CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Avelumab, Axitinib

Clinical Study Report Synopsis: Protocol B9991002

Protocol Title: A Phase 1b, Open-Label, Dose-Finding Study to Evaluate Safety, Pharmacokinetics and Pharmacodynamics of Avelumab (MSB0010718C) in Combination With Axitinib (AG-013736) in Patients With Previously Untreated Advanced Renal Cell Cancer

Study Centers: The study was conducted at 14 centers in 3 countries (United Kingdom [UK], United States [US], and Japan).

Publication Based on the Study:

Choueiri TK, Larkin J, Oya M, et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. Lancet Oncol 2018;19:451-60.

Study Initiation and Completion Dates: The study was initiated on 15 October 2015 (first patient first visit) and the study was ongoing at data cutoff 03 April 2018 (primary completion date).

Report Date: 23 October 2018

Previous Report Dates: Not applicable

Phase of Development: Phase 1b

Study Objectives:

The primary objective of this study was:

- To assess the safety and tolerability of avelumab in combination with axitinib in patients with previously untreated advanced renal cell carcinoma (aRCC) in order to estimate the maximum tolerated dose (MTD) and select the recommended Phase 2 dose (RP2D).

The secondary objectives of this study were:

- To evaluate the overall safety profile of avelumab in combination with axitinib in patients with previously untreated aRCC.

- To assess the preliminary antitumor activity of avelumab in combination with axitinib in patients with previously untreated aRCC.

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- To evaluate the overall survival (OS) of avelumab in combination with axitinib in patients with previously untreated aRCC.

- To characterize the pharmacokinetics (PK) of avelumab and axitinib when administered in combination, and to assess the effect of avelumab on the PK of axitinib.

- To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that may aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib.

- To assess the immunogenicity of avelumab when combined with axitinib.

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METHODS

Study Design: This was a Phase 1b, open-label, multicenter, multiple-dose, safety, PK, and pharmacodynamic study of avelumab in combination with axitinib in treatment-naïve adult patients with aRCC. This clinical study was composed of a Dose Finding Phase and a Dose Expansion Phase.

The Dose Finding Phase estimated the MTD and selected the RP2D in patients with aRCC with clear cell histology who did not receive prior systemic therapy for advanced disease, using the modified toxicity probability interval (mTPI) method, with 3 potential dose levels (DLs) tested:

- DL1: avelumab 10 mg/kg every 2 weeks (Q2W) + axitinib 5 mg twice daily (BID).

- DL-1A: avelumab 5 mg/kg Q2W + axitinib 5 mg BID.

- DL-1B: avelumab 10 mg/kg Q2W + axitinib 3 mg BID.

To understand the extent of any effects of avelumab on axitinib PK, a 7-day lead-in period with single-agent axitinib was included prior to Cycle 1 for all patients in the Dose Finding Phase. Since avelumab has a half-life of 3 to 5 days, it was not feasible to run a lead-in with avelumab alone to study the PK of avelumab alone. Therefore, the effect of axitinib on

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avelumab was evaluated by comparing avelumab trough concentrations at steady state in the presence of axitinib with those reported for avelumab alone in prior studies.

The Dose Finding Phase led to the identification of the dose of avelumab in combination with axitinib to be evaluated in the Dose Expansion Phase in patients with aRCC who did not receive prior systemic therapy for their advanced disease; this dose for the combination in the Dose Expansion Phase was planned to be either the MTD or the RP2D. The Dose Expansion Phase planned to evaluated avelumab in combination with axitinib was evaluated in up to approximately 40 treatment-naïve patients with aRCC.

Based on the emerging PK data, and after completion of the Dose Finding Phase, up to approximately 8 additional patients may have been enrolled to further assess the effect of avelumab on the PK of axitinib. These additional patients underwent the same evaluations and procedures and were treated concurrently with the initiation of the Dose Expansion Phase. With the exception of the mTPI-related assessments leading to determination of MTD, any other assessments or procedures described for the Dose Finding Phase also applied to these additional patients.

The number of patients planned to be enrolled in the Dose Finding Phase depended on the observed safety profile and the number of tested dose levels. Up to approximately 55 patients (including Dose Finding and Dose Expansion Phases) were projected to be enrolled and treated in the study.

Diagnosis and Main Criteria for Inclusion: The study population consisted of treatment-naïve patients, aged ≥18 years (≥20 years in Japan), with histologically or cytologically confirmed aRCC with clear cell component, and an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.

Study Treatment:

Avelumab was administered on Day 1 of each 14-day cycle after all procedures and assessments had been completed. Avelumab may have been administered up to 3 days before or after the scheduled Day 1 of each cycle. Avelumab was administered as a 1-hour intravenous infusion Q2W. In order to mitigate infusion-related reactions (IRRs), a premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to each dose of avelumab was mandatory. This may have been modified based on local treatment standards and guidelines, as appropriate. The exact duration of infusion was recorded in both source documents and case report forms (CRFs). The dose amount that was required to prepare the avelumab infusion solution was based on the patient's weight in kilograms. All patients should have been weighed within 3 days prior to dosing for every cycle. Avelumab dose reduction for toxicity management was not permitted; however, next cycle administration may have been omitted due to persisting toxicity.

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Axitinib was taken per os BID by the patient, approximately 12 hours apart and at approximately the same time in the morning and evening, on a continuous dosing schedule (ie, without a break in dosing in the absence of drug-related toxicity). Tablets must not have been crushed, split, or dissolved, and patients were instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing. A dosing card was provided to the patients to provide guidance for the correct use of axitinib. Patients were instructed that if they missed a dose or vomited any time after taking a dose, they must not have "made it up" with an extra dose, but instead should have resumed subsequent doses as prescribed. Any missed dose may have been taken late, up to 3 hours before the next scheduled dose of that day, otherwise, it should have been skipped and dosing resumed with subsequent doses as prescribed. If doses were missed or vomited or if an extra dose was taken, this must have been indicated in the source documents and CRFs. If a patient inadvertently took 1 extra dose during a day, the patient should not have taken the next dose.

Investigational product information is provided in Table S1.

Table S1. Investigational Product Description

Investigational Product Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
Avelumab	[redacted]	[redacted]	20.0 mg/mL	Solution for intravenous use
Axitinib	[redacted]	[redacted]	1 mg	Film-coated tablets for oral use
	[redacted]	[redacted]	5 mg	Film-coated tablets for oral use

Efficacy Evaluations:

In this study, assessment of antitumor activity was a secondary objective. The secondary efficacy endpoints included objective response (OR) and disease control (DC) as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, and time-to-event endpoints (duration of response ([DR], progression-free survival [PFS], time to tumor response [TTR], and OS).

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Pharmacokinetic, Pharmacodynamic, and Other Evaluations:

Pharmacokinetics

The following avelumab serum and axitinib plasma PK parameters in Table S2 were calculated for each patient and treatment, as applicable, using noncompartmental analysis of plasma concentration-time data. Specimens for avelumab PK were collected from all patients in the study. Axitinib PK specimens were collected from all patients in the Dose Finding Phase and up to approximately 8 additional patients enrolled to assess the effect of avelumab on the PK of axitinib.

Table S2. Pharmacokinetic Parameters for Avelumab[a] and Axitinib

Parameter	Definition	Method of Determination
AUC_{last}	Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (C_{last})	Linear/Log trapezoidal method
AUC_{0-12}	Area under the plasma concentration-time profile after single dose from time zero to 12 hours	Linear/Log trapezoidal method
$AUC_{ss,tau}$	Area under the plasma concentration-time profile from time zero to time tau, the dosing interval (at steady state)	Linear/Log trapezoidal method
C_{max}	Maximum observed plasma concentration	Observed directly from data
T_{max}	Time for C_{max}	Observed directly from data as time of first occurrence
$t_{½}$[b]	Terminal half-life	$Log_e(2)/k_{el}$, where k_{el} is the terminal phase rate constant calculated by a linear regression of the log linear concentration time-curve. Only those data points judged to describe the terminal log linear decline were used in the regression.
C_{trough}	Predose concentration during multiple dosing	Observed directly from data
CL/F[b]	Apparent clearance	Dose / AUC_{tau} for steady state
V_z/F[b]	Apparent volume of distribution	Dose / ($AUC_{tau} \cdot k_{el}$) for steady state
AUC_{last}(dn)	Dose normalized AUC_{last}	AUC_{last} / Dose
C_{max}(dn)	Dose normalized C_{max}	C_{max} / Dose

a. Only C_{max} and C_{trough}
b. If data permit.

Pharmacodynamics

The tumor tissue biomarkers that were analyzed as secondary endpoints included programmed death-ligand 1 (PD-L1) expression, tumor-infiltrating CD8+ T lymphocytes, and CD68. Archival, recent or de novo, and de novo End of Treatment tumor tissue specimens were collected at specified time points. Peripheral blood specimens will be

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banked and may be used to identify or characterize cells, DNA, RNA, or protein markers known or suspected to be of relevance to the mechanisms of action, or the development of resistance to avelumab used in combination with axitinib.

Immunogenicity

The immunogenicity endpoints included anti-drug antibodies (ADAs) of avelumab when combined with axitinib. Whole blood specimens were collected at the designated times to provide serum for evaluation of avelumab immunogenicity. All of the specimens that were positive for ADA were characterized for neutralizing antibodies (nAb).

Safety Evaluations: The primary endpoint was dose-limiting toxicities (DLTs) within the first 4 weeks (2 cycles) of treatment with avelumab in combination with axitinib in the Dose Finding Phase.

Safety evaluations included adverse events (AEs), serious AEs (SAEs), AEs of special interest, safety laboratory assessments, pregnancy testing, vital signs, physical examinations, and 12-lead electrocardiograms (ECGs).

Statistical Methods:

Efficacy

The data set used for the analyses of the efficacy parameters was the full analysis set (FAS), which included all patients who received at least 1 dose of study drug. Assessment of response by the investigator was made using RECIST v1.1.

Best overall response (BOR) by RECIST v1.1 was assessed based on reported overall lesion responses at different evaluation time points from the date of the first dose of study treatment until the first documentation of progressive disease (PD). Only tumor assessments performed on or before the start date of any further anticancer therapies were considered in the assessment of BOR.

OR was defined as confirmed BOR of complete response (CR) or partial response (PR). Objective response rate (ORR) was the proportion of patients with OR in the analysis set. ORR by treatment group was also calculated along with the 2-sided 95% confidence interval (CI) using the Clopper-Pearson method. BOR was derived according to the following rules:

- CR: at least 2 determinations of CR at least 4 weeks apart and before first documentation of PD.
- PR: at least 2 determinations of PR or better (PR followed by PR or PR followed by CR) at least 4 weeks apart and before first documentation of PD (and not qualifying for a CR).

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- Stable disease (applicable only to patients with measurable disease at baseline) = at least 1 stable disease assessment (or better) ≥6 weeks after the first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).

- Non-CR/non-PD (applicable only to patients with non-measurable disease at baseline) = at least 1 non-CR/non-PD assessment (or better) ≥6 weeks after the first dose of study treatment and before first documentation of PD (and not qualifying for CR or PR).

- PD = first documentation of PD ≤12 weeks after the first dose of study treatment (and not qualifying for CR, PR, stable disease, or non-CR/non-PD).

- Not evaluable (NE): all other cases.

DC was defined as BOR of CR, PR, non-CR/non-PD, or stable disease by RECIST v1.1. The DC rate (DCR) was the proportion of patients with DC. The DCR was summarized by frequency counts and percentages.

DR was defined, for patients with OR by RECIST v1.1, as the time from the first documentation of OR (CR or PR) to the date of first documentation of PD or death due to any cause. Censoring rules for DR were as described below for PFS. DR was displayed graphically and analyzed using Kaplan-Meier methodology. Kaplan-Meier estimates (product-limit estimates) were presented by treatment group together with a summary of associated statistics including the median DR time with 2-sided 95% CI calculated according to the Brookmeyer and Crowley method.

TTR was defined, for patients with OR, as the time from the first dose of study treatment to the first documentation of OR (CR or PR) which was subsequently confirmed. TTR was summarized using simple descriptive statistics.

PFS was defined as the time from the first dose of study treatment to the date of the first documentation of PD or death due to any cause, whichever occurred first. PFS data were censored on the date of the last adequate tumor assessment for patients who did not have an event (PD or death), for patients who started a new anticancer therapy prior to an event, or for patients with an event after 2 or more missing tumor assessments. Patients who did not have an adequate baseline tumor assessment or who did not have an adequate post-baseline tumor assessment were censored on the date of the first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (ie, ≤12 weeks after the first dose of study treatment) in which case the death was considered an event. Kaplan-Meier estimates (product-limit estimates) were presented by treatment group together with a summary of associated statistics including the median PFS time with 2-sided 95% CI calculated according to the Brookmeyer and Crowley method.

OS was defined as the time from the first dose of study treatment to the date of death due to any cause. Kaplan-Meier estimates (product-limit estimates) were presented by treatment

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group together with a summary of associated statistics including the median OS time with 2-sided 95% CI calculated according to the Brookmeyer and Crowley method.

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Pharmacokinetics

The PK concentration analysis set was a subset of the safety analysis set and included patients who had at least 1 postdose concentration measurement above the lower limit of quantification (LLQ) for avelumab or axitinib. The PK parameter analysis set was a subset of the safety analysis set and included patients who had at least 1 of the PK parameters of interest for avelumab or axitinib.

For avelumab and axitinib, C_{trough} and C_{max} were summarized descriptively (n, mean, standard deviation [SD], coefficients of variation [CV], median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, cycle, and day. Other standard parameters for axitinib were calculated including, but not limited to T_{max}, AUC_{last}, AUC_{tau}, T_{last}, $t_{½}$, CL/F, and V_z/F, as data permitted. Multiple-dose $T_{ss,max}$, $AUC_{ss,tau}$, $t_{½}$, $C_{ss,av}$, CL/F, and V_z/F were also calculated as data permitted.

Dose normalized parameters (eg, dose-normalized C_{max}, dose-normalized C_{trough}) were reported as appropriate. The trough concentrations for avelumab and axitinib were plotted for each dose using a box whisker plot by cycle and day in order to assess the attainment of steady state.

The effect of repeated avelumab dosing on steady-state axitinib PK was evaluated using C_{max} and AUC_{tau} of axitinib on Lead-in Day 7 and Cycle 4 Day 1 as the primary PK parameters. The ratio of geometric means of C_{max} and AUC_{tau} (axitinib in presence of avelumab/axitinib alone) were computed to assess the magnitude of the effect. The associated 90% CIs were computed for the geometric mean ratios.

Pharmacodynamics

The biomarker analysis set for biomarkers that were measured only at screening was a subset of the safety analysis set and included patients who had at least 1 screening biomarker assessment. The biomarker analysis set for biomarkers that were measured sequentially was a subset of the safety analysis set and included patients who had at least 1 screening and 1 on-treatment biomarker assessment for the same marker. Analysis sets were defined separately for blood-based and tumor tissue-based biomarkers.

Tumor tissues collected prior to the first dose of study treatment were analyzed by immunohistochemistry for the expression of PD-L1 and the quantitation of tumor infiltrating

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CD8+ lymphocytes and tumor-associated CD68+ macrophages in relation to clinical outcome.

Summary statistics at each time point and ratio to screening (for continuous markers) were provided separately for each dose escalation cohort, the dose expansion cohort, and dose expansion cohort plus the same dose escalation cohort. For continuous biomarkers, ratio to screening within each cohort was tested using the Wilcoxon Sign-Rank Test when n ≥5 for a specific time point.

Immunogenicity

The immunogenicity analysis set was used as the basis for the analyses of immunogenicity endpoints. The immunogenicity analysis set was a subset of the safety analysis set and included patients who had at least one ADA/nAb specimen collected for avelumab. The incidence of ADA against avelumab was summarized as data permitted. The percentage of patients with positive ADA was summarized by treatment group. For patients with positive ADA, the magnitude (titer), time of onset, and duration of ADA response were also described, as data permitted. The impact of ADA on PK, safety, and efficacy was also assessed, as data permitted. The specimen analysis for nAb will be conducted after finalization of the assay methodology, and data analyses for nAb will be reported separately at a later date.

Safety

The DLT-evaluable set included all enrolled patients during the Dose Finding Phase who received at least 1 dose of avelumab and axitinib and either experienced DLT during the first 2 cycles of combination axitinib + avelumab treatment or completed the primary DLT observation period for the first 2 cycles of combination treatment (4 weeks). Dose-limiting toxicities were summarized based on the DLT-evaluable set by treatment group including data from the Dose Finding Phase only. DLTs were also listed.

The safety analysis set included all patients who received at least 1 dose of study drug and was the primary population for safety evaluations. Summaries of AEs and other safety parameters were based on the safety analysis set by treatment group. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system. The severities of the AEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v4.03 whenever possible. Emphasis in the analysis was placed on AEs classified as treatment emergent. AEs leading to death or discontinuation of study treatment, Grade 3 or higher AEs, treatment-related AEs (defined as related to either 1 of the study drugs in the combination), and SAEs were summarized by treatment group.

RESULTS

Subject Disposition and Demography: A total of 80 patients were screened for participation in the study; 25 patients were screen failures, and 55 patients completed

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screening and received at least 1 dose of study drug. At the time of data cutoff, 20 patients were still on treatment: 17 patients (30.9%) with the combination, 1 patient (1.8%) with avelumab single agent, and 2 patients (3.6%) with axitinib single agent (Table S3). Additionally, 1 patient (1.8%) was in follow up and 13 patients (23.6%) were in long-term follow-up for OS.

The primary reason for discontinuation of avelumab and the primary reason for discontinuation of axitinib was PD. The primary reasons for discontinuation during follow-up and long-term follow-up were Other (start of new therapy) and Death, respectively.

A total of 55 patients were enrolled in 3 countries: US (31 patients [56.4%]), Japan (5 patients [9.1%]), and UK (19 patients [34.5%]). The median time from the initial diagnosis of RCC to the date of first dose of study treatment was 8.77 months. The median time from diagnosis of recurrent/metastatic disease to the date of first dose of study treatment was 2.79 months.

Table S3. End of Treatment Disposition for Subjects in Combination Group - Full Analysis Set - Protocol B9991002 - (Cutoff date: 03Apr2018, Snapshot Date: 17May2018)

		Avelumab	Axitinib		
		Discontinued n (%)	Ongoing n (%)	All Subjects n (%)
DL1 with Lead-in	Discontinued, n (%)	9 (56.3)	0	9 (56.3)
	Ongoing, n (%)	0	7 (43.8)	7 (43.8)
	Total, n (%)	9 (56.3)	7 (43.8)	16 (100.0)
DL1	Discontinued, n (%)	26 (66.7)	2 (5.1)	28 (71.8)
	Ongoing, n (%)	1 (2.6)	10 (25.6)	11 (28.2)
	Total, n (%)	27 (69.2)	12 (30.8)	39 (100.0)
Total	Discontinued, n (%)	35 (63.6)	2 (3.6)	37 (67.3)
	Ongoing, n (%)	1 (1.8)	17 (30.9)	18 (32.7)
	Total, n (%)	36 (65.5)	19 (34.5)	55 (100.0)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group. Status of discontinued or ongoing is based on End of Treatment Disposition CRF page.

Efficacy Results:

Avelumab in combination with axitinib was clinically active as evidenced by the ORR of 60% (95% CI: 45.9, 73.0). Forty-five of 54 treated patients with target lesions and a post-baseline tumor assessment had at least some degree of tumor shrinkage in the target lesions during the study. ORRs were similar among all Memorial Sloan Kettering Cancer

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Center and Heng Prognostic criteria subgroups with observed ORR ranging from 57.1% to 61.5%.

Responses to avelumab in combination with axitinib in general had an early onset (median TTR of 1.6 months) with 20 of 33 responses occurring at the time of the first tumor assessment. Responses were durable (the probability of being event-free for DR at 18 months was 0.644 (95% CI: 0.447, 0.787)). The median DR based on the Kaplan-Meier method had not been reached at the time of data cutoff. According to investigator assessment, 4 patients with PR subsequently achieved a CR with continued study treatment; the CRs were ongoing for these patients at the time of data cutoff. Overall, 21 of 33 patients who responded were still in response at the time of data cutoff.

At the time of data cutoff, 56.4% of patients had an event (PD or death) for the analysis of PFS. The median PFS based on the Kaplan-Meier method was 8.3 months (95% CI: 5.3, NE), with a probability of being event-free for PFS at 18 months of 0.431 (95% CI: 0.296, 0.559). The median duration of follow-up for PFS was 22.0 months (95% CI: 19.5, 23.5), estimated using the reverse Kaplan-Meier method which reverses the event/censoring flag used in the PFS analysis.

At the time of data cutoff, 13 patients (23.6%) had died. The probability of being event-free for OS at 18 months was 0.826 (95% CI: 0.691, 0.906) and median OS based on the Kaplan-Meier method had not been reached. The median duration of follow-up for OS was 22.3 months (95% CI: 19.8, 23.4), estimated using the reverse Kaplan-Meier method which reverses the event/censoring flag used in the OS analysis.

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Pharmacokinetic, Pharmacodynamic, and Immunogenicity Results:

Pharmacokinetics

Mean axitinib plasma concentrations versus time were similar following co-administration of multiple oral doses of axitinib (5 mg BID) with multiple intravenous (IV) doses of avelumab (10 mg/kg Q2W; Cycle 4 Day 1) and following administration of axitinib alone (Lead-in Day 7). The variability was high (%CV of the mean ranged from 90% to 149%) due to the small sample size. Avelumab concentrations appeared to reach steady state at Cycle 2 and serum trough concentrations of avelumab did not appear to increase over time. Axitinib exposures as measured by dose-normalized AUC_{last}, AUC_{tau}, and C_{max} values following co-administration of avelumab were similar to those following administration of axitinib alone.

The geometric mean ratios for axitinib dose-normalized AUC_{last}, AUC_{tau}, and C_{max} ranged from 0.77 to 0.91, with 90% CIs overlapping 1, indicating similar exposures following co-administration of avelumab with axitinib versus axitinib alone.

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Pharmacodynamics

The majority (41 of 52) of patients had PD-L1-positive tumors at the 1% cutoff defined as PD-L1 staining of any intensity in tumor-associated immune cells (ICs) covering ≥1% of tumor area.

Patients with PD-L1-expressing tumor-associated ICs within the tumor area were more likely to have OR than patients with PD-L1-negative tumors. Patients with confirmed OR had more CD8+ cells within the tumor area than patients with no confirmed OR. No meaningful difference was observed in the numbers of CD68+ cells within the tumor area for patients with confirmed OR versus patients with no confirmed OR. There was no meaningful difference in the proportion of patients achieving DC for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff.

At the time of data cutoff, 28 of 52 patients assessed for PD-L1 status had PFS events (PD or death). The Kaplan-Meier estimate of median PFS was greater for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff (15.44 months (95% CI: 6.9, NE) versus 4.17 months (95% CI: 0.9, NE), respectively). The probability of being event-free for PFS at 18 months was greater for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff (0.50 (95% CI: 0.33, 0.64) versus 0.30 (95% CI: 0.07, 0.58), respectively. A favorable hazard ratio (HR) was observed for patients with PD-L1-positive tumors at the 1% cutoff (PD-L1-positive vs PD-L1-negative, 0.50 (95% CI: 0.21, 1.18)).

The probability of being event-free for OS at 18 months was greater for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff (0.87 (95% CI: 0.71, 0.94) versus 0.72 (95% CI: 0.35, 0.90), respectively. A favorable HR was observed for patients with PD-L1-positive tumors at the 1% cutoff (PD-L1-positive vs PD-L1-negative; 0.37 with 95% CI: 0.12, 1.16).

Forty-three of 51 patients assessed for PD-L1 status had tumor shrinkage in the target lesions, among whom 33 had best shrinkage of 30% or greater in the target lesions. Of these 33 patients, 29 had PD-L1 staining of any intensity in tumor-associated ICs covering ≥1% of tumor area and 21 had PD-L1 staining of any intensity in tumor-associated ICs covering ≥5% of tumor area.

Immunogenicity

Of the 9 patients with treatment-induced ADA, the median time to ADA response was 4.14 weeks (range: 2.14, 14.29). Treatment-induced ADA-positive patients generally had lower serum avelumab C_{trough} values (the geometric mean C_{trough} ranged from 8.5 to 63.9 μg/mL) versus C_{trough} values (the geometric mean C_{trough} ranged from 1.0 to 67.5 μg/mL) of ADA-never-positive or baseline ADA-positive patients. Although a difference was observed between the groups, variability was high, with geometric CV ranging from 27% to 645% for treatment-induced ADA-positive patients and from 52% to 181% for

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ADA-never-positive or baseline ADA-positive patients. Overall, no clinically meaningful impact of ADA on the safety profile was identified. The percentage of patients reporting treatment-emergent AEs (TEAEs) was the same (100%) for treatment-induced ADA positive patients and ADA never-positive or baseline ADA positive patients. Similarly, the percentage of patients reporting TEAEs was the same (100%) for ADA ever-positive versus ADA never-positive patients. Of the 10 ADA ever-positive patients with target lesions and a post-baseline tumor assessment in the immunogenicity analysis set, 8 patients had a decrease from baseline in the sum of diameters of target lesions.

Safety Results: There was a single DLT reported at DL1 during the DLT-evaluable period (proteinuria). The MTD of avelumab in combination with axitinib was estimated to be equal to or greater than avelumab 10 mg/kg IV Q2W + axitinib 5 mg oral BID. The RP2D of avelumab in combination with axitinib was determined to be avelumab 10 mg/kg IV Q2W + axitinib 5 mg oral BID.

All 55 patients (100%) who received at least 1 dose of study drug were reported with TEAEs. Twenty-three of 55 patients (41.8%) had serious TEAEs and 13 of 55 patients (23.6%) had serious TEAEs related to study treatment as assessed by the investigator. Overall, 3 patients (5.5%) were reported to have TEAEs leading to death. Out of the 13 patients (23.6%) who discontinued any study drug due to TEAEs, 11 patients (20%) discontinued due to TEAEs considered related to study treatment.

Based on the immune-related adverse event (irAE) case definition and subsequent medical review, a total of 24 patients (43.6%) experienced irAEs. Overall, 5 patients (9.1%) were reported to have Grade ≥3 irAEs, of which, 4 patients (7.3%) were reported to have Grade 3 irAEs and 1 patient (1.8%) was reported to have a Grade 5 irAE. A total of 6 patients (10.9%) experienced serious irAEs.

Based on the IRR case definition, a total of 18 patients (32.7%) experienced an infusion-related reaction (IRR). One patient (1.8%) was reported to have a Grade 3 IRR with onset at the second infusion of avelumab that was reported as an SAE. In addition to this case, there was another serious IRR of Grade 2 severity. Most patients with IRRs (17 out of 18) had the first IRR at the first infusion.

The laboratory results are generally consistent with the known safety profile of avelumab and axitinib. No patient met the criteria of a possible Hy's Law case.

Three patients were reported with clinical significant ECG abnormalities, 2 of which were reported as TEAEs.

All patients had an ECOG performance score of 0 (36 patients, 65.5%) or 1 (19 patients, 34.5%) at Baseline. Four and 3 patients (7.3% and 5.5%) worsened to an ECOG of 2 and 3 during the on-treatment period, respectively.

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CLINICAL STUDY REPORT SYNOPSIS

There were no clinically notable changes from Screening in physical examinations reported during the study.

Conclusions:

- The MTD of avelumab in combination with axitinib was estimated to be equal to or greater than avelumab 10 mg/kg IV Q2W + axitinib 5 mg oral BID. The RP2D of avelumab in combination with axitinib was determined to be avelumab 10 mg/kg IV Q2W + axitinib 5 mg oral BID.

- The safety profile of avelumab in combination with axitinib in treatment-naïve patients with aRCC was generally manageable, well tolerated, and consistent with the known safety profiles of avelumab and axitinib as single agents.

- Clinically significant antitumor activity of avelumab in combination with axitinib was observed. The combination treatment was associated with a high ORR in treatment-naïve patients with aRCC irrespective of PD-L1 expression on tumor-associated ICs. Responses were generally durable, rapid in onset, and included both CRs and PRs.

- Overall survival data are immature, and no definitive conclusions can be drawn at this time.

- Co-administration of multiple IV doses of avelumab with multiple oral doses of axitinib had no clinically meaningful effect on the PK of axitinib.

- A higher probability of response was observed for patients whose tumors were PD-L1-positive at the 1% cutoff versus those whose tumors were PD-L1-negative, and a similar trend was also observed for patients with higher proportions of CD8+ cells within their pre-treatment tumor samples. The value of testing PD-L1 status is further explored in a randomized Phase 3 study.

- No clinically meaningful impact of ADA on the PK or safety of avelumab was observed.

- [redacted]

- Overall, these data support further investigation of avelumab in combination with axitinib in a randomized Phase 3 study.

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