CLINICAL STUDY REPORT SYNOPSIS

Sponsor: Pfizer, Inc.

Investigational Product: Avelumab, Axitinib

Clinical Study Report Synopsis: Protocol B9991024

Protocol Title: An Open Label, Single Arm Phase 1B Study of Avelumab Plus Axitinib as First Line Treatment in Patients With Advanced Hepatocellular Carcinoma

Investigators: Refer to Appendix 16.1.4.1 for a list of investigators involved in this study.

Study Center(s): Seven centers in Japan participated in the study. Refer to Appendix 16.1.4.1 for a list of sites involved in this study.

Publications Based on the Study: None

Study Initiation Date: 08 September 2017

Study Completion Date: 25 October 2019

Report Date: 13 July 2020

Previous Report Date(s): Not applicable

Phase of Development: Phase 1b

Primary and Secondary Study Objectives and Endpoints: The study objectives and endpoints of this study are presented in Table S1.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary		
Safety	To evaluate the safety and tolerability of avelumab in combination with axitinib as first line treatment in patients with advanced HCC.	AEs and laboratory abnormalities as graded by NCI CTCAE v4.03.
Secondary		
Efficacy	To evaluate antitumor effect of avelumab in combination with axitinib as first line treatment in patients with advanced HCC per RECIST v1.1.	TTP, PFS, OR, DC, TTR and DR, per RECIST v1.1.
	To evaluate the OS of avelumab in combination with axitinib in patients with advanced HCC.	OS.
PK	To evaluate the PK of avelumab and axitinib when administered in combination.	PK parameters including trough and maximum concentrations (C_{trough}, C_{max}) of avelumab and axitinib.
Pharmacodynamics	To evaluate candidate predictive biomarkers in pre-treatment tumor tissue that could aid in the identification of a patient subpopulation most likely to benefit from treatment with avelumab in combination with axitinib.	Tumor tissue biomarker status (ie, positive or negative based on, eg, PD-L1 expression and/or quantitation of tumor-infiltrating CD8+ T lymphocytes as assessed by IHC).
Immunogenicity	To assess the immunogenicity of avelumab when combined with axitinib.	ADAs and nAbs for avelumab when in combination with axitinib.

Abbreviations: ADA=anti-drug antibodies; AE=adverse event; C_{max}=maximum observed concentration; CTCAE=Common Terminology Criteria for Adverse Events; C_{trough}=predose concentration during multiple dosing; DC=disease control; DR=duration of response; HCC=hepatocellular carcinoma; IHC=immunohistochemistry; nAb=neutralizing antibody; NCI=National Cancer Institute; OR=objective response; OS=overall survival; PD-L1=programmed death Ligand 1; PFS=progression-free survival; PK=pharmacokinetic; RECIST=Response Evaluation Criteria in Solid Tumors; TTP=time to progression; TTR=time to tumor response.

METHODS

Study Design: This was an open-label, multicenter, single arm, Phase 1b study to evaluate the safety, efficacy and pharmacokinetic (PK) of avelumab in combination with axitinib as first line treatment in patients with advanced hepatocellular carcinoma (HCC).

Twenty-two patients with advanced HCC who did not have the prior systemic therapy were enrolled in this study. The overall safety profile of these patients was assessed after a minimum follow-up of 3 months (ie, at least 3 months from the last patient first dosing). Significant toxicities including immune-related adverse events (irAEs) which occurred up to 3 months of follow-up after the last dose of study treatment were also to be included in the assessment. Patients received avelumab 10 mg/kg every 2 weeks (Q2W) in combination with axitinib 5 mg twice daily (BID). If this dose level for the combination was not

CLINICAL STUDY REPORT SYNOPSIS

tolerable, a lower axitinib dose in the combination (avelumab 10 mg/kg [intravenous {IV}] Q2W plus axitinib 3 mg BID) may have been evaluated with adding new cohorts of patients. In addition, a cohort of patients aimed to evaluate avelumab 800 mg flat dose Q2W in combination with axitinib 5 mg BID may have been added after the tolerability of avelumab 10 mg/kg Q2W in combination with axitinib 5 mg BID was confirmed.

Diagnosis and Main Criteria for Inclusion:

Diagnosis of locally advanced or metastatic HCC, obtained by histology/cytology (on a prior tumor biopsy) or by imaging (acceptable imaging modalities include triphasic contrast-enhanced helical computerized tomography [CT], triphasic dynamic contrast-enhanced magnetic resonance imaging [MRI] and contrast-enhanced ultrasonography) with serum α-fetoprotein ≥400 ng/mL, and the patients who had provided at least 1 archival tumor specimen. If archival tumor specimen was no longer available, de novo tumor biopsy was required during screening were included in the study.

Patients with prior systemic treatment for advanced HCC, including prior treatment with approved or investigational drugs and with any prior locoregional therapy (such as hepatic arterial embolization, targeted through the hepatic artery combined with embolization, hepatic arterial infusion, radiofrequency ablation, percutaneous ethanol injection or cryoablation) within 4 weeks and radiotherapy or surgical procedure within 2 weeks (4 weeks for major surgery) of starting the study treatment were excluded from the study. Prior palliative radiotherapy to metastatic lesion(s) was permitted, provided it had been completed at least 48 hours prior to starting the study treatment.

Study Treatment:

Avelumab was formulated as a 20.0 mg/mL solution and was supplied by the sponsor in single-use glass vials, stoppered with a rubber septum and sealed with an aluminum polypropylene flip-off seal. For application in this study, avelumab drug product was diluted with 0.9% saline solution (sodium chloride injection). Avelumab was administered on Day 1 of each 14-day cycle after all procedures/assessments had been completed, and it may have been administered up to 3 days before or after the scheduled Day 1 of each dose.

Avelumab was administered as a 1-hour IV infusion Q2W. In order to mitigate avelumab infusion-related reactions, patients had to be premedicated approximately 30 to 60 minutes prior to the first 4 infusions of avelumab. Premedication should have been administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. Premedication included an antihistamine (eg, 25-50 mg diphenhydramine IV or oral equivalent), and paracetamol (acetaminophen) (eg, 500-650 mg paracetamol [acetaminophen] IV or oral equivalent).

Axitinib was administered orally BID 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. Axitinib tablets were to be taken approximately 12 hours apart and

CLINICAL STUDY REPORT SYNOPSIS

could have been administered without regard to meals. Tablets were not to be crushed, split, or dissolved, and patients were instructed to swallow the study medication whole without manipulation or chewing of the medication prior to swallowing. The study drug information is provided in Table S2.

Table S2. Study Drug Description

Study Drug Description	Vendor Lot Number	Pfizer Lot Number	Strength/Potency	Dosage Form
AG-013736 1 mg A immediate release film coated tablet	L34589	15-004995	1 mg	Tablet
AG-013736 5 mg immediate release film coated tablet	L22422	15-004998	5 mg	Tablet
MSB0010718C solution for infusion, 20 mg/mL (10 mL/vial)	PD1G001	16-000917	200 mg	Solution

Efficacy Evaluations:

In this study, the efficacy evaluation included assessment of antitumor activity. Tumor assessments included all known or suspected disease sites. Imaging may have included chest, abdomen, and pelvis CT or MRI scans; it could also include brain CT or MRI scan at baseline and whenever brain metastases were suspected. The CT and MRI scans were performed with contrast agents unless contraindicated for medical reasons. The same imaging technique used to characterize each identified and reported lesion at baseline was employed for tumor assessments. The antitumor activity was assessed based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 through radiological tumor assessments for secondary endpoints.

The efficacy evaluations were conducted at baseline, and every 8 weeks thereafter until confirmed progressive disease (PD) per RECIST v1.1 and at the end of treatment (EOT)/withdrawal.

Pharmacokinetic, Pharmacodynamic and Immunogenicity Evaluations:

Pharmacokinetics

The PK evaluation in this study included calculation of following PK parameters of avelumab and axitinib:

- Predose concentration during multiple dosing (C_{trough}); and
- Maximum observed concentration (C_{max})

Blood samples (3.5 mL) for avelumab PK were collected in all patients: predose and at the end of infusion (immediately before the end of avelumab infusion) on Day 1 of Cycle 1, 2, 3 and 4. After that, trough (predose) samples were collected at Cycles 6 and 8 and then every

CLINICAL STUDY REPORT SYNOPSIS

4 cycles, ie, every 8 weeks thereafter until Cycle 24. Predose samples could have be taken up to 2 hours prior to the start of avelumab infusion.

Blood samples for axitinib (3 mL) were collected at predose and 2 hours postdose on Day 1 of Cycle 1, Cycle 2 and Cycle 3.

PK blood samples were assayed for avelumab and axitinib using validated analytical methods.

Pharmacodynamics

Blood samples for pharmacodynamic evaluations were collected at Day 1 of Cycle 1, 2, 3, 4, and 6 and the EOT/withdrawal visit enabled investigation of potential mechanisms of resistance to the drug combination. Mandatory archival or de novo formalin-fixed and paraffin-embedded tumor tissue were collected at the time of screening.

Archived tumor tissue samples and de novo biopsies of primary and/or metastatic lesions were used to analyze the programmed death Ligand 1 (PD-L1) and CD8.

Immunogenicity

One blood sample (3.5 mL) for anti-avelumab antibodies was collected into a serum separator tube to provide the serum for the evaluation of avelumab immunogenicity at predose on Day 1 of Cycles 1, 2, 3, 4, 6, and 8 and then every 4 cycles until Cycle 32, ie, every 8 weeks thereafter until Cycle 32.

The immunogenicity blood samples were assayed for anti-avelumab antibodies using a validated analytical method. All of the samples that were positive for anti-drug antibodies (ADA) might have also undergone characterization for neutralizing antibodies (nAbs).

Safety Evaluations: Safety assessments consisted of the collection of adverse events (AEs), serious adverse events (SAEs), vital signs, physical examination, 12-lead electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), laboratory assessments, including pregnancy tests.

Safety was monitored at regular intervals throughout, and the AEs were recorded at each visit in the study.

Statistical Methods:

Efficacy

The efficacy endpoints, objective response (OR), disease control (DC), duration of response (DR), time to tumor response (TTR), time to progression (TTP), progression-free survival (PFS) and overall survival (OS) analyses were based on the full analysis set (FAS)

CLINICAL STUDY REPORT SYNOPSIS

by treatment group. FAS included all patients who received at least 1 dose of study drug. Assessment of response was made using RECIST v1.1. Tumor-related endpoints were analyzed separately based on investigator assessment and blinded independent central review (BICR) assessment.

Best Overall Response and Objective Response

Best overall response was assessed based on reported overall lesion responses at different evaluation time points from the first dose of study treatment until the first documentation of PD, according to the following rules. Only tumor assessments performed on or before the start date of any further anti-cancer therapies were considered in the assessment of best overall response. Clinical deterioration was not to be considered as documentation of disease progression.

The OR was defined as complete response (CR) or partial response (PR) according to RECIST v1.1 from the date of first dose of study treatment until the date of the first documentation of progression of disease. Both CR and PR was confirmed by repeat assessments performed at least 4 weeks apart after the criteria for response were first met.

The OR rate by treatment group was also calculated along with the 2-sided 95% confidence interval (CI) using the Clopper-Pearson method.

Disease Control

The DC was defined as CR, PR, non-CR/non-PD or stable disease. Criteria for stable disease and non-CR/non-PD were met at least 8 weeks after date of first dose of study treatment. DC rate was summarized by frequency counts and percentages.

Duration of Response

The DR was defined, for patients with an OR, 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.

If a patient has not had an event (PD or death), DR was censored at the date of last adequate tumor assessment. 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% CIs. If the number of patients with OR was small, the Kaplan-Meier method could not provide reliable estimates. In this case, only descriptive statistics or listings were provided.

Time to Response

The TTR was defined, for patients with an OR, as the time from the date of first dose of study treatment to the first documentation of OR (CR or PR) which was subsequently

CLINICAL STUDY REPORT SYNOPSIS

confirmed. TTR was summarized using simple descriptive statistics (mean, standard deviation [SD], median, minimum, maximum, first quartile [Q1] and third quartile [Q3]).

Time to Progression

TTP was defined as the time from the date of first dose of study treatment to the date of the first documentation of progression of disease.

TTP data were censored on the date the last adequate tumor assessment for patients without PD, for patients who started new anti-cancer therapy prior to PD, for patients who died without PD, or for patients with PD after ≥2 missing tumor assessments. Patients who did not have a baseline tumor assessment or who did not have any post-baseline tumor assessments were censored on the date of first dose of study treatment.

Kaplan-Meier estimates (product-limit estimates) were presented by treatment group together with a summary of associated statistics including the median TTP time with 2-sided 95% CIs.

Progression-Free Survival

PFS was defined as the time from the date of first dose of study treatment to the date of the first documentation of progression of disease 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 anti-cancer therapy prior to an event or for patients with an event after ≥2 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 first dose of study treatment unless death occurred on or before the time of the second planned tumor assessment (ie, ≤16 weeks after date of 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% CIs.

Overall Survival

The OS was defined as the time from the date of first dose of study treatment to the date of death due to any cause. Patients who were last known to be alive, were censored at date of last contact. Kaplan-Meier estimates (product-limit estimates) were presented by treatment group together with a summary of associated statistics including the median OS time with 2-sided 95% CIs.

CLINICAL STUDY REPORT SYNOPSIS

Subset Analysis

Subset analyses using PD-L1 status (thresholds were <1%/≥1% and <10%/≥10%) at baseline were performed for OR and PFS as per investigator assessment and BICR assessment based on RECIST v1.1, and for OS, based on the FAS.

Pharmacokinetics

PK concentration analysis set: 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 quantitation for avelumab or axitinib.

PK parameter analysis set: 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.

The following PK analyses were based on the PK analyses set by treatment group.

C_{trough} and C_{max} for avelumab and axitinib were summarized descriptively (n, mean, SD, coefficient of variation [CV], median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment group, cycle, and day.

PK parameters for avelumab and axitinib were taken from observed values or derived from concentration-time data.

Pharmacodynamics

Biomarker data were summarized based on the biomarker analysis set by treatment group. 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 data were summarized at all time points described below:

- Archived tumor biospecimens and de novo tumor biopsy: Screening.
- Banked blood biospecimens: Cycle 1 Day 1, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Cycle 6 Day 1.

Summary statistics, using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum), at each time point, ratio to screening and percent change from the value at Screening/Cycle 1 Day 1 if available (for continuous markers) were provided by treatment group.

Some biomarker analyses of tumor and blood specimens are reported separately.

CLINICAL STUDY REPORT SYNOPSIS

Immunogenicity

Immunogenicity data were summarized based on the immunogenicity analysis set by treatment group. The immunogenicity analysis set was a subset of the safety analysis set and included patients who had at least 1 ADA/nAb sample collected for avelumab.

Safety

The safety analysis set was the primary population for safety evaluations. It included all patients who received at least 1 dose of study drug. Summaries of AEs and other safety parameters were based on the safety analysis set by treatment group.

Laboratory results were classified according to the National Cancer Institute - Common Terminology Criteria for Adverse Events criteria Version 4.03. Quantitative data were summarized descriptively.

The other safety evaluation parameters ie, vital signs, ECGs, LVEF, physical examination and Eastern Cooperative Oncology Group performance status were summarized descriptively in the study.

All analyses were carried out as detailed earlier, except for summarizing by treatment group since there was only 1 treatment group in this study.

RESULTS

Patient Disposition and Demography:

The patient disposition for avelumab and axitinib is provided in Table S3 and Table S4, respectively. A total of 22 patients were enrolled in the study and all patients discontinued the study treatments. The primary reason for discontinuation of avelumab and axitinib was PD. One patient discontinued axitinib due to AE, and then, discontinued avelumab due to PD.

Note: Group A refers to the study treatment “Avelumab 10 mg/kg + Axitinib 5 mg”.

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Patient Disposition for Avelumab at End of Treatment - Full Analysis Set

Number of Patients	Group A (N=22)
	n (%)
Disposition phase: end of treatment	
Discontinued	22 (100.0)
Reason for discontinuation	
Adverse event	2 (9.1)
Progressive disease	18 (81.8)
Withdrawal by patient	2 (9.1)
Ongoing	0

The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.

Table S4. Patient Disposition for Axitinib at End of Treatment - Full Analysis Set

Number of Patients	Group A (N=22)
	n (%)
Disposition phase: end of treatment	
Discontinued	22 (100.0)
Reason for discontinuation	
Adverse event	3 (13.6)
Progressive disease	17 (77.3)
Withdrawal by patient	2 (9.1)
Ongoing	0

The denominator to calculate percentages is N, the number of patients in the full analysis set within each treatment group.

A total of 22 Japanese patients (20 male [90.9%] and 2 female [9.1%]) were included in the study. The median age (range) of patients was 68.5 (20-84) years. The median time from the initial diagnosis of HCC to the date of first dose of study treatment was 16.59 months. The median time from diagnosis of recurrent/metastatic disease to the date of first dose of study treatment was 2.42 months.

The majority of patients (17 of 20) had PD-L1 positive tumors at the 1% cutoff defined as PD-L1 staining of any intensity in tumor-associated immune cells (ICs) and tumor cells (TCs) covering ≥1% of tumor area.

CLINICAL STUDY REPORT SYNOPSIS

Efficacy Results:

Best Overall Response and Objective Response

ORs (ie, CR + PR) were observed in 3 patients (13.6% [95% CI: 2.9, 34.9]) per investigator assessment.

DC (ie, CR + PR + stable disease + non-CR/non-PD) was observed in 15 patients (68.2% [95% CI: 45.1, 86.1]) per investigator assessment (RECIST v1.1). Fifteen of 21 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.

As per BICR assessment, OR was observed in 1 patient (4.5% [95% CI: 0.1, 22.8]) and DC was observed in 15 patients (68.2% [95% CI: 45.1, 86.1]).

Time to Tumor Response and Duration of Response

The median TTR observed for avelumab in combination with axitinib was 1.91 months (range: 1.9, 3.7). The median DR using Kaplan-Meier estimates (RECIST v1.1) was 7.29 months (95% CI: 3.71, 12.94).

Time to Progression

The results of TTP showed that at the time of data cutoff, 21 patients (95.5%) had an event (PD) for the analysis of TTP. The median TTP using Kaplan-Meier estimates (RECIST v1.1) was 5.52 months (95% CI: 1.91, 7.39).

Progression-Free Survival

The PFS results per investigator assessment (RECIST v1.1) showed that at the time of data cutoff, 21 patients (95.5%) had an event (PD or death) for the analysis of PFS. The median PFS was 5.52 months (95% CI: 1.91, 7.39), and the PFS rates at 6 and 12 months were 38.1% (95% CI: 18.3, 57.8) and 9.5% (95% CI: 1.6, 26.1), respectively.

The median duration of follow-up for PFS based on investigator assessment was not applicable (NA) (95% CI: NA, NA), estimated using reverse Kaplan-Meier method.

As per BICR assessment, median PFS was 5.55 months (95% CI: 2.79, 9.33). The PFS rates at 6 and 12 months were 46.4% (95% CI: 24.4, 65.9) and 18.6% (95% CI: 3.9, 41.7), respectively. The median duration of follow-up for PFS based on BICR assessment was 11.07 months (95% CI: 5.55, 14.65), estimated using reverse Kaplan-Meier method.

CLINICAL STUDY REPORT SYNOPSIS

Overall Survival

The results of OS showed that at the time of data cutoff, 12 patients (54.5%) had an event (death) for the analysis of OS. The median OS was 14.05 months (95% CI: 7.95, NA) and OS rate at 12 months was 54.5% (95% CI: 32.1, 72.4).

The median duration of follow-up for OS was 23.23 months (95% CI: 20.34, 23.95), estimated using reverse Kaplan-Meier method.

Subset Analysis by Patients With PD-L1-Positive and PD-L1-Negative Tumors

Objective Response and Disease Control

In the IC + TC combined group, results of OR and DC evaluation were as follows:

Based on the investigator assessment (RECIST v1.1), the OR for patients with PD-L1-positive and PD-L1-negative tumors at the 1% cutoff was observed in 3 patients (17.6% [95% CI: 3.8, 43.4]), and no patient (95% CI: 0.0, 70.8), respectively.

The DC for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff was observed in 13 patients (76.5% [95% CI: 50.1, 93.2]), and 1 patient (33.3% [95% CI: 0.8, 90.6]), respectively.

Progression-Free Survival

In the IC + TC combined group, results of PFS evaluation were as follows:

Based on the investigator assessment (RECIST v1.1), the Kaplan-Meier estimate of median PFS for patients (95% CI) with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff was 5.55 months (1.91, 9.17) and 5.49 months (1.77, 9.20), respectively. The probability of being event-free for PFS (95% CI) at 6 months for patients with PD-L1-positive tumors at the 1% cutoff was 41.2% (18.6, 62.6), and was 50.0% (0.6, 91.0) for PD-L1-negative tumors. The probability of being event-free for PFS (95% CI) at 12 months for patients with PD-L1-positive tumors at the 1% cutoff was 11.8% (2.0, 31.2), and was not applicable for PD-L1-negative tumors.

Overall Survival

In the IC + TC combined group, the Kaplan-Meier estimate of median OS for patients (95% CI) with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff was NA (8.71, NA), and 7.95 months (6.05, NA) respectively. The probability of being event-free (95% CI) for OS at 12 months for patients with PD-L1-positive tumors at the 1% cutoff was 64.7% (37.7, 82.3) and was 33.3% (0.9, 77.4) for PD-L1-negative tumors.

CLINICAL STUDY REPORT SYNOPSIS

Pharmacokinetic, Pharmacodynamic and Immunogenicity Results:

Pharmacokinetics

Avelumab serum concentrations appeared to reach steady state at Cycle 2. After Cycle 2 Day 1, avelumab C_{trough} concentrations trended slightly upward upto Cycle 28 Day 1. However, the variability in mean C_{trough} ranged from 19% to 51%, with mostly overlapping distribution of concentration over time. Therefore, the interpretation of the time dependency in C_{trough} was limited due to a decrease in sample size over time.

Mean and median axitinib plasma C_{trough} concentrations remained stable on Cycle 2 Day 1 and Cycle 3 Day 1, in the presence of avelumab.

Mean and median axitinib plasma C_{max} concentrations also remained stable on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1, in the presence of avelumab. The variability in mean C_{trough} and C_{max} ranged from 73% to 106%, with overlapping distribution of concentration over time. This indicated that axitinib exposure was not affected by the administration of avelumab on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1.

Pharmacodynamics

Biomarkers in the study included PD-L1 status and CD8+ cells.

For the PD-L1 target, the median (range) of IC% was 2.50% (0.0, 15.0). The majority (17 of 20) of patients had PD-L1-positive tumors at the 1% cutoff defined as PD-L1 staining of any intensity in tumor-associated ICs and TCs covering 1% of tumor area.

The median (range) of CD8+ cells invasive margin (%) and CD8+ cells total area (%) were 2.06% (0.2, 5.4) and 0.55% (0.1, 5.9), respectively.

Immunogenicity

There were low incidences of ADA reported in the study. Three patients (13.6%) were reported as ADA ever-positive. Treatment-induced ADA response was observed in 3 patients (13.6%); with all having persistent ADA response (3 patients [13.6%]).

The median duration of time to ADA response was 10.14 weeks (range: 4.00-14.14). A Kaplan-Meier plot of duration of ADA response showed that out of the 3 patients with treatment-induced ADA, the median duration of ADA response was 8.14 weeks (95% CI: 4.57, 9.14).

Three patients (13.6%) were reported as nAb ever-positive. The median duration of time to nAb response was 10.14 weeks (range: 8.43-14.14). A Kaplan-Meier plot of duration of nAb showed that out of the 3 patients with treatment-induced nAb, the median duration of nAb response was 8.14 weeks (95% CI: 0.14, 9.14).

CLINICAL STUDY REPORT SYNOPSIS

The interpretation of the ADA impact on avelumab PK was very limited due to the small number of treatment-induced ADA-positive patients (n=3) compared to ADA never-positive or baseline ADA positive patients (n=19).

Safety Results:

Treatment-Emergent Adverse Events

All patients in the study experienced at least 1 treatment-emergent adverse event (TEAE). Twenty-one patients (95.5%) experienced treatment-related TEAEs.

Seventeen patients (77.3%) reported Grade ≥3 TEAEs, which were treatment-related in 16 patients (72.7%). Discontinuation of all study drugs due to TEAEs was reported in 2 patients (9.1%) and was not due to treatment-related TEAEs.

The all-causality and treatment-related TEAEs that occurred in ≥20% of patients and Grade ≥3 TEAEs that occurred in ≥5% patients are presented by SOC and PT in Table S5.

The most common all-causality (TEAEs) reported in ≥20% of patients were Hypertension (17 patients [77.3%]), Decreased appetite (12 patients [54.5%]), Dysphonia and Palmar-plantar erythrodysaesthesia syndrome (11 patients [50.0%] each), Stomatitis and Weight decreased (9 patients [40.9%] each), Hypothyroidism, Constipation and Malaise (7 patients [31.8%] each), Diarrhea, Pyrexia, Dysgeusia, Proteinuria and Rash (6 patients [27.3%] each). The most common Grade ≥3 TEAEs reported in ≥5% of patients were Hypertension (11 patients [50.0%]), Palmar-plantar erythrodysaesthesia syndrome (5 patients [22.7%]), Decreased appetite (3 patients [13.6%]), Stomatitis and Fatigue (2 patients [9.1%] each).

The most common treatment-related TEAEs reported in ≥20% of patients were Hypertension (17 patients [77.3%]), Decreased appetite (12 patients [54.5%]), Dysphonia and Palmar-plantar erythrodysaesthesia syndrome (11 patients [50.0%] each), Stomatitis (9 patients [40.9%]), Weight decreased, Hypothyroidism and Malaise (7 patients [31.8%] each), Diarrhea, Dysgeusia, Proteinuria and Rash (6 patients [27.3%] each). The most common Grade ≥3 treatment-related TEAEs reported in ≥5% of patients were Hypertension (11 patients [50.0%]), Palmar-plantar erythrodysaesthesia syndrome (5 patients [22.7%]), Decreased appetite (3 patients [13.6%]), Stomatitis and Fatigue (2 patients [9.1%] each).

Due to the very limited number of ADA positive patients (n=3) compared to ADA negative patients (n=19), potential effect of ADA on safety was not evaluated appropriately. Under such a limited condition, no clinically meaningful impact of ADA on the safety profile was identified. The percentage of patients reporting TEAEs was same for ADA never-positive patients and ADA ever-positive patients (100% and 100%, respectively).

CLINICAL STUDY REPORT SYNOPSIS

The percentage of patients reporting TEAEs for treatment-induced ADA was same for ADA never-positive or baseline ADA positive patients (100% and 100%, respectively).

CLINICAL STUDY REPORT SYNOPSIS

Table S5. Most Common Treatment-Emergent Adverse Events (Any Grade in ≥20% Patients or Grade 3 in ≥5% Patients) by System Organ Class and Preferred Term - Safety Analysis Set

	Group A (N=22)			
System Organ Class and Preferred Term	**All TEAEs n (%)**	**Related TEAEs n (%)**	**Grade ≥3 TEAEs n (%)**	**Related Grade ≥3 TEAEs n (%)**
Patients with events	22 (100.0)	21 (95.5)	17 (77.3)	16 (72.7)
Endocrine disorders	8 (36.4)	8 (36.4)	0	0
Hypothyroidism	7 (31.8)	7 (31.8)	0	0
Gastrointestinal disorders	18 (81.8)	14 (63.6)	5 (22.7)	5 (22.7)
Constipation	7 (31.8)	0	0	0
Diarrhoea	6 (27.3)	6 (27.3)	1 (4.5)	1 (4.5)
Stomatitis	9 (40.9)	9 (40.9)	2 (9.1)	2 (9.1)
General disorders and administration site conditions	15 (68.2)	11 (50.0)	2 (9.1)	2 (9.1)
Fatigue	3 (13.6)	3 (13.6)	2 (9.1)	2 (9.1)
Malaise	7 (31.8)	7 (31.8)	0	0
Pyrexia	6 (27.3)	1 (4.5)	0	0
Investigations	13 (59.1)	12 (54.5)	2 (9.1)	1 (4.5)
Weight decreased	9 (40.9)	7 (31.8)	0	0
Metabolism and nutrition disorders	12 (54.5)	12 (54.5)	3 (13.6)	3 (13.6)
Decreased appetite	12 (54.5)	12 (54.5)	3 (13.6)	3 (13.6)
Nervous system disorders	8 (36.4)	7 (31.8)	1 (4.5)	1 (4.5)
Dysgeusia	6 (27.3)	6 (27.3)	0	0
Renal and urinary disorders	6 (27.3)	6 (27.3)	1 (4.5)	1 (4.5)
Proteinuria	6 (27.3)	6 (27.3)	1 (4.5)	1 (4.5)
Respiratory, thoracic and mediastinal disorders	13 (59.1)	11 (50.0)	0	0
Dysphonia	11 (50.0)	11 (50.0)	0	0
Skin and subcutaneous tissue disorders	15 (68.2)	15 (68.2)	5 (22.7)	5 (22.7)
Palmar-plantar erythrodysaesthesia syndrome	11 (50.0)	11 (50.0)	5 (22.7)	5 (22.7)
Rash	6 (27.3)	6 (27.3)	0	0
Vascular disorders	17 (77.3)	17 (77.3)	11 (50.0)	11 (50.0)
Hypertension	17 (77.3)	17 (77.3)	11 (50.0)	11 (50.0)

The denominator to calculate percentages is N, the number of patients in the safety analysis set within each treatment group.
Patients reporting >1 TEAE within a preferred term were counted only once in that preferred term.
Patients reporting multiple preferred terms within the same SOC were counted only once within each SOC.
Treatment-related TEAEs include TEAEs related to at least 1 study drug in the combination.
MedDRA Version 22.1 coding dictionary and CTCAE Version 4.03 applied.
Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; SOC=system organ class; TEAE=treatment-emergent adverse event.

CLINICAL STUDY REPORT SYNOPSIS

Permanent Discontinuations due to Adverse Events

Out of the 3 patients (13.6%) who discontinued any study drug due to TEAEs, 1 patient (4.5%) discontinued due to a TEAE (diverticulum intestinal haemorrhagic) considered related to study treatment. Discontinuation of all study drugs due to TEAEs was reported in 2 patients (9.1%) and was not due to treatment-related TEAEs.

Dose Reductions or Temporary Discontinuations due to Adverse Events

Eight patients (36.4%) reported TEAEs leading to interruption of avelumab, and 14 patients (63.6%) reported TEAEs leading to interruption of axitinib. The dose of axitinib was reduced for 13 patients (59.1%). Avelumab dose reductions were not permitted by protocol, and no TEAEs resulted in dose reduction of avelumab.

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

Deaths

A total of 12 patients (54.5%) died in the study, and the most common cause of death was disease progression (11 patients [50.0%]). One patient died due to an unknown cause. No patient died within 30 days after the last dose of study treatment, and no TEAEs leading to death were reported in the study. No patient died due to study treatment toxicity.

Other Serious Adverse Events

SAEs were reported in 8 patients (36.4%), of which SAEs reported in 6 patients (27.3%) were considered to be treatment-related.

Other Significant Adverse Events

Immune-Related Adverse Events

A total of 10 patients (45.5%) reported irAEs in the study which included hypothyroidism (7 patients [31.8%]), hyperthyroidism (3 patients [13.6%]), adrenal insufficiency, pruritus and rash (2 patients [9.1%] each), thyroiditis chronic and rash maculo-popular (1 patient [4.5%] each). No serious, Grade ≥3 irAEs and irAEs leading to death were reported in the study. No discontinuations of study drug (avelumab/axitinib) due to irAEs were reported in the study.

Infusion-Related Reactions

A total of 3 patients (13.6%) reported infusion-related reactions (IRR) events in the study which included chills in 1 patient (4.5%) and infusion related reaction in 2 patients (9.1%). No serious, Grade ≥3 IRRs and IRRs leading to death were reported in the study. No

CLINICAL STUDY REPORT SYNOPSIS

discontinuations of study drug (avelumab/axitinib) due to IRRs were reported in the study. The IRRs occurred at the first infusion in the study and were Grade 1 or Grade 2.

Laboratory Evaluations and Other Parameters Related to Safety

The most common Grade 1-4 hematology abnormal values included anemia and platelet count decreased (reported in 16 patients [72.7%] each) followed by lymphocyte count decreased (14 patients [63.6%]). Grade 3 hematology abnormal values included lymphocyte count decreased, reported in 1 patient (4.5%). There were no Grade 4 hematology laboratory values.

In the chemistry laboratory evaluations, the most common Grade 3 abnormal values included gamma glutamyl transferase increased, reported in 7 patients (31.8%) followed by alkaline phosphatase increased, reported in 3 patients (13.6%).

The Grade 4 chemistry laboratory values included cholesterol high and hypokalemia, reported in 1 patient (4.5%) each.

For the liver function tests, no potential Hy's law cases were observed in the study.

No clinically significant ECG abnormalities were observed during the study.

Conclusions:

- The safety profile of avelumab 10 mg/kg Q2W with axitinib 5 mg BID as first line treatment in patients with advanced HCC was manageable, tolerated, and consistent with the known safety profiles of avelumab and axitinib as single agents.

- The antitumor activity of avelumab in combination with axitinib as first line treatment was observed in patients with advanced HCC per RECIST v1.1.

- The majority (17 of 20) of patients had PD-L1-positive tumors at the 1% cutoff defined as PD-L1 staining of any intensity in tumor-associated ICs and TCs covering 1% of tumor area. The interpretation is limited due to the small number of patients with PD-L1-negative tumors. There was no meaningful difference in the proportion of patients achieving OR and PFS for patients with PD-L1-positive versus PD-L1-negative tumors at the 1% cutoff. Longer OS was more likely to be observed in patients with PD-L1-positive tumors than in patients with PD-L1-negative tumors.

- Avelumab serum concentrations appeared to reach steady state at Cycle 2 and appeared to increase slightly over time, however, the interpretation of the time dependency in avelumab serum concentrations is limited due to a decrease in sample size over time and relatively moderate to large variability. Axitinib exposure was not affected by the administration of avelumab on Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1.

CLINICAL STUDY REPORT SYNOPSIS

- The interpretation of the ADA impact on avelumab PK is very limited due to the small number of treatment-induced ADA-positive patients (n=3) compared to ADA never-positive or baseline ADA positive patients (n=19). ADA did not appear to impact the safety of the combination treatment, however, interpretation of the ADA impact on the safety is also very limited.