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ORIGINAL RESEARCH

A phase II open-label trial of avelumab plus axitinib in previously treated non-small-cell lung cancer or treatment-naïve, cisplatin-ineligible urothelial cancer

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Background: We hypothesized that avelumab plus axitinib could improve clinical outcomes in patients with advanced non-small-cell lung cancer (NSCLC) or urothelial carcinoma (UC).

Patients and methods: We enrolled previously treated patients with advanced or metastatic NSCLC, or untreated, cisplatin-ineligible patients with advanced or metastatic UC. Patients received avelumab 800 mg every 2 weeks (Q2W) and axitinib 5 mg orally two times daily. The primary endpoint was objective response rate (ORR). Immunohistochemistry was used to assess programmed death-ligand 1 (PD-L1) expression (SP263 assay) and the presence of CD8+ T cells (clone C8/144B). Tumor mutational burden (TMB) was assessed by whole-exome sequencing.

Results: A total of 61 patients were enrolled and treated (NSCLC, $n = 41$; UC, $n = 20$); 5 remained on treatment at data cut-off (26 February 2021). The confirmed ORR was 31.7% in the NSCLC cohort and 10.0% in the UC cohort (all partial responses). Antitumor activity was observed irrespective of PD-L1 expression. In exploratory subgroups, ORRs were higher in patients with higher (≥median) CD8+ T cells in the tumor. ORRs were higher in patients with lower TMB (<median) in the NSCLC cohort and higher TMB (≥median) in the UC cohort. Treatment-related adverse events (TRAEs) occurred in 93.4% of patients, including grade ≥3 TRAEs in 55.7%. Avelumab exposures with 800 mg Q2W dosing were similar to those observed with 10 mg/kg Q2W dosing.

Conclusions: In previously treated patients with advanced/metastatic NSCLC, ORR appeared to be superior to anti-PD-L1 or anti-programmed cell death protein 1 monotherapy, irrespective of PD-L1 status, whereas in untreated, cisplatin-ineligible patients with advanced/metastatic UC, ORR was lower than expected, potentially limited by small patient numbers.

Trial registration: Clinicaltrial.gov NCT03472560; https://clinicaltrials.gov/ct2/show/NCT03472560

Key words: immune checkpoint inhibitor, avelumab plus axitinib, urothelial carcinoma, non-small-cell lung cancer

INTRODUCTION

Immune checkpoint inhibitors (ICIs) that target the anti-programmed cell death protein 1 (PD-1)—anti-programmed death-ligand 1 (PD-L1) axis have been associated with improved clinical outcomes and durable responses in several solid tumors.[1-5] Avelumab, an anti-PD-L1 monoclonal antibody, is approved as monotherapy for the treatment of metastatic

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Merkel cell carcinoma and locally advanced or metastatic urothelial carcinoma [UC; first-line (1L) maintenance and second-line (2L) therapy], and in combination with axitinib, a tyrosine kinase inhibitor (TKI) of vascular endothelial growth factor (VEGF) receptor, for advanced renal cell carcinoma (RCC).[6] Avelumab was initially approved with weight-based dosing of 10 mg/kg every 2 weeks (Q2W), which was changed to flat dosing with 800 mg Q2W in several countries (including the United States and European countries) based on modeling and simulations that showed similar exposures and no meaningful differences in exposure—safety/exposure—efficacy profiles for the two dosing regimens.[7]

The VEGF pathway is known to be activated in several solid cancers, and agents that target the VEGF pathway, including VEGF receptor TKIs (e.g. nintedanib) and anti-VEGF antibodies (e.g. bevacizumab and ramucirumab), have shown activity in non-small-cell lung cancer (NSCLC) and UC.[8-10] Regimens in advanced NSCLC that feature a VEGF pathway-targeting agent include 1L bevacizumab in combination with chemotherapy with or without atezolizumab (approved in the European Union and United States), 1L ramucirumab in combination with erlotinib in patients with epidermal growth factor receptor exon 19 deletions or exon 21 mutations (approved in the European Union and United States), 2L nintedanib in combination with docetaxel (approved in the European Union), and ramucirumab plus docetaxel in patients with disease progression on or after platinum-based chemotherapy (approved in the European Union and United States).[9,11-14] In UC, monotherapy with VEGF pathway-targeting agents has shown limited clinical activity[8] and combinations with chemotherapy showed clinical activity in patients with platinum-refractory disease but did not improve overall survival (OS).[10,15]

Axitinib has been studied in patients with NSCLC as monotherapy and in combination with chemotherapy.[16-19] In a phase II trial, axitinib demonstrated a manageable safety profile and preliminary single-agent antitumor activity, including an objective response rate (ORR) of 9% and disease control rate of 41%.[17] In a single-arm phase II trial of axitinib in combination with cisplatin/gemcitabine in chemotherapy-naïve patients with NSCLC, the ORR was 39.5%.[18] In a randomized phase II trial of cisplatin/pemetrexed with or without axitinib in patients with nonsquamous NSCLC, the ORR was numerically higher with the axitinib—chemotherapy combination, but no significant difference was seen in progression-free survival (PFS) between treatment arms.[19]

In addition to the antiangiogenic activity, VEGF pathway-targeting therapies, including axitinib, have shown immunomodulatory properties,[20-22] providing a basis for potential synergy and enhanced antitumor activity for the combination of ICIs and VEGF pathway inhibitor therapy compared with either agent alone.[23] In the phase III JAVELIN Renal 101 study, the combination of avelumab and axitinib resulted in significantly prolonged PFS versus sunitinib as 1L treatment in patients with advanced RCC.[1] Furthermore, in the phase III IMpower150 study, the combination of atezolizumab plus chemotherapy and bevacizumab showed superior PFS versus chemotherapy and bevacizumab as 1L treatment of patients with advanced nonsquamous NSCLC.[24] We hypothesized that the combination of avelumab and axitinib could improve clinical outcomes in patients with advanced NSCLC or UC. Here, we report results from JAVELIN Medley VEGF (NCT03472560), a phase II trial that investigated avelumab in combination with axitinib in patients with advanced or metastatic NSCLC who had received one or more prior platinum-containing chemotherapy regimens and patients with cisplatin-ineligible, treatment-naïve advanced or metastatic UC.

PATIENTS AND METHODS

Study design and patients

JAVELIN Medley VEGF is a phase II, open-label, multicenter trial of avelumab in combination with axitinib with two cohorts. Patients eligible for the NSCLC cohort had histologically or cytologically confirmed locally advanced or metastatic NSCLC and no activating epidermal growth factor receptor mutations, anaplastic lymphoma kinase translocations or rearrangements, or ROS proto-oncogene 1, receptor tyrosine kinase translocations or rearrangements where testing is standard of care. Patients with NSCLC had received one or more prior platinum-containing chemotherapy regimens, two or fewer prior lines of systemic therapy, and no prior ICI therapy. Patients eligible for the UC cohort had histologically or cytologically confirmed locally advanced or metastatic transitional cell carcinoma of the urothelium (e.g. bladder, urethra, ureter, or renal pelvis), had received no prior systemic treatment, and were ineligible for cisplatin-based chemotherapy [Eastern Cooperative Oncology Group performance status (ECOG PS) of 2; renal dysfunction (defined as creatinine clearance $<$60 ml/min); grade $\geq$2 peripheral neuropathy; grade $\geq$2 hearing loss]. Additional inclusion criteria were measurable disease per RECIST version 1.1; ECOG PS of 0 or 1 for patients with NSCLC and 0-2 for patients with UC; and adequate hepatic, renal, and bone marrow function. Exclusion criteria included prior treatment with a TKI of the VEGF pathway and newly diagnosed brain metastases or known symptomatic brain metastases requiring steroids. The trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written, informed consent prior to enrollment. The protocol was approved by the institutional review board or independent ethics committee at each participating center. Patients and the public were not involved in the study design.

Treatment and assessments

Avelumab was administered by intravenous infusion at a dose of 800 mg Q2W on days 1 and 15 of a 28-day cycle. Axitinib was orally administered at a dose of 5 mg two times per day. Treatment was continued until confirmed disease progression, patient withdrawal, loss to follow-up, or

unacceptable toxicity. Patients with disease progression who benefited from study treatment could continue with avelumab and/or axitinib treatment at the discretion of the treating physician. Avelumab dose reductions were not permitted; however, the next administration could be omitted in cases of persisting toxicity. Axitinib dose interruptions were permitted in the event of toxicity; dose reduction could occur dependent on the severity of toxicity.

Tumors were assessed radiologically at baseline, every 8 weeks for 12 months, and every 12 weeks thereafter until disease progression, irrespective of discontinuation of study treatment or the initiation of subsequent anticancer therapy. Occurrences of complete response or partial response (PR) per RECIST version 1.1 were confirmed by repeat imaging $\geq$4 weeks apart.

Adverse events (AEs) were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.03. Infusion-related reactions (including drug hypersensitivity reactions) and immune-related AEs (irAEs) were identified as AEs of special interest for avelumab and were based on a prespecified list of MedDRA preferred terms followed by comprehensive medical review.

Whole-blood samples were collected at various timepoints and were analyzed for pharmacokinetics (PK) and immunogenicity. Baseline tumor tissue samples were collected for biomarker analysis. Immunohistochemistry was carried out on tumor tissue samples to assess PD-L1 and CD8 expression using the SP263 assay and clone C8/144B (M71030; Cell Carta), respectively. PD-L1+ status was defined as PD-L1 expression in $\geq$1% of tumors cells for NSCLC and using an algorithm that combines the assessment of PD-L1 staining on tumor cells and immune cells, scored by pathologists, for UC.[25] CD8 expression was scored via a quantitative method using image analysis software (Visiopharm). Tumor mutational burden (TMB) was assessed by whole-exome sequencing (Personalis, ACE ImmunoID) and was described according to the number of nonsynonymous somatic mutations (single-nucleotide variants and indels; mut) per megabase (Mb).

Outcomes

The primary endpoint was confirmed objective response (OR), defined as complete response or PR based on investigator assessment per RECIST version 1.1. The secondary endpoints were duration of response (DOR), defined as the time from the first documentation of tumor response to first documentation of disease progression or death; PFS, defined as the time from the first dose of study treatment to the time of disease progression or death; OS, defined as the time from the first dose of study treatment to the date of death; time to response, defined for patients with confirmed OR as the time from the first dose of study treatment to the first documentation of objective tumor response; PK; biomarker analyses; and safety.

Statistical analysis

Efficacy and safety were assessed in all patients who received one or more doses of study treatment. PK analyses included all patients who had one or more postdose concentrations above the lower limit of quantitation for avelumab or axitinib. Biomarkers were analyzed in patients who had one or more baseline tissue assessments for CD8 and TMB, and in all patients who received one or more doses of study treatment for PD-L1.

Enrollment of ~40 patients per cohort was planned; however, enrollment in the UC cohort was closed on 3 June 2019, per sponsor's decision, and did not meet the target of 40 patients. The ORR for each cohort was determined using collated OR data and two-sided exact 95% confidence intervals (CIs) were calculated. DOR and PFS were analyzed using the Kaplan–Meier method.

RESULTS

Patients and treatment

Between 24 May 2018, and 29 July 2019, 61 patients from 19 sites in 7 countries were enrolled and treated. The data cut-off date was 26 February 2021. Forty-one patients were enrolled in the NSCLC cohort and 20 patients were enrolled in the UC cohort (Table 1). The median age in the overall patient population was 66.0 years, and most patients had stage IV disease (82.0%). Patients with NSCLC had a median age of 64.0 years, were mostly enrolled in Asia (51.2%) and Europe (43.9%), and had an ECOG PS of 0 (46.3%) or 1 (53.7%). Patients with UC had a median age of 71.0 years, were mostly enrolled in Europe (75.0%), and had an ECOG PS of 0, 1, or 2 in 20.0%, 40.0%, and 40.0%, respectively. In the UC cohort, the most common reason for cisplatin ineligibility was renal dysfunction (55.0%).

At data cut-off, 56 patients had discontinued treatment and 5 patients remained on treatment (Table 2). The most common reason for avelumab or axitinib treatment discontinuation was disease progression (49.2% and 44.3%, respectively). Three patients in the NSCLC cohort and 2 patients in the UC cohort were still receiving avelumab and axitinib at data cut-off. The median durations of avelumab or axitinib treatment in the NSCLC and UC cohorts were 18.1 and 13.1 weeks, respectively. Across both cohorts, relative dose intensities of avelumab and axitinib were 81.1% and 81.8%, respectively.

Overall efficacy by cohort

In the NSCLC cohort, the confirmed ORR was 31.7% (95% CI 18.1% to 48.1%) and all responses were PRs ($n = 13$; Table 3); 16 patients (39.0%) had stable disease as the best response. Responses occurred irrespective of histology, although patient numbers were small (nonsquamous, $n = 7$; squamous, $n = 6$; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101173). ORRs were comparable in patients who had received one (8/27, 29.6%) or two or more (5/14, 35.7%) prior lines of treatment. The median DOR was 7.5 months (95% CI 3.7-15.5 months; Table 3, Figure 1). The median PFS and OS were 5.5 months (95% CI 2.5-7.0 months) and 21.3 months (95% CI 14.9-24.6

Table 1. Patient demographics and baseline characteristics

Characteristics	NSCLC (n = 41)	UC (n = 20)	Total (N = 61)
Age, years			
<65, n (%)	22 (53.7)	4 (20.0)	26 (42.6)
≥65, n (%)	19 (46.3)	16 (80.0)	35 (57.4)
Median (range)	64.0 (43.0-84.0)	71.0 (51.0-83.0)	66.0 (43.0-84.0)
Race, n (%)			
White	20 (48.8)	17 (85.0)	37 (60.7)
Asian	21 (51.2)	1 (5.0)	22 (36.1)
Multiracial	0	1 (5.0)	1 (1.6)
Not reported	0	1 (5.0)	1 (1.6)
Sex, n (%)			
Female	11 (26.8)	8 (40.0)	19 (31.1)
Male	30 (73.2)	12 (60.0)	42 (68.9)
Geographic region, n (%)			
North America	2 (4.9)	4 (20.0)	6 (9.8)
Europe	18 (43.9)	15 (75.0)	33 (54.1)
Asia	21 (51.2)	1 (5.0)	22 (36.1)
ECOG PS, n (%)			
0	19 (46.3)	4 (20.0)	23 (37.7)
1	22 (53.7)	8 (40.0)	30 (49.2)
2[a]	0	8 (40.0)	8 (13.1)
Histopathological classification, n (%)			
Adenocarcinoma	24 (58.5)	—	—
Large cell carcinoma	2 (4.9)	—	—
Mixed adenocarcinoma	1 (2.4)	—	—
Squamous carcinoma	13 (31.7)	—	—
Not otherwise specified	1 (2.4)	—	—
Urothelial carcinoma	—	17 (85.0)	—
Urothelial carcinoma with glandular differentiation	—	1 (5.0)	—
Urothelial carcinoma with squamous differentiation	—	1 (5.0)	—
Urothelial carcinoma with variant histology	—	1 (5.0)	—
TNM stage, n (%)			
IIIA	4 (9.8)	1 (5.0)	5 (8.2)
IIIB	4 (9.8)	2 (10.0)	6 (9.8)
IV	33 (80.5)	17 (85.0)	50 (82.0)
Cisplatin ineligibility by inclusion criteria, n (%)			
Grade ≥2 hearing loss	—	3 (15.0)	—
Grade ≥2 peripheral neuropathy	—	1 (5.0)	—
Renal dysfunction	—	11 (55.0)	—
PD-L1 status[b]			
Positive	8 (19.5)	5 (25.0)	13 (21.3)
Negative	24 (58.5)	11 (55.0)	35 (57.4)
Unknown	9 (22.0)	4 (20.0)	13 (21.3)
Number of prior systemic therapies, n (%)			
1	27 (65.9)	—	27 (44.3)
≥2	14 (34.1)	—	14 (23.0)

ECOG, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; TNM, tumor—node—metastasis; UC, urothelial carcinoma.
[a]ECOG PS of 2 was a reason for cisplatin ineligibility in the UC cohort.
[b]PD-L1+ status (SP263 assay) was defined as expression in ≥1% of tumor cells for NSCLC and by a US Food and Drug Administration-approved algorithm scored by pathologists for UC. PD-L1—unknown status indicates that a sample was not available or was not analyzable.

months), respectively (Table 3, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101173).

In the UC cohort, the ORR was 10.0% (95% CI 1.2% to 31.7%) and both responses were PRs; 5 patients (25.0%) had stable disease as the best response. The median DOR was not reached (95% CI 5.6 months-not reached; Table 3, Figure 1). The median PFS and OS were 2.3 months (95% CI 1.8-5.6 months) and 21.2 months (95% CI 3.7-22.6 months), respectively (Table 3, Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101173).

Efficacy in biomarker subgroups

In total, 48 of 61 patients (78.6%; NSCLC, n = 32; UC, n = 16) had tumors that were evaluable for PD-L1 expression (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101173). Of these, tumors were PD-L1+ in 25.0% of patients with NSCLC and 31.3% of patients with UC. Tumor shrinkage in both cohorts was observed irrespective of PD-L1 expression status (Figure 1, Supplementary Figure S4, available at https://doi.org/10.1016/j.esmoop.2023.101173). In patients with NSCLC, ORRs by PD-L1 expression level in tumor cells were <1%, 33.3% (8/24 patients); ≥1%, 37.5% (3/8 patients); ≥5%, 16.7% (1/6 patients); ≥25%, 20.0% (1/5 patients); and ≥50%, 50.0% (1/2 patients; Supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.esmoop.2023.101173). The median PFS in patients with PD-L1+ (n = 8) or PD-L1− (n = 24) NSCLC tumors was 3.7 months (95% CI 1.2-11 months) and 5.5 months (95% CI 2-7.3

Table 2. Patient disposition and treatment exposure

Disposition or treatment exposure	NSCLC (n = 41)	UC (n = 20)	Total (N = 61)
Discontinued avelumab, n (%)	38 (92.7)	18 (90.0)	56 (91.8)
Adverse event	5 (12.2)	2 (10.0)	7 (11.5)
Death	6 (14.6)	4 (20.0)	10 (16.4)
Physician decision	1 (2.4)	0 (0)	1 (1.6)
PD	22 (53.7)	8 (40.0)	30 (49.2)
Patient withdrawal	4 (9.8)	0 (0)	4 (6.6)
Global deterioration of health status	0 (0)	4 (20.0)	4 (6.6)
Avelumab treatment ongoing, n (%)	3 (7.3)	2 (10.0)	5 (8.2)
Discontinued axitinib, n (%)	38 (92.7)	18 (90.0)	56 (91.8)
Adverse event	5 (12.2)	4 (20.0)	9 (14.8)
Death	6 (14.6)	4 (20.0)	10 (16.4)
Physician decision	1 (2.4)	0 (0)	1 (1.6)
PD	21 (51.2)	6 (30.0)	27 (44.3)
Patient withdrawal	4 (9.8)	0 (0)	4 (6.6)
Global deterioration of health status	0 (0)	4 (20.0)	4 (6.6)
Other	1 (2.4)	0 (0)	1 (1.6)
Axitinib treatment ongoing, n (%)	3 (7.3)	2 (10.0)	5 (8.2)
Exposure to avelumab			
Duration of treatment, mean (SD), weeks	30.0 (29.25)	27.2 (32.77)	29.1 (30.20)
Duration of treatment, median weeks	18.1	13.1	16.1
Relative dose intensity, mean (SD), %	82.5 (12.96)	78.3 (13.50)	81.1 (13.18)
Exposure to axitinib			
Duration of treatment, mean (SD), weeks	29.1 (27.95)	26.1 (32.74)	28.1 (29.37)
Duration of treatment, median weeks	19.9	11.9	16.0
Relative dose intensity, mean (SD), %	80.8 (22.68)	83.8 (16.33)	81.8 (20.72)

NSCLC, non-small-cell lung cancer; PD, progressive disease; SD, standard deviation; UC, urothelial carcinoma.

months), respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101173). In patients with PD-L1+ or PD-L1− UC tumors, ORRs were 20.0% (1/5 patients) and 9.1% (1/11 patients; Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2023.101173), and the median PFS was 1.9 months (95% CI 1.9-7.4 months) and 3.0 months (95% CI 1.5-5.6 months), respectively (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101173).

In total, 31 of 35 patients with NSCLC and 15 of 17 patients with UC were evaluable for CD8 expression at baseline (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101173). The percentage of CD8+ cells in the total tumor area ranged from 0.03% to 35.1% in patients with NSCLC (median 0.8%) and 0.06% to 5.1% (median 0.9%) in patients with UC (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2023.101173). ORRs were higher in patents with higher (≥median) versus lower (<median) percentages of CD8+ cells in the total tumor area, both in the NSCLC cohort (43.8%, 95% CI 19.8% to 70.1%, 7/16 patients, versus 20.0%, 95% CI 4.3% to 48.1%, 3/15 patients) and in the UC cohort (25.0%, 95% CI 3.2% to 65.1%, 2/8 patients, versus 0%, 95% CI 0.0% to 41.0%, 0/7 patients; Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101173). The median PFS was 5.5 months (95% CI 1.9-7.3 months) for patients with NSCLC and a higher (≥median) percentage of CD8+ cells and 2.5 months (95% CI 1.6-7.0 months) for patients with lower (<median) percentages of CD8+ cells [hazard ratio (HR) 1.02, 95% CI 0.484-2.142; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101173]. The median PFS was 2 months (95% CI 1.8-7.4 months) for patients with UC and a higher (≥median) percentage of CD8+ cells and 3.7 months (95% CI 1.5-22.1 months) for patients with lower (<median) percentage of CD8+ cells (HR 1.07, 95% CI 0.295-3.861; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101173).

TMB was evaluable in tumors from 24 of 35 patients with NSCLC and 15 of 17 patients with UC (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2023.101173). The median TMB at baseline in the NSCLC and UC cohorts was 1.3 mut/Mb (range 0.2-10.4 mut/Mb) and 1.6 mut/Mb (range 0.4-17.7 mut/Mb), respectively (Supplementary Table S5, available at https://doi.org/10.

Table 3. Summary of efficacy endpoints

Endpoints	NSCLC (n = 41)	UC (n = 20)
Confirmed best overall response, n (%)		
CR	0 (0)	0 (0)
PR	13 (31.7)	2 (10.0)
SD	16 (39.0)	5 (25.0)
PD	9 (22.0)	6 (30.0)
NE[a]	3 (7.3)	7 (35.0)
ORR, n (%); 95% CI	13 (31.7); 18.1-48.1	2 (10.0); 1.2-31.7
Median DOR (95% CI), months	7.5 (3.7-15.5)	Not reached (5.6-not reached)
Median TTR (range), months	1.9 (1.8-5.3)	2.8 (1.8-3.7)
Median PFS (95% CI), months	5.5 (2.5-7.0)	2.3 (1.8-5.6)
Median OS (95% CI), months	21.3 (14.9-24.6)	21.2 (3.7-22.6)

CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TTR, time to response; UC, urothelial carcinoma.
[a]Reasons for NE in the NSCLC and UC cohorts, respectively, were no postbaseline assessment due to early death [2 (4.9%) and 1 (5.0%)] and no baseline assessment due to other reasons [1 (2.4%) and 5 (25.0%)]; all postbaseline assessments had an overall response of NE (0%) and 1 (5.0%).

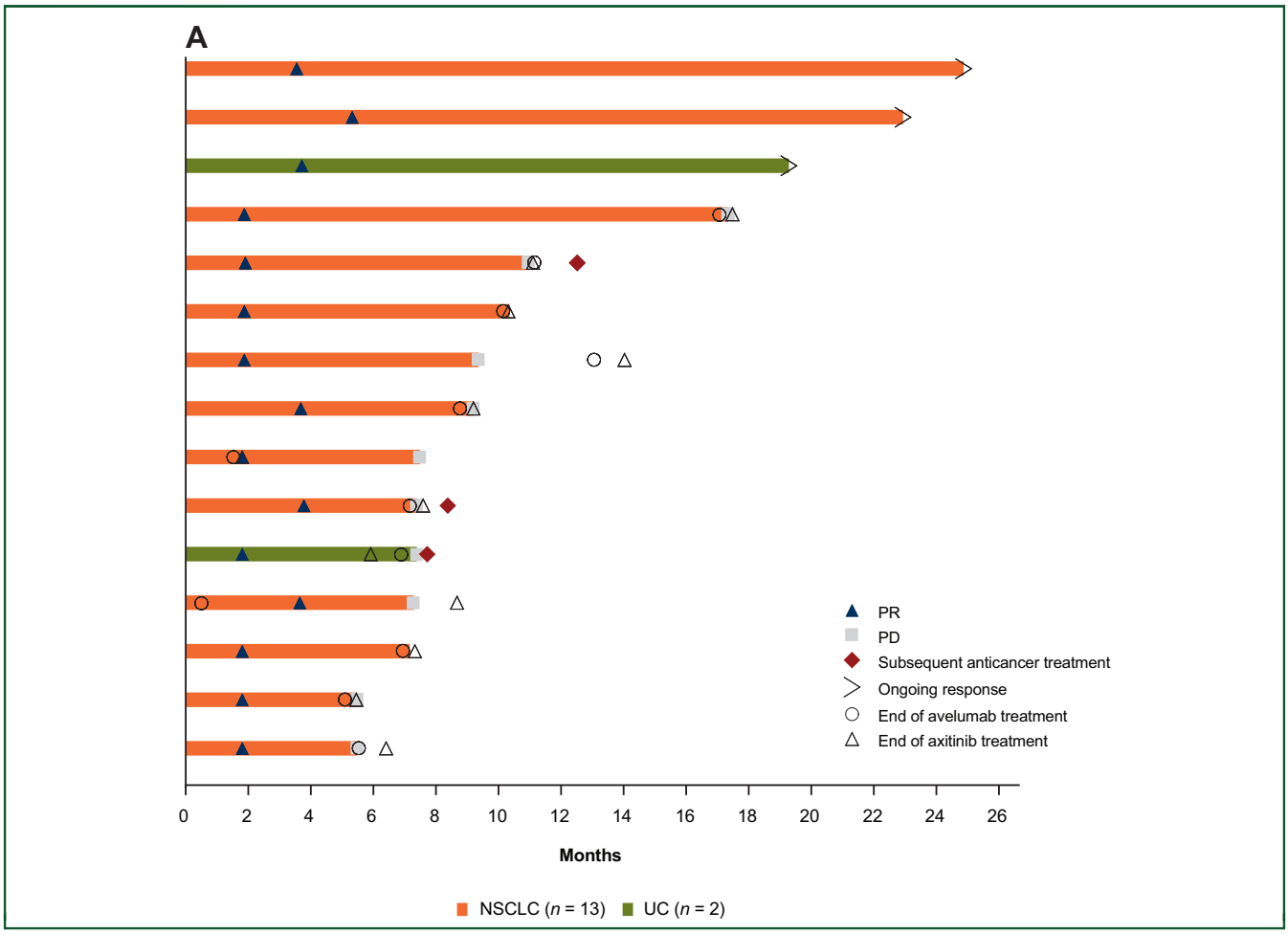

Figure 1. Summary of tumor analyses. (A) Time to and duration of response by investigator assessment per RECIST version 1.1. Percent change from baseline in sum of diameters for target lesions according to PD-L1 status in patients in the (B) NSCLC cohort and (C) UC cohort. Panels (B) and (C) include patients with target lesions at baseline and one or more postbaseline assessment up to the time of PD or new anticancer therapy. PD-L1-positive status (SP263 assay) was defined as expression in ≥1% of tumor cells for NSCLC and by a US Food and Drug Administration-approved algorithm scored by pathologists for UC. PD-L1-unknown status indicates that a sample was not available or was not analyzable.
NSCLC, non-small-cell lung cancer; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; UC, urothelial carcinoma.

1016/j.esmoop.2023.101173). The ORR was higher in the NSCLC cohort for patients with a TMB <median (41.7%, 95% CI 15.2% to 72.3%, 5/12 patients) versus ≥median (25.0%, 95% CI 5.5% to 57.2%), 3/12 patients). By contrast, in the UC cohort, the ORR for patients with a TMB <median versus ≥median was 0% (95% CI 0.0% to 41.0%, 0/7 patients) versus 25.0% (95% CI 3.2% to 65.1%, 2/8 patients), respectively. For patients with NSCLC and a TMB ≥median or <median, the median PFS was 5.5 months (95% CI 1.7-7.5 months) and 3.5 months (95% CI 1.8-11.0 months), respectively (HR 1.22, 95% CI 0.505-2.931). For patients with UC and a TMB ≥median or <median, the median PFS was 2 months (95% CI 1.8-7.4 months) and 2.3 months (95% CI 1.5-22.1 months), respectively (HR 0.98, 95% CI 0.273-3.509; Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2023.101173).

PK

PK was evaluated in all 61 patients. The maximum and minimum concentrations of avelumab were comparable between the NSCLC and UC cohorts (Supplementary Figure S2, available at https://doi.org/10.1016/j.esmoop.2023.101173). Axitinib exposure was comparable to that observed for axitinib monotherapy.[26] The mean axitinib serum concentrations 1 h after administration on cycle 1 day 1, cycle 1 day 15, and cycle 2 day 1 were 239.7, 275.7, and 297.9 μg/ml in the NSCLC cohort and 206.5, 231.1, and 261.8 μg/ml in the UC cohort, respectively. Avelumab exposures at 800 mg Q2W were similar to those observed previously in patients with solid tumors treated with 10 mg/kg Q2W (Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2023.101173).

Safety

All 61 patients had an AE of any grade related or unrelated to treatment, including grade ≥3 AEs in 78.7% ($n = 48$). Treatment-related AEs (TRAEs) occurred in 93.4% ($n = 57$) of patients, including grade ≥3 TRAEs in 55.7% ($n = 34$; Table 4). The most common TRAEs of any grade were hypertension ($n = 19$, 31.1%), decreased appetite ($n = 14$, 23.0%), fatigue ($n = 12$, 19.7%), hypothyroidism ($n = 12$, 19.7%), diarrhea ($n = 10$, 16.4%), and weight decrease

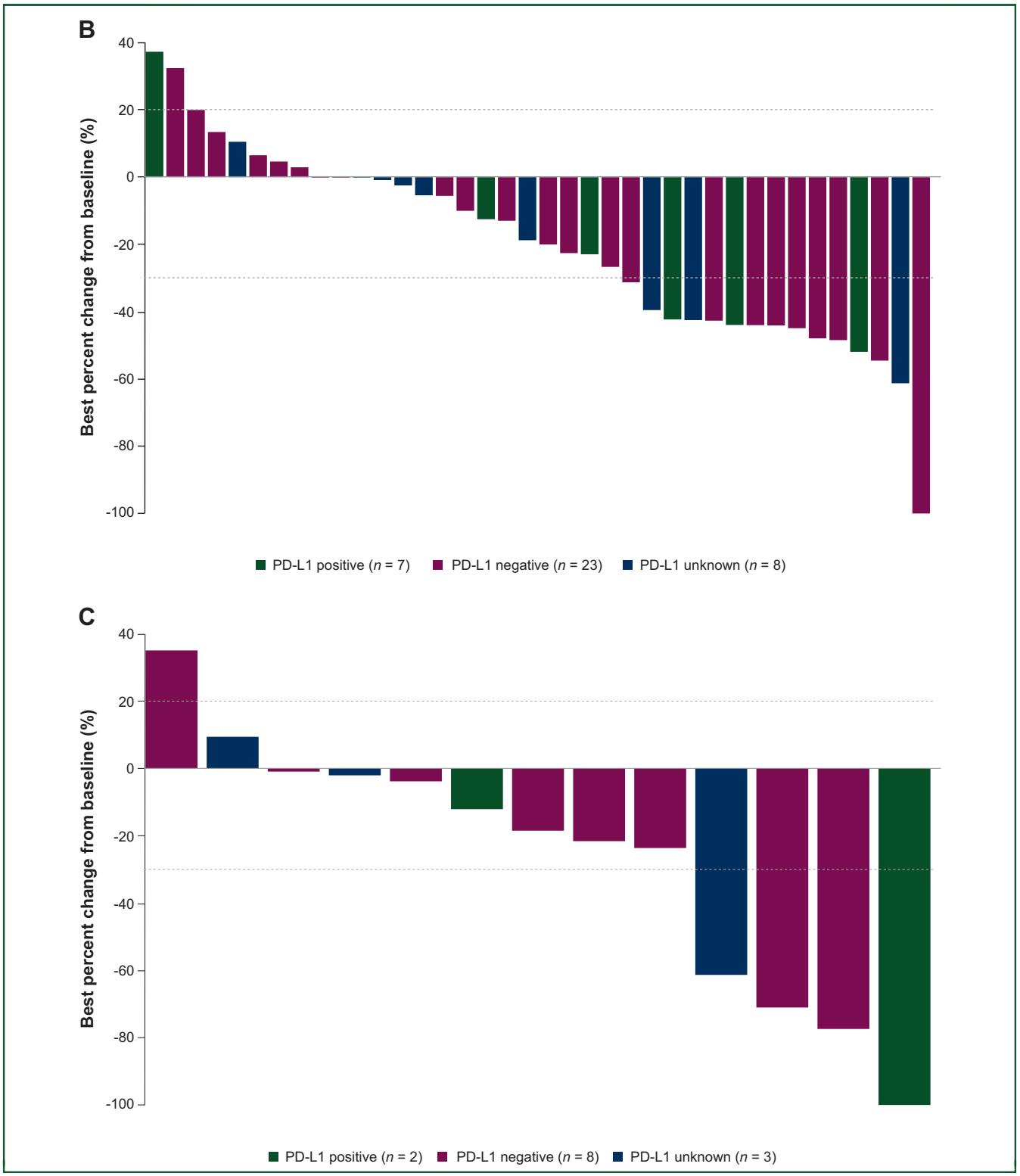

Figure 1. **(continued).**

(n = 10, 16.4%). The most common grade ≥3 TRAEs were hypertension (n = 7, 11.5%), decreased appetite (n = 4, 6.6%), fatigue (n = 3, 4.9%), alanine aminotransferase increase (n = 3, 4.9%), palmar-plantar erythrodysesthesia syndrome (n = 3, 4.9%), and amylase increase (n = 3, 4.9%). TRAEs led to discontinuation of avelumab or axitinib in 13.1% (n = 8) and 14.8% (n = 9) of patients, respectively. Serious TRAEs occurred in 12 patients (19.7%). Two patients (3.3%) died because of a TRAE (gastric perforation and urinary bladder hemorrhage). irAEs and infusion-related reactions were assessed as AEs of special interest. Overall, 24 patients (39.3%) had an irAE of any grade, including

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Table 4. Most common TRAEs (any grade ≥10% or grade ≥3 in ≥5% of patients)

TRAEs	NSCLC (n = 41)		UC (n = 20)		Total (N = 61)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Any TRAE	40 (97.6)	24 (58.5)	17 (85.0)	10 (50.0)	57 (93.4)	34 (55.7)
Hypertension	16 (39.0)	7 (17.1)	3 (15.0)	0 (0)	19 (31.1)	7 (11.5)
Decreased appetite	11 (26.8)	2 (4.9)	3 (15.0)	2 (10.0)	14 (23.0)	4 (6.6)
Fatigue	9 (22.0)	2 (4.9)	3 (15.0)	1 (5.0)	12 (19.7)	3 (4.9)
Hypothyroidism	12 (29.3)	0 (0)	0 (0)	0 (0)	12 (19.7)	0 (0)
Diarrhea	9 (22.0)	1 (2.4)	1 (5.0)	0 (0)	10 (16.4)	1 (1.6)
Weight decreased	7 (17.1)	1 (2.4)	3 (15.0)	0 (0)	10 (16.4)	1 (1.6)
ALT increase	7 (17.1)	2 (4.9)	2 (10.0)	1 (5.0)	9 (14.8)	3 (4.9)
AST increase	6 (14.6)	0 (0)	3 (15.0)	1 (5.0)	9 (14.8)	1 (1.6)
Dysphonia	6 (14.6)	0 (0)	3 (15.0)	1 (5.0)	9 (14.8)	1 (1.6)
PPE	6 (14.6)	1 (2.4)	2 (10.0)	2 (10.0)	8 (13.1)	3 (4.9)
Asthenia	3 (7.3)	0 (0)	4 (20.0)	2 (10.0)	7 (11.5)	2 (3.3)
Chills	6 (14.6)	0 (0)	1 (5.0)	0 (0)	7 (11.5)	0 (0)
Constipation	5 (12.2)	0 (0)	2 (10.0)	0 (0)	7 (11.5)	0 (0)
Rash	6 (14.6)	0 (0)	1 (5.0)	0 (0)	7 (11.5)	0 (0)
Infusion-related reaction	6 (14.6)	1 (2.4)	0 (0)	0 (0)	6 (9.8)	1 (1.6)
Mucosal inflammation	4 (9.8)	0 (0)	2 (10.0)	0 (0)	6 (9.8)	0 (0)
Nausea	3 (7.3)	0 (0)	3 (15.0)	1 (5.0)	6 (9.8)	1 (1.6)
Amylase increase	3 (7.3)	1 (2.4)	2 (10.0)	2 (10.0)	5 (8.2)	3 (4.9)
Proteinuria	4 (9.8)	1 (2.4)	1 (5.0)	1 (5.0)	5 (8.2)	2 (3.3)
Stomatitis	4 (9.8)	0 (0)	1 (5.0)	1 (5.0)	5 (8.2)	1 (1.6)
Vomiting	2 (4.9)	0 (0)	2 (10.0)	0 (0)	4 (6.6)	0 (0)
Anemia	1 (2.4)	0 (0)	2 (10.0)	0 (0)	3 (4.9)	0 (0)
Dry skin	1 (2.4)	0 (0)	2 (10.0)	0 (0)	3 (4.9)	0 (0)
Lipase increase	2 (4.9)	1 (2.4)	1 (5.0)	1 (5.0)	3 (4.9)	2 (3.3)
Dehydration	1 (2.4)	1 (2.4)	1 (5.0)	1 (5.0)	2 (3.3)	2 (3.3)
Hypoalbuminemia	0 (0)	0 (0)	2 (10.0)	0 (0)	2 (3.3)	0 (0)
Hyponatremia	0 (0)	0 (0)	2 (10.0)	1 (5.0)	2 (3.3)	1 (1.6)
Aortic aneurysm	0 (0)	0 (0)	1 (5.0)	1 (5.0)	1 (1.6)	1 (1.6)
Urinary bladder hemorrhage	0 (0)	0 (0)	1 (5.0)	1 (5.0)	1 (1.6)	1 (1.6)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSCLC, non-small-cell lung cancer; PPE, palmar—plantar erythrodysesthesia syndrome; TRAE, treatment-related adverse event; UC, urothelial carcinoma.

grade ≥3 irAEs in 4 patients (6.6%; all in the hepatitis category); no grade 4 irAEs or immune-related deaths occurred. The most frequently reported categories of irAEs (those occurring in ≥1 patient) were thyroid disorders (n = 16, 26.2%), adrenal insufficiency (n = 5, 8.2%), colitis (n = 4, 6.6%), hepatitis (n = 4, 6.6%), and rash (n = 2, 3.3%). Infusion-related reactions occurred in 11 patients (18.0%) and were grade 3 in 1 patient (1.6%).

DISCUSSION

Treatment with avelumab plus axitinib resulted in antitumor activity in patients with advanced or metastatic NSCLC and UC. The ORR (31.7%) and median OS (21.3 months) observed with avelumab plus axitinib as 2L treatment for advanced or metastatic NSCLC after 1L platinum-based chemotherapy in this study compared favorably with those reported in phase III studies of 2L avelumab monotherapy (ORR 15%; median OS 10.5 months) and 2L ramucirumab plus docetaxel (ORR 23%; median OS 10.5 months) after 1L platinum-based chemotherapy.[27,28] In addition, the ORR was similar to that seen in a phase Ib/II study of pembrolizumab plus lenvatinib in patients with previously treated NSCLC (33.3%) and compared favorably with the ORR reported in a phase Ib study of 2L atezolizumab plus cabozantinib in patients with ICI-treated NSCLC (23%).[29,30] However, cross-trial comparisons should be interpreted with caution, and small patient numbers in the current study prevent any definitive conclusions being drawn. The ORR with avelumab plus axitinib in previously untreated, cisplatin-ineligible patients with UC (10.0%) was lower than expected, based on the ORR observed with avelumab monotherapy as 2L or later therapy in 242 patients with platinum-treated metastatic UC in a previous study (16.5%).[31] However, the number of patients with UC in the current study was small (n = 20).

No association was seen in either cohort between ORR and PD-L1 expression, and tumor reductions were observed irrespective of PD-L1 status. The low proportion of patients with PD-L1+ tumors may have impacted the overall study results and does not allow definitive conclusions to be drawn about the association between PD-L1 expression and clinical benefit for the combination of avelumab and axitinib in these indications. The low proportion of PD-L1+ tumors may be attributed to the increased availability of approved treatments for patients specifically with PD-L1+ NSCLC and UC since the study was initiated.

With the caveat of small patient numbers, exploratory analyses suggested an association between the presence of a higher (≥median) percentage of CD8+ cells in tumors and higher ORR. PFS was also longer in patients with NSCLC and high CD8+ cells, whereas the opposite was observed in patients with UC. Increased CD8 infiltration has been associated with response to ICIs and the presence of CD8+

cells within the invasive margin of tumor samples has been correlated with response.[32] Unfortunately, the specific location of CD8+ cells within tumor tissue in this study could only be assessed in a small number of samples, hence correlation with clinical outcomes in relation to the localization of CD8+ cells in specific tumor regions could not be fully analyzed and may limit interpretation of the data.

High TMB (defined using cut-offs of between 5 and 10 mut/Mb) has been associated with greater efficacy of ICI treatment in patients with NSCLC and UC, albeit based on limited data in UC.[33-35] In our study, median TMB values, which were used as cut-offs, were 1.3 and 1.6 mut/Mb in the NSCLC and UC cohorts, respectively, which are lower than TMB cut-offs used in other studies. In fact, only 2 patients had a TMB $\geq$10 mut/Mb (1 with NSCLC and 1 with UC). The low number of patients with high TMB in our study may reflect the increased availability of ICIs for the treatment of NSCLC and UC. This may have contributed to differences in the associations of TMB levels with ORR and PFS within the cohorts and limits interpretation of the data. However, high TMB has not been associated with improved PFS and OS with ICI treatment in all tumors.[36]

The combination of avelumab plus axitinib had a manageable safety profile, which was consistent with that observed with avelumab plus axitinib as 1L treatment for patients with advanced RCC, and with findings from other studies of both drugs administered alone or in combination.[1,27,31,37,38] PK profiles of avelumab and axitinib administered in combination in patients with NSCLC and UC were comparable to those reported for either agent given as monotherapy.[7,39] Furthermore, flat dosing with avelumab 800 mg produced similar PK exposures to weight-based dosing with the 10 mg/kg dose; thus no change in the benefit-to-risk ratio is expected with 800 mg Q2W dosing.[7] Established practical advantages of flat dosing versus weight-based dosing are ease of preparation, decreased chance of dosing errors, and reduced drug waste.[7]

Since this study was initiated, treatment outcomes in patients with advanced NSCLC or advanced cisplatin-ineligible UC have improved, raising the bar for studies of novel combinations. Use of ICIs in the 1L NSCLC treatment setting has become standard of care, either as monotherapy in PD-L1-high tumors, in combination with ipilimumab, or in combination with chemotherapy (plus bevacizumab with atezolizumab in patients with nonsquamous NSCLC) irrespective of PD-L1 status.[40,41] In addition, the treatment landscape for patients with advanced UC has changed substantially following the results of the phase III JAVELIN Bladder 100 trial. In JAVELIN Bladder 100, avelumab 1L maintenance plus best supportive care significantly prolonged OS and PFS versus best supportive care alone in patients with advanced UC that had not progressed with 1L platinum-based chemotherapy, leading to its approval in various countries and its recommendation in international treatment guidelines for cisplatin-eligible and cisplatin-ineligible patients (i.e. following completion of cisplatin- or carboplatin-based chemotherapy), irrespective of PD-L1 status.[42-44] Conversely, phase III studies investigating the combination of ICIs and chemotherapy as 1L treatment for advanced UC have not shown a survival benefit.[45,46]

In summary, this study of the combination of avelumab plus axitinib in patients with advanced or metastatic platinum-treated NSCLC or cisplatin-ineligible UC showed acceptable safety and antitumor activity. In the NSCLC cohort, the ORR and OS compared favorably with prior studies of single-agent ICIs, irrespective of PD-L1 status, whereas in the UC cohort, the ORR was lower than expected, potentially limited by small patient numbers.

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DISCLOSURE

IL has received honoraria from AstraZeneca, BMS, F. Hoffmann-La Roche Ltd, MSD, and Takeda; has acted as a consultant for AstraZeneca, BMS, Eli Lilly, MSD, Novartis, Pfizer, Takeda, MedPacto, Abion, and ONO; and has received research funding from F. Hoffmann-La Roche Ltd, Ono, Pfizer, and Takeda. BCC is the founder of DAAN Biotherapeutics; sits on the board of directors of Gencurix Inc and Interpark Bio-Convergence Corp; has received royalties from Champions Oncology; has acted as a consultant or advisor for Novartis, AstraZeneca, Boehringer-Ingelheim, Roche, BMS, Ono, Yuhan, Pfizer, Eli Lilly, Janssen, Takeda, MSD, MedPacto, Blueprint Medicines, KANAPH Therapeutic Inc, BridgeBio Therapeutics, Cyrus Therapeutics, Guardant Health, and Joseah Bio; has received research funding from Novartis, Bayer, AstraZeneca, MOGAM Institute, Dong-A ST, Champions Oncology, Janssen, Yuhan, Ono, Dizal Pharma, MSD, AbbVie, MedPacto, GI Innovation, Eli Lilly, Blueprint Medicines, and Interpark Bio-Convergence Corp; owns stock in TheraCanVac Inc, Gencurix Inc, BridgeBio Therapeutics, KANAPH Therapeutic Inc, Cyrus Therapeutics, and Interpark Bio-Convergence Corp. M-JA has received honoraria from AstraZeneca, BMS, MSD, ONO Pharmaceutical, and Roche; and has acted as a consultant or advisor for AstraZeneca,

BMS, Takeda, MSD, Novartis, Roche, and Alpha Pharmaceutical. J-YH has received honoraria from AstraZeneca, BMS, F. Hoffmann-La Roche Ltd, MSD, and Takeda; has acted as a consultant or advisor for AstraZeneca, BMS, Eli Lilly, MSD, Novartis, Pfizer, Takeda, MedPacto, Abion, and ONO Pharmaceutical; and has received research funding from F. Hoffmann-La Roche Ltd, ONO Pharmaceutical, Pfizer, and Takeda. W-CS has acted as a consultant or advisor for Bayer, Eli Lilly, Merck, MSD, and Roche. DHL has received honoraria from AstraZeneca, Boehringer-Ingelheim, BMS, CJ Healthcare, Eli Lilly, Chong Keun Dang, Janssen, Merck, MSD, Mundipharma, Novartis, Ono, Pfizer, Roche, Samyang Biopharm, ST Cube, AbbVie, Genexine, Menarini, BC Pharma, and Takeda; and has received nonfinancial support from Takeda and Blueprint Medicines. DLE has received speaker fees from Janssen, Astellas, Pfizer, Bayer, BMS, and AstraZeneca; and travel grants from Janssen, AstraZeneca, and Pfizer. ZH has received honoraria from Eli Lilly, Merck, MSD, Novartis, Pfizer, and Roche. AGo is an employee of and owns stock in Pfizer and Merck. AP is an employee of and owns stock in Pfizer. JW is an employee of Pfizer. DAM is an employee of and owns stock in Pfizer. AA was an employee of and owned stock in Pfizer. GG, EVP, RJH, SHD, AGh, ML, PS, VRH, YJK, and VV have declared no conflicts of interest.

DATA SHARING

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual deidentified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The trial was conducted in accordance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All patients provided written, informed consent prior to enrollment. The protocol was approved by the institutional review board or independent ethics committee at each participating center. Patients and the public were not involved in the study design.

CONSENT FOR PUBLICATION

All authors contributed to the writing of the manuscript and approved the final version. All authors had access to all of the data reported, and the lead author had final responsibility for the decision to submit the manuscript for publication.

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