Received: 23 July 2021 | Accepted: 27 January 2022 | Published on: 3 March 2022

DOI: 10.1111/ajco.13765

REVIEW

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# Clinical evidence and insights supporting the use of avelumab first-line maintenance treatment in patients with advanced urothelial carcinoma in the Asia-Pacific region

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**Funding information**
Pfizer; Merck (CrossRef Funder ID: 10.13039/100009945)

## Abstract

Until recently, international and Asia-specific guidelines for advanced urothelial carcinoma (UC) recommended first-line (1L) platinum-based chemotherapy, followed by second-line (2L) anti-PD-1 or anti-PD-L1 immune checkpoint inhibitor (ICI) therapy where possible, or 1L ICI therapy in cisplatin-ineligible patients with PD-L1+ tumors. However, long-term outcomes remain poor and only a minority of patients receive 2L therapy. The JAVELIN Bladder 100 trial—which assessed avelumab (anti-PD-L1 antibody) as 1L maintenance therapy plus best supportive care (BSC) versus BSC alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy—is the only phase 3 trial of ICI-based treatment in the 1L setting to show significantly improved overall survival, and this treatment approach is now recommended in updated treatment guidelines. Available data from the trial suggest that efficacy and safety in patients enrolled in the Asia-Pacific region were similar to findings in the overall population. In this review, we discuss the treatment of advanced UC, with a specific focus on studies in the Asia-Pacific region, and summarize key findings supporting the use of avelumab 1L maintenance as a standard of care in this setting both in cisplatin-eligible and cisplatin-ineligible patients and irrespective of PD-L1 status.

**KEYWORDS**
Asia-Pacific, avelumab, checkpoint inhibitor, immunotherapy, urothelial carcinoma

## 1 | EPIDEMIOLOGY OF UROTHELIAL CANCER IN THE ASIA-PACIFIC REGION

Urothelial carcinoma (UC), which originates in the cells lining the bladder and urinary tract, is a commonly occurring cancer. Bladder cancer, which accounts for >90% of cases of UC, is the 11th most common cancer worldwide and the 14th most common cancer in Asia. Approximately 573,000 new cases and approximately 213,000 new deaths were expected in 2020 globally (Table 1).[1] Incidence and mortality rates of bladder cancer vary significantly across geographic regions. Compared with Western countries, where the incidence is highest, incidence and mortality rates are slightly lower in Australia/New Zealand and lower still in Asian countries (including Eastern Asia and India; Figure 1). This variability is largely due to variations in environmental

**TABLE 1** Estimated incidence and mortality in patients with bladder cancer in 2020 by pooled geographic region

| | Number | Crude rate[a] | Age-standardized rate[a] | Cumulative lifetime risk[b] |
|---|---|---|---|---|
| Incidence | | | | |
| Asia | 208,091 | 4.5 | 3.6 | 1.16 |
| Europe | 203,983 | 27.2 | 11.3 | 3.31 |
| Northern America | 89,997 | 24.4 | 10.9 | 3.59 |
| Latin America and the Caribbean | 33,840 | 5.2 | 4.0 | 1.36 |
| Africa | 33,196 | 2.5 | 4.5 | 1.35 |
| Oceania | 4,171 | 9.8 | 5.3 | 2.04 |
| Mortality | | | | |
| Asia | 90,610 | 2.0 | 1.5 | 0.69 |
| Europe | 67,289 | 9.0 | 3.0 | 1.31 |
| Northern America | 21,045 | 5.7 | 2.1 | 1.04 |
| Africa | 18,747 | 1.4 | 2.7 | 1.14 |
| Latin America and the Caribbean | 13,100 | 2.0 | 1.5 | 0.65 |
| Oceania | 1,745 | 4.1 | 1.9 | 1.03 |

Data source: International Agency for Research on Cancer. Cancer Today. http://gco.iarc.fr/today. Accessed June 3, 2021.
[a]Annual rates per 100,000 individuals at risk.
[b]Of 100 individuals.

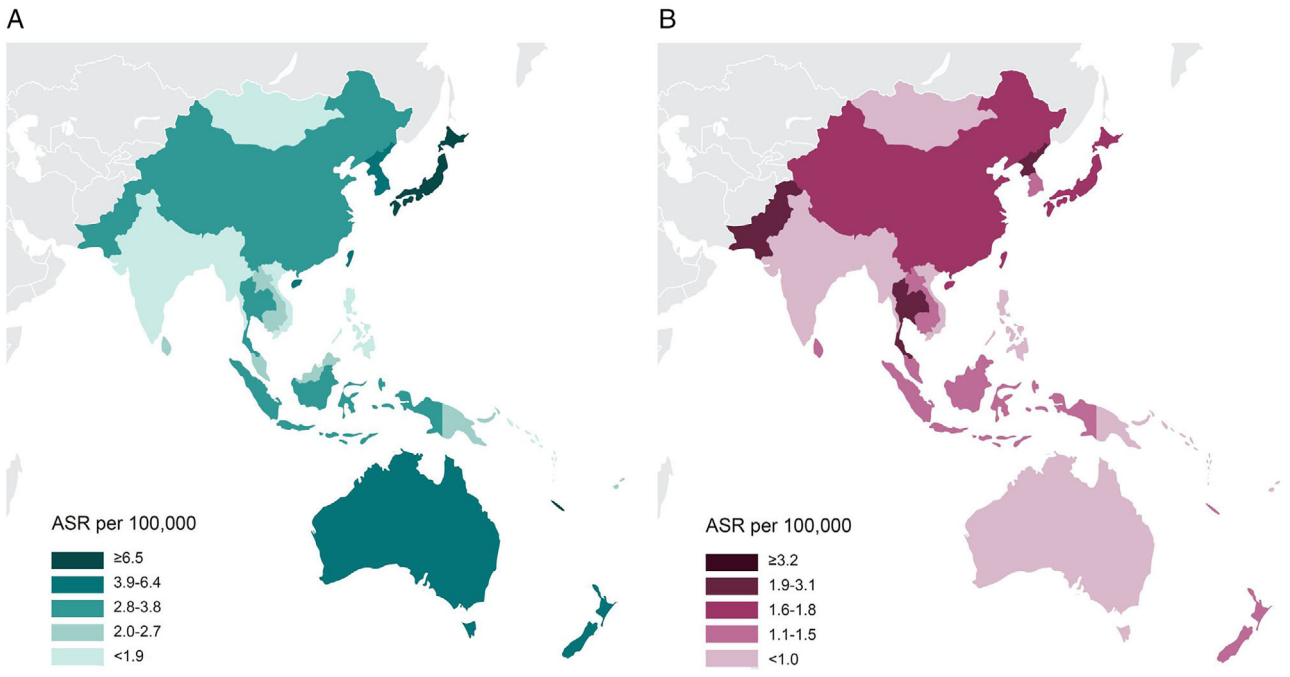


**FIGURE 1** Estimated age-standardized (A) incidence rates and (B) mortality rates of bladder cancer in the Asia-Pacific region (2020 data). ASR, age-standardized rate. Data source: International Agency for Research on Cancer. Cancer Today. http://gco.iarc.fr/today. Accessed June 3, 2021 [Colour figure can be viewed at wileyonlinelibrary.com]

and intrinsic risk factors. Among environmental risk factors, tobacco smoking accounts for approximately 50% of diagnoses[2]; other environmental risk factors include exposure to workplace chemicals or arsenic in drinking water, and chronic infections/conditions affecting the urinary tract.[3] Intrinsic risk factors associated with a higher incidence include older age, male sex, and White ethnicity.[4] Incidence rates of bladder cancer are generally increasing over time across all regions, which is consistent with an aging population, whereas mortality trends

vary by region. In patients from Eastern Asia, South Central Asia, and Australia/New Zealand, mortality-to-incidence ratios for 2020 in males were 0.40, 0.56, and 0.29, respectively, compared with 0.21 in North America and 0.29 in Europe, with similar data observed for females.[5]

Patients with unresectable locally advanced or metastatic UC (generally referred to as advanced UC) have a poor prognosis, with an estimated 5-year survival rate of ≈6%.[6] Established risk factors for shorter overall survival (OS) include an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 and presence of visceral metastases, which are factors used to determine the Bajorin risk score.[7] Other variables associated with shorter OS that have been identified in subsequent analyses of real-world patients with advanced UC include higher white blood cell count, lower body mass index, Hispanic/Latino ethnicity, and prior perioperative chemotherapy.[8] It has also been shown that prognostic models for advanced UC, which were developed using data from Western patients, were valid in a Japanese real-world population.[9]

Studies in UC suggest that the prevalence of prognostic factors varies between Asian and non-Asian patients. Across all regions, UC tumors originate much less frequently in the upper urinary tract (renal pelvis or ureter; <10%) than in the lower urinary tract (bladder or urethra; >90%); however, the proportion of UC cases due to upper urinary tract tumors appears to be higher in some Asian countries than in Western countries.[10,11] Studies have suggested a link between this higher prevalence of upper urinary tract UC and increased exposure to environmental risk factors in Asian countries, specifically arsenic-contaminated water and aristolochic acid in Chinese traditional medicines.[12–15] Furthermore, in an exploratory analysis of pooled data from phase 2/3 trials in patients with metastatic UC ($N = 600$), which included 81 Asian patients, Asian patients had higher frequencies of bone metastases and renal dysfunction in addition to a higher frequency of upper urinary tract primary tumors.[16]

## 2 | ESTABLISHED FIRST-LINE TREATMENT FOR ADVANCED UC

Advanced UC is considered a chemotherapy-sensitive disease, although only a small proportion experience a long-term benefit. Platinum-based chemotherapy has been considered standard-of-care first-line (1L) treatment for advanced UC for >20 years, with 65%–75% of patients achieving an objective tumor response or having stable disease.[17–19] International guidelines, including those developed by the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and European Association of Urology (EAU), in addition to Asia-specific guidelines, including those from the Japanese Urological Association (JUA) and the National Health Commission of the People's Republic of China, recommend tailored treatment with either cisplatin- or carboplatin-based combinations as a standard of care according to whether patients are eligible or ineligible for 1L cisplatin-based chemotherapy.[20–24] Factors used to determine cisplatin ineligibility include renal impairment, poor performance status, hearing loss, peripheral neuropathy, and symptomatic heart failure.[20,21,25–27] Recommended 1L treatment regimens for cisplatin-eligible patients include up to six cycles of cisplatin plus gemcitabine or a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC), generally administered as a dose-dense regimen.[20] In a phase 3 trial of cisplatin plus gemcitabine versus MVAC in patients with advanced UC, the objective response rate (ORR) was 49% in the cisplatin plus gemcitabine arm and 46% in the MVAC arm[17]; however, despite the high proportion of responders, median OS was only 14–15 months in both arms and only ≈10% of patients remained alive and progression free after 5 years (median progression-free survival [PFS] was 8 months in both arms).[17,28] In a retrospective Taiwanese study, 203 patients with metastatic UC were treated with cisplatin plus gemcitabine or MVAC. For patients with upper tract tumors, ORRs were 46% versus 61%, median PFS was 4.0 versus 7.3 months, and median OS was 10.5 and 17.0 months, respectively; and for patients with UC of the bladder, ORRs were 60% versus 64%, median PFS was 6.3 versus 6.8 months, and median OS was 13.0 versus 16.3 months.[29] Additional data suggest that long-term outcomes with 1L cisplatin-based chemotherapy for advanced UC are similar between Asian and non-Asian patients. In a pooled analysis of patients who received cisplatin-based chemotherapy in phase 2/3 trials, the ORR was 64% in Asian patients versus 46% in non-Asian patients; however, median PFS was 8.0 versus 8.0 months and median OS was 15.5 versus 13.3 months ($P = 0.122$), respectively. In a multivariable analysis, ethnicity (Asian vs. non-Asian) was not significantly associated with survival.[16]

In patients who are ineligible for cisplatin-based chemotherapy, who account for approximately 50% of those receiving 1L therapy, guidelines recommend 1L chemotherapy with carboplatin plus gemcitabine.[20,30,31] In subgroups of patients who received carboplatin plus gemcitabine in the control arms of recent phase 3 trials, who would be expected to be less fit than cisplatin recipients, median OS was 12.3–13.0 months,[32,33] indicating that carboplatin plus gemcitabine is an active regimen in this setting.

Although up to 6 cycles of platinum-based chemotherapy is recommended by treatment guidelines for patients with advanced UC,[20] the optimal number is unknown. A retrospective analysis that assessed the association between the number of cycles of platinum-based chemotherapy (3–5 cycles [median, 4] vs. 6–9 cycles [median, 6]) and patient outcomes in an international population ($N = 472$) concluded that four cycles of 1L platinum-based chemotherapy did not significantly compromise OS and may avoid cumulative toxicity.[34] Similarly, in a retrospective analysis of 61 Japanese patients with advanced UC, the median number of cycles of cisplatin plus gemcitabine received was 4, and the number of cycles (≤4 vs. > 4) was found not to be an independent prognostic factor.[35] To provide a prospective comparison, an ongoing phase 3 study in Korea (FOCUS; NCT03296306) is comparing OS with 4 versus 6 cycles of cisplatin-based chemotherapy in patients with advanced UC.

Patients who have disease progression following 1L chemotherapy for advanced UC often have a high symptom burden and experience rapid clinical deterioration.[36,37] Consequently, real-world studies performed in U.S. and European populations found that only

27%–40% of patients initiating 1L chemotherapy subsequently received 2L treatment.[38–45] UC is considered an immunogenic tumor, which has led to various trials of immune checkpoint inhibitors (ICIs; including avelumab, nivolumab, and pembrolizumab), initially as second-line (2L) treatment for patients with advanced UC that had progressed following platinum-containing chemotherapy.[46–48] In addition, atezolizumab and pembrolizumab were approved in the United States and Europe for use as 1L treatment in the specific population of cisplatin-ineligible patients with advanced UC with programmed cell death 1 ligand 1–positive (PD-L1+) tumors (or platinum-ineligible patients in the United States).[20,21,49] These approvals were based on data from two single-arm phase 2 trials, IMvigor210 (atezolizumab) and KEYNOTE-052 (pembrolizumab), which showed ORRs of 23% (95% confidence interval [CI], 16%–31%) and 28.6% (95% CI, 24.1%–33.5%) and median OS of 15.9 months (95% CI, 10.4 months to not estimable) and 11.3 months (95% CI, 9.7–13.1 months), respectively, in the overall trial populations.[50,51] However, confirmatory phase 3 trials assessing 1L monotherapy with atezolizumab or pembrolizumab in advanced UC were not positive, as discussed in the next section. Therefore, alternative ICI-based approaches are needed to improve efficacy.

Access to established treatments for advanced UC varies greatly across Asia-Pacific countries. In countries classified by the World Bank[52] as high income (e.g., Australia, Japan, Republic of Korea, or Singapore) or upper-middle income (e.g., China, Malaysia, or Thailand), standard cancer treatments such as platinum agents are mostly available on formulary and at a subsidized cost to patients, whereas patients in lower-middle-income countries (e.g., Bangladesh, India, the Philippines, and Vietnam) often incur full out-of-pocket costs and unreliable supplies.[53] Furthermore, newer treatments, such as ICIs, are often reimbursed only in high-income countries, whereas access may be limited elsewhere by issues such as lack of regulatory approval, budget limitations, and supplier issues.[53] Thus, the practical implementation of standard-of-care treatment for advanced UC is highly dependent on accessibility within each country.

## 3 | PHASE 3 TRIALS OF 1L ICI-BASED TREATMENT FOR ADVANCED UC

New 1L treatment strategies are needed to improve outcomes in patients with advanced UC. Results were reported recently from several phase 3 trials assessing different ICI-based regimens in this setting (Table 2).

### 3.1 | JAVELIN Bladder 100: Avelumab 1L maintenance treatment

Switch maintenance is a treatment strategy that uses agents with different mechanisms of action, with the aim of prolonging and potentially enhancing the clinical benefits achieved with 1L therapy. JAVELIN Bladder 100 was an international, randomized, phase 3 trial that assessed avelumab as 1L switch maintenance treatment.[54] Eligible patients had advanced UC without disease progression after 4–6 cycles of standard-of-care 1L platinum-containing chemotherapy (either cisplatin plus gemcitabine or carboplatin plus gemcitabine). Patients were randomized to receive either avelumab 1L maintenance plus best supportive care (BSC; avelumab arm, $n = 350$) or BSC alone (control arm, $n = 350$). The primary endpoint was OS assessed in the overall population and in patients with PD-L1+ tumors. In the overall population, avelumab 1L maintenance plus BSC significantly prolonged OS (median, 21.4 vs. 14.3 months; hazard ratio [HR], 0.69 [95% CI, 0.56–0.86]; $P = 0.001$; Figure 2) and PFS (median, 3.7 vs. 2.0 months; HR, 0.62 [95% CI, 0.52–0.75]) compared with BSC alone. Significant efficacy benefits were also observed in the PD-L1+ population (avelumab plus BSC vs. BSC alone: median OS, not estimable vs. 17.1 months, respectively; HR, 0.56 [95% CI, 0.40–0.79]; median PFS, 5.7 vs. 2.1 months, respectively; HR, 0.56 [95% CI, 0.43–0.73]). The safety profile of avelumab 1L maintenance plus BSC was consistent with that seen in prior studies of avelumab monotherapy, and no new safety signals were identified.

UC is considered an immunogenic tumor type, which is due to its high mutational burden and genomic instability, and these features are associated with increased activity of ICI therapy.[20,55,56] Chemotherapies have immune-priming effects, such as recruitment of immune cells into the tumor microenvironment, depletion of immunosuppressive cell types, enhanced antigen presentation, and induction of immunogenic cell death.[57] In addition, chemotherapy has direct cytotoxic activity, which may control or reduce tumor burden, and clinical evidence suggests that ICIs are more effective in patients with a smaller tumor burden.[57–60] Together, these observations provided the rationale for administering an ICI as maintenance therapy, instead of waiting for disease progression, to provide enhanced clinical activity versus platinum-based chemotherapy alone without the risk of cumulative toxicity.[34,57,61] Before JAVELIN Bladder 100, maintenance treatment was already an established strategy in other tumor types, including pemetrexed for non-small cell lung cancer and poly (ADP-ribose) polymerase inhibitors for ovarian cancer.[62,63] However, phase 3 trials of non-ICI maintenance treatments in advanced UC were negative (lapatinib or sunitinib) or resulted in a PFS benefit but not an OS improvement (vinflunine).[64–67]

A randomized phase 2 trial performed in the United States assessed pembrolizumab maintenance versus placebo in 108 patients with advanced UC that had not progressed after 1L platinum-containing chemotherapy. Pembrolizumab maintenance significantly prolonged PFS compared with placebo, which was the primary endpoint of the trial. OS was not significantly prolonged, although the study was not powered to assess any difference in OS. The trial had a crossover design but only 52% of patients with progression in the placebo arm crossed over to receive pembrolizumab. The authors highlighted that a notable proportion of patients in the placebo arm died before receiving any 2L therapy (13%), supporting the rationale for a switch-maintenance approach.[68] A randomized phase 3 trial assessing pemetrexed maintenance in patients with advanced UC that has not progressed with 1L platinum-based chemotherapy is ongoing (PREMIER; NCT03193788).

**TABLE 2** Overall survival in phase 3 trials of immune checkpoint inhibitors as maintenance therapy, upfront monotherapy, or in combination with chemotherapy during first-line treatment of advanced urothelial carcinoma

| Trial | Median OS (95% CI) (months) | | HR (95% CI) |
|---|---|---|---|
| | ICI arm | Comparator arm | |
| JAVELIN Bladder 100 (NCT02603432)[54] | | | |
| Avelumab maintenance plus BSC vs. BSC alone | 21.4 (18.9–26.1)[a] | 14.3 (12.9–17.9)[a] | 0.69 (0.56–0.86) |
| IMvigor130 (NCT02807636)[69] | | | |
| Atezolizumab plus chemotherapy vs. chemotherapy alone | 16.0 (13.9–18.9) | 13.4 (12.0–15.2) | 0.83 (0.69–1.00) |
| Atezolizumab monotherapy vs. chemotherapy alone | 15.7 (13.1–17.8) | 13.1 (11.7–15.1) | 1.02 (0.83–1.24) |
| KEYNOTE-361 (NCT02853305)[71] | | | |
| Pembrolizumab plus chemotherapy vs. chemotherapy alone | 17.0 (14.5–19.5) | 14.3 (12.3–16.7) | 0.86 (0.72–1.02) |
| Pembrolizumab monotherapy vs. chemotherapy alone | 15.6 (12.1–17.9) | 14.3 (12.3–16.7) | 0.92 (0.77–1.11) |
| DANUBE (NCT02516241)[72] | | | |
| Durvalumab monotherapy vs. chemotherapy (high–PD-L1+ population) | 14.4 (10.4–17.3) | 12.1 (10.4–15.0) | 0.89 (0.71–1.11) |
| Durvalumab plus tremelimumab vs. chemotherapy (overall population) | 15.1 (13.1–18.0) | 12.1 (10.9–14.0) | 0.85 (0.72–1.02) |

Abbreviations: 1L, first line; BSC, best supportive care; HR, hazard ratio; ICI, immune checkpoint inhibitor; OS, overall survival; PD-L1, programmed cell death 1 ligand 1.

[a]In JAVELIN Bladder 100, median OS was measured from the end of 1L chemotherapy (in the other trials shown, OS was measured from the start of 1L treatment).

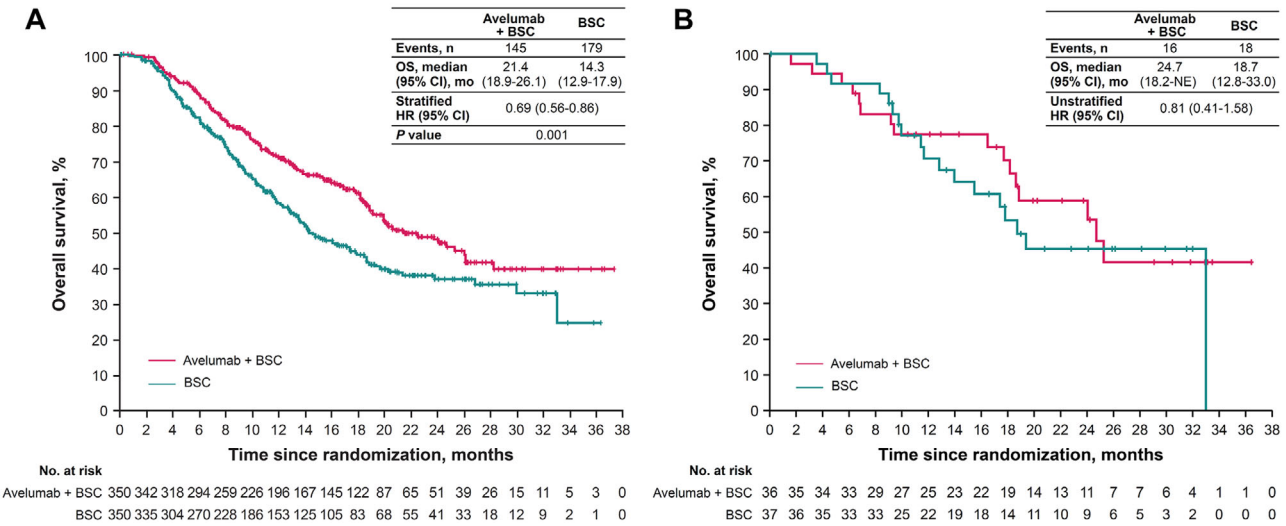


**FIGURE 2** Median overall survival in the (A) overall JAVELIN Bladder 100 population[54] and (B) population enrolled in Japan.[84] BSC, best supportive care; HR, hazard ratio; NE, not estimable; OS, overall survival. Panel A: from Powles T, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, New England Journal of Medicine, Volume 383, Pages 1218–1230. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission. Panel B: from Tomita Y, et al. Avelumab first-line maintenance plus best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma: JAVELIN Bladder 100 Japanese subgroup analysis, International Journal of Clinical Oncology (in press); published under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/) [Colour figure can be viewed at wileyonlinelibrary.com]

## 3.2 | IMvigor130: 1L atezolizumab with or without chemotherapy

IMvigor130 was an international, randomized, phase 3 trial of atezolizumab with or without chemotherapy versus chemotherapy alone as 1L treatment for advanced UC.[69] Patients were randomized to receive atezolizumab plus platinum-based chemotherapy (group A; $n = 451$), atezolizumab monotherapy (group B; $n = 362$), or placebo plus platinum-based chemotherapy (group C; $n = 400$ overall, $n = 359$ for comparisons with group A [post-protocol amendment]). Primary endpoints were PFS and OS in group A versus C and OS in group B versus C. PFS was prolonged with atezolizumab plus chemother-

apy versus chemotherapy alone (median, 8.2 vs. 6.3 months; HR, 0.82 [95% CI, 0.70–0.96]; $P = 0.007$); however, OS was not significantly different at the first interim analysis (median, 16.0 vs. 13.4 months; HR, 0.83 [95% CI, 0.69–1.00]). OS was also not significantly different with atezolizumab monotherapy versus chemotherapy alone (median, 15.7 vs. 13.1 months; HR, 1.02 [95% CI, 0.83–1.24]). In the second interim analysis, OS findings were consistent with the first interim analysis, with no significant differences observed.[33,70] Follow-up is continuing until the final OS analysis.

### 3.3 | KEYNOTE-361: 1L pembrolizumab with or without chemotherapy

KEYNOTE-361 was an international, randomized, phase 3 trial of pembrolizumab plus chemotherapy ($n = 351$), pembrolizumab alone ($n = 307$), or chemotherapy alone ($n = 352$) as 1L treatment for patients with advanced UC. The primary endpoints were PFS and OS.[71] Compared with chemotherapy alone, the addition of pembrolizumab to platinum-containing chemotherapy did not significantly improve PFS (median, 8.3 vs. 7.1 months; HR, 0.78 [95% CI, 0.65–0.93]; $P = 0.0033$) or OS (median, 17.0 vs. 14.3 months; HR, 0.86 [95% CI, 0.72–1.02]; $P = 0.0407$). Because these analyses were negative, further analyses of pembrolizumab monotherapy versus chemotherapy alone could not be tested statistically; in exploratory analyses, however, OS was also not improved in this arm (median, 16.1 vs. 15.2 months; HR, 1.01 [95% CI, 0.77–1.32]).

### 3.4 | DANUBE: 1L durvalumab with or without tremelimumab

DANUBE was an international, randomized, phase 3 trial of durvalumab alone ($n = 346$), durvalumab plus tremelimumab (anti-cytotoxic T-lymphocyte protein 4 monoclonal antibody; $n = 342$), or chemotherapy alone ($n = 344$) as 1L treatment for advanced UC.[72] The primary endpoints were OS with durvalumab monotherapy versus chemotherapy in the high-PD-L1+ population and OS with durvalumab plus tremelimumab versus chemotherapy in the overall population. Durvalumab did not significantly improve OS versus chemotherapy either as monotherapy in the high-PD-L1+ population (median, 14.4 vs. 12.1 months; HR, 0.89 [95% CI, 0.71–1.11]; $P = 0.30$) or in combination with tremelimumab in the overall population (median, 15.1 vs. 12.1 months; HR, 0.85 [95% CI, 0.72–1.02]; $P = 0.075$).

### 3.5 | Ongoing phase 3 trials of ICI-based treatment

Several phase 3 trials of 1L ICI-based treatment for advanced UC are ongoing. These include CheckMate 901 (NCT03036098), a trial of nivolumab plus ipilimumab or chemotherapy versus chemotherapy alone in patients with advanced UC[73]; EV-302 (NCT04223856), a trial of pembrolizumab in combination with enfortumab vedotin (antibody–drug conjugate directed to Nectin-4) and/or chemotherapy versus chemotherapy alone for platinum-ineligible patients with PD-L1+ advanced UC[74]; and NILE (NCT03682068), a trial of durvalumab plus chemotherapy versus durvalumab plus tremelimumab versus chemotherapy alone in patients with advanced UC.[75] Results are pending.

## 4 | INTEGRATING AVELUMAB 1L MAINTENANCE INTO TREATMENT PRACTICE FOR ADVANCED UC IN THE ASIA-PACIFIC REGION

Avelumab (administered as 1L maintenance) is the only ICI to show significantly prolonged OS in the 1L treatment setting in patients with advanced UC, unlike ICI monotherapy or combination approaches in other randomized trials.[54] Furthermore, avelumab 1L maintenance yielded the longest median OS reported to date in a phase 3 trial in patients with advanced UC, despite OS being measured from end of chemotherapy. The significant OS benefit with avelumab was seen despite a relatively high frequency of subsequent treatment in the control arm (61.7%), including ICIs (43.7%).[54] These results suggest that the JAVELIN Bladder regimen, that is, 1L platinum-based standard-of-care chemotherapy followed by avelumab as 1L maintenance treatment in patients without disease progression, provides a greater efficacy benefit than deferring ICI treatment as a 2L approach after disease progression and enables a greater proportion of patients to benefit from ICI treatment. It is uncertain whether this is due to patient selection (i.e., treating only patients without disease progression after 1L chemotherapy) and/or administration of an ICI at the right time to enable a significant benefit (i.e., building on the direct cytotoxic or immunologic effects of chemotherapy) or other reasons. A real-world study of ICI treatment found that resistance to chemotherapy was not associated with cross-resistance to ICIs.[76] However, the similar PFS seen with 1L ICI monotherapy and ICI/chemotherapy combination approaches in the phase 3 trials discussed in the previous section suggests that combination treatment is not detrimental to ICI therapy but does not provide a substantial additive effect, while also increasing toxicity.[69,71]

Irrespective of the mechanisms that enabled significant efficacy benefits to be achieved, the JAVELIN Bladder 100 trial provided level 1 evidence that supported the inclusion of avelumab 1L maintenance in revised NCCN, ESMO, EAU, and JUA treatment guidelines for both cisplatin-eligible and cisplatin-ineligible patients without disease progression after 1L standard-of-care chemotherapy, irrespective of PD-L1 status.[20–22,77] Among countries in the Asia-Pacific region, avelumab 1L maintenance has already been approved in Japan, Australia, and Taiwan, and further availability in the region may be expected depending on local regulatory discussions. Thus, consideration is needed about how to optimally incorporate avelumab into standard treatment for patients with advanced UC in this region.

Subgroup and post hoc analyses reported from JAVELIN Bladder 100 suggest that avelumab 1L maintenance treatment can improve clinical outcomes in a broad population of patients with advanced

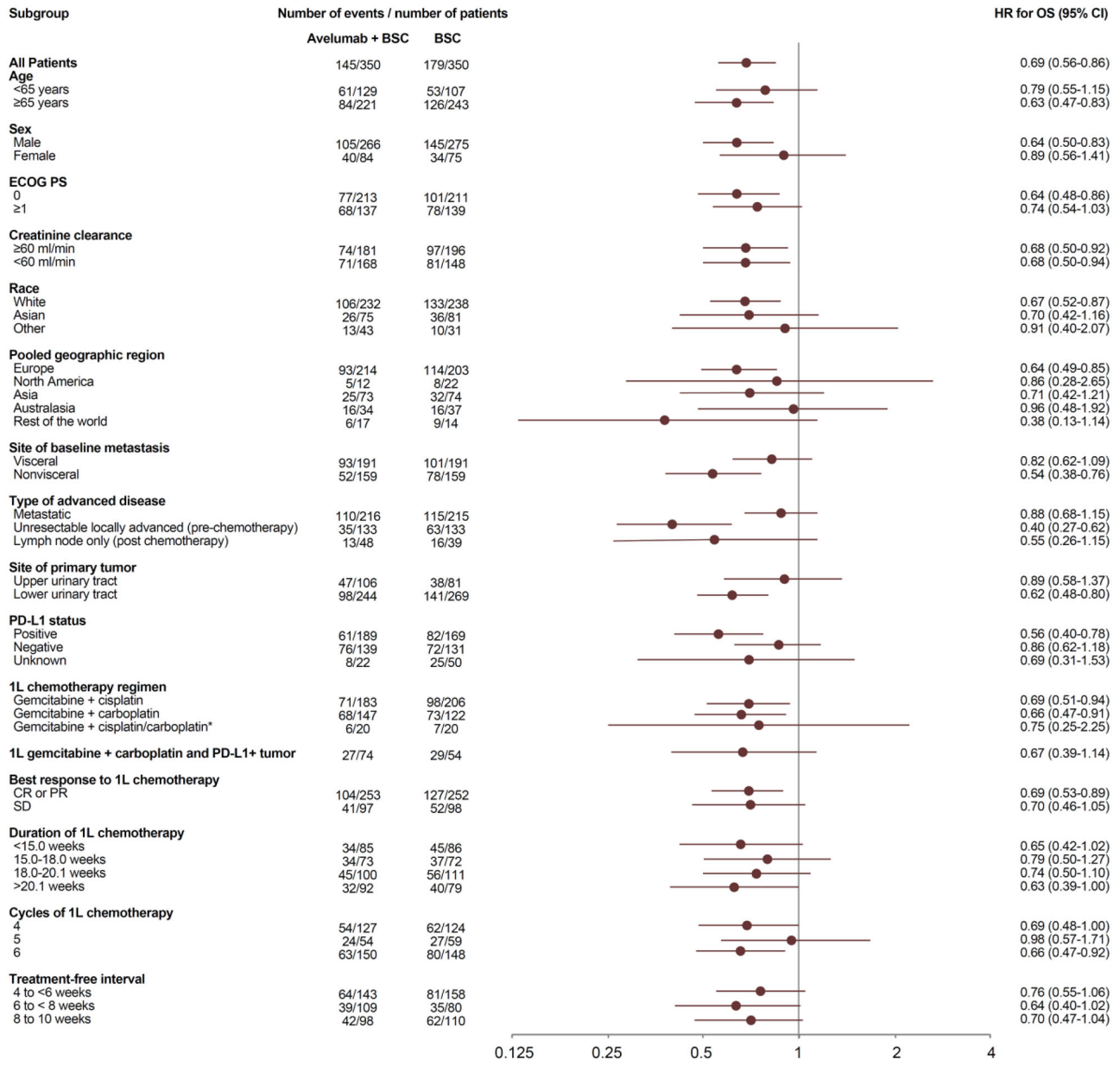


**FIGURE 3** Subgroup analyses of overall survival from the JAVELIN Bladder 100 trial, including prespecified and post hoc analyses.[54,78–80] 1L, first line; BSC, best supportive care; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PR, partial response; SD, stable disease. Adapted from Powles T, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, New England Journal of Medicine, Volume 383, Pages 1218–1230. *Includes patients who switched platinum regimens while receiving 1L chemotherapy. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission [Colour figure can be viewed at wileyonlinelibrary.com]

UC who are progression free after completing 1L platinum-based chemotherapy.[54,78–80] Notably, OS and PFS favored avelumab 1L maintenance versus control irrespective of PD-L1 status or 1L chemotherapy regimen received (cisplatin plus gemcitabine or carboplatin plus gemcitabine; Figure 3).[54] Thus, unlike other ICIs, which are approved only for the subset of cisplatin-ineligible patients with PD-L1+ tumors, avelumab 1L maintenance can be expanded to a wider population, particularly in locations where PD-L1 testing is not available or not commonly performed.[81] In addition, OS and PFS analyses from JAVELIN Bladder 100 favored the avelumab arm versus the control arm in other prespecified subgroups, including those defined by patient characteristics (e.g., age, sex, or creatinine clearance) and response to 1L standard-of-care chemotherapy (complete or partial response or stable disease).[54] OS and PFS analyses also favored avelumab in patients with risk factors associated with poor outcomes, including visceral metastases at baseline, ECOG PS ≥1, and upper urinary tract primary tumors, as well as in patients with metastatic or unresectable locally advanced disease at enrollment.[54]

In post hoc analyses from the JAVELIN Bladder 100 trial, longer OS and PFS were observed with avelumab 1L maintenance irrespective of the duration/number of cycles of 1L chemotherapy received prior to randomization (patients who received 4–6 cycles were enrolled)

**TABLE 3** Patient enrollment by country in the Asia-Pacific region in the JAVELIN Bladder 100 trial[83]

| Country, *n* (%) | Patients (*N* = 700) |
|---|---|
| Japan | 73 (10.4) |
| Australia | 59 (8.4) |
| Republic of Korea | 45 (6.4) |
| Taiwan | 21 (3.0) |
| New Zealand | 12 (1.7) |
| India | 6 (0.9) |
| Hong Kong | 2 (0.3) |

and length of the treatment-free interval after 1L chemotherapy (a treatment-free interval of 4–10 weeks was specified in the eligibility criteria).[78,79] These findings highlight that the timing for starting avelumab maintenance can be based on individual patient considerations. Furthermore, in patients with PD-L1+ tumors who received 1L gemcitabine plus carboplatin—who represent a comparable population to those who might be eligible for ICI monotherapy—the OS improvement with avelumab 1L maintenance (median OS, 24.0 vs. 16.1 months with BSC alone; HR, 0.67 [95% CI, 0.39–1.14]) was consistent with findings in the overall trial population.[80]

In the JAVELIN Bladder 100 trial, the incidence of adverse events (related or unrelated to treatment) was higher with avelumab versus control (grade ≥3 in 47.4% vs. 25.2%, respectively), which was as expected for a trial comparing active treatment versus no active treatment, and the safety profile was consistent with those in other trials of ICI monotherapy. The incidence of grade 3 immune-related adverse events was 7.0% in the avelumab arm (no grade ≥4), and high-dose steroids were administered to 9.0% of patients in the avelumab arm.[54] The trial assessed patient-reported outcomes using clinically validated instruments as a secondary endpoint to determine whether avelumab 1L maintenance affected patients' quality of life. Initial findings showed that quality of life was maintained, indicating no detrimental effect of avelumab 1L maintenance on patient-reported outcomes, providing reassurance about patient experiences with this extended 1L treatment strategy.[82]

Available data suggest that the efficacy and safety of avelumab 1L maintenance in Asia-Pacific patients enrolled in the JAVELIN Bladder 100 trial were similar to results seen in the overall trial population. Of 700 patients enrolled overall, 156 (22.3%) were of Asian race (avelumab arm, *n* = 75; control arm, *n* = 81), 147 (21.0%) were recruited in Asia (avelumab arm, *n* = 73; control arm, *n* = 74), and 71 (10.1%) were recruited in Australia/New Zealand (avelumab arm, *n* = 34; control arm, *n* = 37; Table 3).[83] HRs for OS in patients of Asian race and those enrolled in Asia (0.70 [95% CI, 0.42–1.16] and 0.71 [95% CI, 0.42–1.21], respectively) were similar to those for the overall population. The HR for patients recruited in Australasia was slightly higher (0.96 [95% CI, 0.48–1.92]), although the smaller number of patients in this subgroup hampers definitive interpretation. Analyses of PFS in these populations were similar to the OS analyses.[54]

More detailed post hoc exploratory analyses have been conducted in the subpopulation of 73 patients from the JAVELIN Bladder 100 trial who were enrolled in Japan.[84] Baseline characteristics were balanced between treatment arms; however, compared with the overall trial population, Japanese patients had several differences, including a lower median weight, higher prevalence of upper urinary tract primary tumors, and lower proportion who had an objective response to 1L standard-of-care chemotherapy. Efficacy results in Japanese patients were generally consistent with those in the overall population (Figure 2); median OS was 24.7 months (95% CI, 18.2 months to not estimable) in the avelumab arm versus 18.7 months (95% CI, 12.8–33.0 months) in the control arm (HR, 0.81 [95% CI, 0.41–1.58]). In the Japanese PD-L1+ population, median OS was similar between arms (18.6 months [95% CI, 9.4 months to not estimable] with avelumab versus 19.4 months [95% CI, 11.7–33.0 months] with control; HR, 1.00 [95% CI, 0.41–2.41]), unlike in the overall population; however, 95% CIs were wide due to small patient numbers in these analyses. Differences in PFS in Japanese patients were consistent with the overall population, both in all Japanese patients (avelumab arm, median of 5.6 months [95% CI, 1.9–9.4 months]; control arm, median of 1.9 months [95% CI, 1.9–3.8 months]; HR, 0.63 [95% CI, 0.36–1.11]) and in those with PD-L1+ tumors (avelumab arm, median of 5.6 months [95% CI, 1.8–11.2 months]; control arm, median of 1.9 months [95% CI, 1.9–3.8 months]; HR, 0.62 [95% CI, 0.30–1.30]). The safety profile of avelumab plus BSC in Japanese patients was consistent with that in the overall population, and no toxicities specific to Japanese patients were identified (Table 4).[84]

Several questions still need to be answered about the optimal use of avelumab 1L maintenance and may require real-world studies or additional clinical trials. These include the degree of benefit in patients who have received 1L platinum-based regimens that were not assessed in the JAVELIN Bladder 100 trial (e.g., MVAC) and outcomes in patients who are generally not eligible for clinical trials of ICIs, such as those with serious comorbidities or those receiving immunosuppressive treatment. In addition, because patients who had received neoadjuvant or adjuvant systemic therapy within the preceding 12 months were ineligible, it is unknown if avelumab 1L maintenance treatment would be beneficial for this patient group. Further studies evaluating ICIs in different UC treatment settings are warranted.

## 5 | CONCLUSIONS

Although UC is less common in Asian countries than in Western countries,[1] mortality rates are generally higher in Asian countries, whereas the epidemiology of UC in Australia and New Zealand is more similar to that in North America and Europe.[5] Asian patients may have a greater prevalence of some negative prognostic factors than non-Asian patients.[10–12,16] However, the prognosis remains poor for patients with UC worldwide who develop advanced disease. After more than two decades without any major treatment developments in the 1L treatment setting, various trials have assessed different ICI-based strategies. JAVELIN Bladder 100, which assessed avelumab 1L

**TABLE 4** Most common adverse events in Japanese patients and comparison with the overall population of treated patients in the JAVELIN Bladder 100 trial[84]

| | Japanese patients ($N = 73$)[a] | | | | Overall population ($N = 689$)[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | Avelumab + BSC ($n = 36$) | | BSC ($n = 37$) | | Avelumab + BSC ($n = 344$) | | BSC ($n = 345$) | |
| | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Any adverse event, n (%) | 36 (100.0) | 18 (50.0) | 21 (56.8) | 3 (8.1) | 337 (98.0) | 163 (47.4) | 268 (77.7) | 87 (25.2) |
| Pyrexia | 10 (27.8) | 0 | 0 | 0 | 51 (14.8) | 1 (0.3) | 12 (3.5) | 0 |
| Anemia | 7 (19.4) | 4 (11.1) | 1 (2.7) | 1 (2.7) | 39 (11.3) | 13 (3.8) | 23 (6.7) | 10 (2.9) |
| Nasopharyngitis | 7 (19.4) | 0 | 5 (13.5) | 0 | 26 (7.6) | 0 | 13 (3.8) | 0 |
| Constipation | 6 (16.7) | 0 | 3 (8.1) | 0 | 56 (16.3) | 2 (0.6) | 31 (9.0) | 0 |
| Hypothyroidism | 6 (16.7) | 0 | 0 | 0 | 40 (11.6) | 1 (0.3) | 2 (0.6) | 0 |
| Nausea | 6 (16.7) | 0 | 0 | 0 | 54 (15.7) | 1 (0.3) | 22 (6.4) | 2 (0.6) |
| Rash | 6 (16.7) | 0 | 0 | 0 | 40 (11.6) | 1 (0.3) | 4 (1.2) | 0 |
| Back pain | 4 (11.1) | 0 | 3 (8.1) | 0 | 55 (16.0) | 4 (1.2) | 34 (9.9) | 8 (2.3) |
| Diarrhea | 4 (11.1) | 0 | 0 | 0 | 57 (16.6) | 2 (0.6) | 17 (4.9) | 1 (0.3) |
| Arthralgia | 4 (11.1) | 0 | 0 | 0 | 56 (16.3) | 2 (0.6) | 19 (5.5) | 0 |
| Pyelonephritis | 3 (8.3) | 2 (5.6) | 1 (2.7) | 0 | 4 (1.2) | 3 (0.9) | 3 (0.9) | 2 (0.6) |
| Urinary tract infection | 3 (8.3) | 1 (2.8) | 1 (2.7) | 0 | 59 (17.2) | 15 (4.4) | 36 (10.4) | 9 (2.6) |
| Pruritus | 3 (8.3) | 0 | 1 (2.7) | 0 | 59 (17.2) | 1 (0.3) | 6 (1.7) | 0 |
| Amylase increased | 2 (5.6) | 2 (5.6) | 0 | 0 | 23 (6.7) | 12 (3.5) | 3 (0.9) | 2 (0.6) |
| Blood triglycerides increased | 2 (5.6) | 2 (5.6) | 0 | 0 | 3 (0.9) | 3 (0.9) | 0 | 0 |
| Fatigue | 2 (5.6) | 1 (2.8) | 1 (2.7) | 0 | 61 (17.7) | 6 (1.7) | 24 (7.0) | 2 (0.6) |
| Asthenia | 0 | 0 | 0 | 0 | 56 (16.3) | 0 | 19 (5.5) | 4 (1.2) |

*Note*: Treatment-emergent adverse events (related or unrelated to treatment) of any grade occurring in ≥15% or grade ≥3 occurring in ≥5% of patients in either arm are shown.

[a]From Tomita Y, et al. Avelumab first-line maintenance plus best supportive care (BSC) vs BSC alone for advanced urothelial carcinoma: JAVELIN Bladder 100 Japanese subgroup analysis, International Journal of Clinical Oncology (in press); published under a Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/).

[b]From Powles T, et al. Avelumab maintenance therapy for advanced or metastatic urothelial carcinoma, New England Journal of Medicine, Volume 383, Pages 1218–1230. Copyright © 2020 Massachusetts Medical Society. Reprinted with permission.

maintenance in patients without disease progression after completing 1L platinum-based standard-of-care chemotherapy,[54] is the first and only phase 3 trial of an ICI therapy that has shown a significant OS benefit in the 1L setting of advanced UC and is also the first phase 3 trial of any agent type in the 1L setting to show significantly improved OS since pivotal trials of platinum-based chemotherapy were reported. Phase 3 trials of 1L ICI monotherapy or ICI-based combinations have not yet shown any significant OS improvement, with results awaited from some other phase 3 trials. Efficacy benefits with avelumab 1L maintenance were generally consistent across all subgroups and treatment was well tolerated. Given that only a minority of patients go on to receive 2L therapy after disease progression with 1L platinum-based chemotherapy,[44] use of avelumab as 1L maintenance could increase the proportion of patients who can obtain a benefit from ICI therapy. The JAVELIN Bladder 100 trial has led to regulatory approvals in several countries, including Japan, Australia, and Taiwan, and has provided level 1 evidence to support updates to international treatment guidelines, which now recommend avelumab 1L maintenance treatment for cisplatin-eligible and cisplatin-ineligible patients with advanced UC that has not progressed with 1L platinum-containing chemotherapy, irrespective of PD-L1 status.[20–22] Available data suggest that efficacy and safety in patients from the Asia-Pacific region were similar to findings in the overall population,[54,84] suggesting that avelumab 1L maintenance should be considered as a standard of care for patients in this region.

## ACKNOWLEDGMENTS

Medical writing support was provided by Abhijith Thippeswamy of ClinicalThinking and funded by Merck (CrossRef Funder ID: 10.13039/100009945) and Pfizer.

Open Access Funding provided by Macquarie University.

[Correction added on 14 May 2022, after first online publication: CAUL funding statement has been added.]

## AUTHOR CONTRIBUTIONS

All authors contributed to the conceptualization, writing the first draft, review, and revision of this article and provided final approval for publication.

## CONFLICT OF INTERESTS

ME has received honoraria from Bristol-Myers Squibb, Chugai, Janssen, Merck, MSD, Novartis, ONO, Pfizer, and Takeda, and has received grants or contracts from Astellas, Bayer, Kissei, ONO, Sanofi, and Takeda. J-LL has received honoraria from AstraZeneca, Ipsen, Merk, MSD, Pfizer, and Roche; has participated on a data safety monitoring board or advisory board for Astella Korea, AstraZeneca, Bristol-Myers Squibb, Merck, MSD, and Pfizer; and has stock or stock options in Amgen, Johnson & Johnson, Merck, and Myovant Sciences. Y-HC declares no disclosures. SG is an employee of Merck Pte. Ltd., Singapore, an affiliate of Merck KGaA. MS is an employee of Pfizer Corporation Hong Kong Ltd. HG has received honoraria from Ipsen, Merck, MSD, and Pfizer and participated on a data safety monitoring board or advisory board for AstraZeneca, Ipsen, Merck, MSD, Pfizer, and Roche.

## PERMISSION TO REPRODUCE MATERIAL FROM OTHER SOURCES

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**How to cite this article:** Eto M, Lee J-L, Chang Y-H, Gao S, Singh M, Gurney H. Clinical evidence and insights supporting the use of avelumab first-line maintenance treatment in patients with advanced urothelial carcinoma in the Asia-Pacific region. *Asia-Pac J Clin Oncol*. 2022;18:e191–e203. https://doi.org/10.1111/ajco.13765