoglobin A_{1c} $\geq 8\%$ (or baseline glucose > 150 mg/dL); grade ≥ 2 sensory or motor neuropathy; any corneal or retinal abnormality; creatinine clearance/glomerular filtration rate ≤ 45 mL/min; or Eastern Cooperative Oncology Group performance status ≥ 2 [19]. Others have argued that fixed ineligibility criteria for EVP would be restrictive and that prescriber education and knowledge sharing to inform clinical judgment are more relevant [20]. However, adaptation of eligibility criteria for treatment based on individual physician experience is standard practice, and it has been highlighted that the potential to build experience in managing EVP-related toxicities may be challenging for physicians working outside of academic institutions or specialized centers, who might only treat a few patients with advanced UC each year, and for whom defined eligibility criteria could provide context and structure for individualized treatment [21].

Several criteria are used to assess eligibility/ineligibility for cisplatin or any platinum chemotherapy, including renal function, performance status, and the presence/severity of peripheral neuropathy, heart failure, or hearing loss [16]. In EV-302, which enrolled only platinum-eligible patients, EVP showed similar efficacy in subgroups classified

as cisplatin-eligible or -ineligible [12]; in JAVELIN Bladder 100, which enrolled only platinum-treated patients, avelumab 1L maintenance showed similar efficacy and safety profiles in subgroups previously treated with 1L cisplatin or carboplatin [29]. Nivolumab plus cisplatin-gemcitabine is approved for cisplatin-eligible patients only [8,9].

Patient fitness is relevant when selecting 1L treatment. In patients at greater risk of treatment-related toxicity based on geriatric assessment tools [6], minimizing the potential for toxicities is likely to be a priority, particularly those that affect physical function or increase the risk of falls (eg, neuropathy). Alternatively, fitter patients may prefer to avoid toxicities that could impact quality of life (eg, neuropathy, alopecia, or gastrointestinal events). Patient chronological age should not be used to determine eligibility for treatment. However, a recent survey of European physicians in 5 countries found that advanced age was the most common reason for not administering systemic treatment [62]. Treatment decisions based on age may inappropriately exclude eligible patients from potentially beneficial treatment, given the older age profile of the UC population. In EV-302, consistent efficacy benefits were reported with EVP vs PBC in patients aged < 65 and ≥ 65 years [12]. In JAVELIN Bladder 100, consistent efficacy benefits and acceptable safety were reported with avelumab plus BSC vs BSC alone in subgroups aged ≥ 65 to < 74 years, ≥ 75 years, and ≥ 80 years [63]. In CheckMate-901, efficacy analyses favored nivolumab plus cisplatin-gemcitabine vs cisplatin-gemcitabine alone in patients aged 65 to < 75 years and ≥ 75 years [37].

Pneumonitis is an uncommon TRAE of ICIs (any grade in $< 5\%$; grade ≥ 3 in $\leq 1\%$) but appears to be more common with EVP (any grade in 9–10%; grade ≥ 3 in 4–5%) [12,27,61,64]. Risk factors for ICI-associated pneumonitis include a prior history of asthma, smoking, or curative-intent radiotherapy [64]; patients with these characteristics should be closely monitored for respiratory changes with any 1L treatment.

Patients with a high body mass index (BMI; ≥ 30 kg/m²) have appeared to be at increased risk of skin toxicities with EV and hyperglycemia with EVP [65,66]. In contrast, in trials of 1L cisplatin-based chemotherapy for advanced UC, no significant differences in AEs or outcomes were observed across BMI categories [67]. Similarly, in a post hoc analysis from JAVELIN Bladder 100, long-term efficacy and safety of avelumab 1L maintenance in patients with a high BMI were generally consistent with overall trial data [68]. No BMI analyses have been reported for nivolumab plus cisplatin-gemcitabine.

Disease characteristics

Patients with visceral or liver metastases have a worse prognosis [69–72]; thus, maximizing efficacy with 1L treatment may be a priority in these patients. Objective response may also be a higher priority in patients with symptomatic disease. ORRs were higher with EVP or nivolumab plus cisplatin-gemcitabine vs PBC/cisplatin-gemcitabine alone in phase 3 trials [12,37]. In EV-302, OS, PFS, and ORR improvements with EVP in subgroups with visceral or liver metastases were generally consistent with benefits in the overall population [73]. In CheckMate-901, the OS improvement with nivolumab plus cisplatin-gemcitabine vs cisplatin-gemcitabine alone in patients with visceral metastases was consistent with data in the overall population, whereas PFS benefits were lower in this subgroup [37]. In JAVELIN Bladder 100, OS and PFS analyses favored avelumab plus BSC vs BSC alone in patients with or without visceral metastases, but benefits were more pronounced in patients with nonvisceral metastases [28,74].

Low tumor burden (eg, lymph node-only disease) and nonvisceral metastases have been associated with a more favorable prognosis [69,70,75]. Subgroup analyses have shown that patients with these disease characteristics had prolonged OS with all recommended 1L options [73,76,77]. In EV-302, median OS with EVP vs PBC in patients with lymph node-only disease was not reached vs 27.5 months, respectively (HR, 0.46 [95% CI, 0.27–0.78]) [73]. In CheckMate-901,

median OS with nivolumab plus cisplatin-gemcitabine vs cisplatin-gemcitabine alone in cisplatin-eligible patients with lymph node–only disease was 46.3 vs 24.9 months, respectively (HR, 0.58 [95% CI, 0.34–1.00]) [77]. In JAVELIN Bladder 100, median OS from start of maintenance with avelumab plus BSC vs BSC alone in patients with lymph node–only disease without progression after 1L PBC was 31.9 vs 22.7 months (HR, 0.86 [95% CI, 0.51–1.47]), and in patients with nonvisceral metastases (including bone; assessed at start of 1L chemotherapy) was 31.4 vs 17.1 months (HR, 0.60 [95% CI, 0.45–0.79]), respectively [76]. Because patients with a low tumor burden may eventually receive multiple lines of treatment, minimizing toxicity during 1L treatment may have greater relevance in these patients. Moreover, in patients with pelvic lymph node–only disease who have a partial or complete response to 1L treatment and are recommended to undergo radical bladder chemoradiation or cystectomy as consolidation, minimizing 1L treatment toxicity is particularly relevant.

Upper-tract primary tumors present a unique challenge due to their aggressive nature [3,4]. However, analyses from EV-302 and the real-world AVENANCE study showed no differences in efficacy of their respective treatment regimens between subgroups with upper or lower tract primary tumors [12,35]. In ≈20% of patients, UC tumors include some non-UC variant histology [78]. Analyses from JAVELIN Bladder 100 showed consistent efficacy with avelumab 1L maintenance among patients with mixed histology tumors (UC with squamous, glandular, or variant) and the overall population [79]. In real-world studies of later-line EV treatment, outcomes were similar among patients with pure or mixed UC, except for tumors with neuroendocrine features, which had worse outcomes [80]; data have not yet been reported for EVP or nivolumab plus cisplatin-gemcitabine.

Subsequent treatment

Despite developments in 1L treatment, most patients eventually have disease progression. Because of patient “attrition” between treatment lines and the inability to predict which patients will be able to receive next-line treatment, considerations regarding subsequent treatment should not affect benefit-risk assessments for 1L treatment. However, options for next-line treatment are a consideration in the overall patient journey.

At present, limited data are available to assess optimal next-line treatment after 1L EVP [59,81]. Treatment guidelines recommend second-line (2L) PBC (without maintenance) or erdafitinib in eligible patients (tumors with selected *FGFR3* alterations) where available [8,9]. Data are needed to assess whether avelumab maintenance (ICI rechallenge) is beneficial in patients without progression following 2L PBC. At data cutoff in the EVP arm of the EV-302 trial, 32.6% were still receiving EVP, and 31.7% had received 2L treatment; thus, 35.7% discontinued without 2L treatment. Of patients who received 2L treatment, 79% received PBC [12]. Outcomes in subgroups with different subsequent treatments have not yet been reported. Persistent peripheral neuropathy with EVP may limit the ability to receive subsequent chemotherapy (cisplatin or taxanes) [44,81]. Real-world studies of subsequent treatment after EVP are needed.

In patients who have received 1L PBC with avelumab 1L maintenance, or 1L nivolumab plus cisplatin-gemcitabine, preferred 2L options in treatment guidelines are EV monotherapy or erdafitinib in eligible patients [8,9]. After long-term follow-up in the avelumab arm of JAVELIN Bladder 100, 12.3% were still receiving avelumab, 52.9% had received 2L treatment, and 34.9% had discontinued without 2L treatment. The most common 2L treatment was PBC (41% of patients who received 2L treatment). Second-line EV or erdafitinib monotherapy was only received by 5% and 1% of patients, respectively [82], reflecting available options when the trial was conducted. Since avelumab was approved, several real-world studies have provided additional data about treatment sequencing. Across 3 studies, median OS with 2L EV after 1L PBC and avelumab 1L maintenance (11.2–13.3 months)

[31,83,84] was similar to median OS in the EV-301 phase 3 trial of EV monotherapy in patients with prior 1L PBC and 2L ICI treatment (12.9 months) [60]. Furthermore, in a post hoc analysis from the AVENANCE real-world study of avelumab 1L maintenance (N = 595), median OS from the start of avelumab treatment by 2L treatment was 36.0 months in the 2L EV subgroup (n = 56), 16.7 months in the 2L PBC subgroup (n = 81), and 13.6 months in the 2L nonplatinum chemotherapy subgroup (n = 163). Median OS from the start of 1L PBC in the subgroup with 2L EV treatment in this selected population without progression after 1L chemotherapy was 41.5 months; however, this analysis should be interpreted with caution because of its known limitations, particularly immortal time bias associated with time on 1L PBC prior to avelumab [35]. At data cutoff in the nivolumab arm of CheckMate-901, 7.6% were still receiving study treatment, and 35.5% had received 2L treatment; thus, 56.9% discontinued without 2L treatment. Of patients who received 2L treatment, PBC was most common (23%), and 2L EV or erdafitinib was received by 9% and 6%, respectively [37].

In patients with progression following 1L PBC (without ICI treatment), pembrolizumab monotherapy is the preferred 2L option in treatment guidelines, and later-line treatment options are the same as those with prior PBC and avelumab or nivolumab treatment [8,9,18,39].

Sacituzumab govitecan (antibody-drug conjugate targeted to Trop-2) was previously a treatment option for patients with prior PBC and PD-(L) 1 inhibitor treatment following accelerated approval by the US Food and Drug Administration. However, approval was withdrawn following the lack of OS benefit reported in the TROPiCS-04 phase 3 trial of sacituzumab govitecan vs physician’s choice of single-agent chemotherapy [85]. Trastuzumab deruxtecan (antibody-drug conjugate targeted to HER2) has received accelerated approval in the US for previously treated patients with advanced/metastatic HER2+ solid tumors (immunohistochemistry 3+) who have no satisfactory alternative treatment options based on the DESTINY-PanTumor02 phase 2 trial [86, 87], and is therefore an additional option for HER2+ UC.

With continued treatment developments, patients with advanced UC are increasingly likely to have received prior treatment for muscle-invasive disease. Options recommended by guidelines include neoadjuvant cisplatin-based chemotherapy, adjuvant nivolumab, and adjuvant cisplatin-based chemotherapy in those with no prior neoadjuvant treatment [9,39]. Additionally, positive outcomes have been reported from phase 3 trials of adjuvant pembrolizumab (AMBAS-SADOR) and perioperative durvalumab with neoadjuvant cisplatin-based chemotherapy (NIAGARA) [88,89]. Studies are needed to assess whether treatment for muscle-invasive disease affects outcomes with subsequent treatment. In recent phase 3 trials of 1L treatment for advanced UC, patients who had received neoadjuvant or adjuvant treatment within 12 months were excluded [12,27,37]. In CheckMate-901, subgroup analyses of OS favored nivolumab plus cisplatin-gemcitabine vs cisplatin-gemcitabine alone in patients with or without previous systemic treatment (neoadjuvant or adjuvant), although details of previous treatment were not reported [77]; no analyses have been reported from phase 3 trials of other 1L regimens. In clinical practice, in patients who have disease progression after adjuvant ICI treatment, choice of subsequent treatment should be guided by timing of progression. A proposed approach is that if disease progression occurs within 1 year of PBC and during adjuvant ICI treatment, or within 6 months of completing adjuvant ICI treatment, EV monotherapy is a reasonable next option. If disease progression occurs > 6 months after completing adjuvant ICI treatment, all recommended 1L options should be considered [90]. This approach enables individualized treatment based on the patient’s clinical course.

Biomarkers

EVP, PBC with avelumab maintenance, and nivolumab plus cisplatin-gemcitabine are all approved and recommended irrespective of biomarker status [8,9,18,39]. PD-L1 status does not predict treatment

benefit [12,28,37,73]; nonetheless, PD-L1+ status is required for access to avelumab 1L maintenance in selected countries. Additionally, use of 1L ICI monotherapy where approved in cisplatin-ineligible patients requires PD-L1+ status. For later-line erdafitinib or trastuzumab deruxtecan treatment, biomarker assessment (*FGFR3* alterations and HER2 expression, respectively) is required to determine eligibility [9].

Preclinical studies have shown that EV activity requires expression of Nectin-4, which is expressed at moderate-to-high levels in a majority of UC tumors, although expression may decrease during metastatic progression [91–93]. Clinical studies supporting approvals of EV enrolled biomarker-unselected populations [12,60,61,65]. In exploratory analyses from EV-302, median OS with 1L EVP vs PBC in subgroups with low, medium, or high overall Nectin-4 expression (H-score < 150, 150 to < 225, or 225–300, respectively) was 18.4 vs 10.4 months (HR, 0.53 [95% CI, 0.27–1.05]), 25.4 vs 11.8 months (HR, 0.44 [95% CI, 0.22–0.86]), and 31.5 vs 17.1 months (HR, 0.47 [95% CI, 0.36–0.61]), respectively [94]. Other analyses have suggested that low membranous Nectin-4 expression (H-score < 100 vs 100–300) and absence of *NECTIN-4* amplification predict lower ORR and shorter OS with later-line EV monotherapy for advanced UC [92]; however, further analyses are needed.

Treatment access and cost

Access to treatment depends on approval and reimbursement in individual countries. The high cost (“financial toxicity”) of EVP has been widely discussed [13,14,44]. According to publicly available data, approximate US costs per cycle for EVP are \$38,000 vs \$300 for cisplatin-gemcitabine [13]. In a health-economic analysis that included drug acquisition, treatment administration, and disease/AE management, estimated annual treatment costs were 3.8-fold higher with EVP vs PBC followed by avelumab 1L maintenance (\$455,630 vs \$120,253) [14,95]. Additionally, the incremental cost-effectiveness ratio of EVP vs PBC in the US and China was estimated to be \$558,973 and \$232,256 per quality-adjusted life-year, respectively, which was not considered cost effective at standard willingness-to-pay thresholds [96,97]. In a separate analysis that compared cost effectiveness vs avelumab 1L maintenance, estimated incremental cost-effectiveness ratios in Germany and the US were €216,140 and \$700,448 for EVP, and €87,340 and \$281,142 for nivolumab plus cisplatin-gemcitabine, respectively [98]. Furthermore, treatment costs vary considerably between countries, and differences in healthcare systems (eg, single- vs multipayer; direct costs to patients) can also affect utilization. While access and cost barriers remain in many countries, the existence of three 1L treatment options with improved efficacy vs PBC alone increases the likelihood of access to at least one life-prolonging option.

Conclusions

An unprecedented range of systemic treatment options are available for patients with advanced UC. In the 1L setting, EVP is standard of care, and alternative options are PBC followed by avelumab 1L maintenance in patients without progression or nivolumab plus cisplatin-gemcitabine followed by nivolumab monotherapy in cisplatin-eligible patients. ICI monotherapy is an option for selected patients. Given the heterogeneity of patients with advanced UC encountered in day-to-day clinical practice, a “one-size-fits-all” approach to treatment is unlikely to be optimal, and 1L options other than EVP may be more appropriate in individual patients. This might include frailer patients, those with specific comorbidities, and those with strong preferences about toxicity profile. Real-world studies assessing outcomes with different options in patients with characteristics of interest would be informative, in addition to prospective de-escalation studies for EV. The differing costs of each treatment option will determine access in individual countries. Overall, the availability of several treatments that prolong survival offers the opportunity for individualized 1L treatment aligned to patient

characteristics and preferences. Patients and physicians should discuss the benefit-risk balance of each option in detail to enable shared and informed decision-making.

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Declaration of competing interest

The authors declare that they have no known competing financial

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Glossary

1L: first line

2L: second line
 AE: adverse event
 BMI: body mass index
 BSC: best supportive care
 CR: complete response
 EORTC: European Organisation for Research and Treatment of Cancer
 EV: enfortumab vedotin
 EVITA: EV-ineligible criteria
 EVP: EV plus pembrolizumab
 HR: hazard ratio
 ICI: immune checkpoint inhibitor
 IRR: infusion-related reaction
 ORR: objective response rate
 OS: overall survival
 PBC: platinum-based chemotherapy
 PFS: progression-free survival
 PRO: patient-reported outcome
 Q-TWIST: quality-adjusted time without cancer symptoms or toxicity
 TRAE: treatment-related adverse event
 UC: urothelial carcinoma.