CLINICAL STUDY REPORT SYNOPSIS

Investigational Product: Avelumab, Compound Number: MSB0010718C

Clinical Study Report Synopsis: Protocol B9991016

Protocol Title: A Randomized Double-Blind Phase 3 Study of Avelumab in Combination With Standard of Care Chemoradiotherapy (Cisplatin Plus Definitive Radiation Therapy) Versus Standard of Care Chemoradiotherapy in the Front-Line Treatment of Patients With Locally Advanced Squamous Cell Carcinoma of the Head and Neck

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

Study Center(s): 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: 28 November 2016

Study Completion Date: 25 August 2020

Report Date: 19 February 2021

Previous Report Date(s): Not applicable.

Phase of Development: Phase 3

Study Objectives and Endpoints: The primary objective for Study B9991016 was to demonstrate that treatment with avelumab in combination with standard of care (SOC) chemoradiotherapy (CRT) is superior to SOC CRT alone in prolonging progression-free survival (PFS). The objectives and endpoints addressed in this supplemental clinical study report (CSR) are summarized in Table S1.

CLINICAL STUDY REPORT SYNOPSIS

Table S1. Study Objectives and Endpoints Table

Type	Objective	Endpoint
Secondary		
Pharmacokinetics	• To evaluate the PK of avelumab. • To evaluate the PK of cisplatin (total and free).	• C_{max} and C_{trough} for avelumab. • AUC_{inf}, C_{max}, CL, T_{max}, $t_{½}$, V_z for cisplatin (total and free), as data permitted.
Immunogenicity	• To assess avelumab ADAs.	• ADA (nAb) against avelumab.
Biomarker	• To evaluate candidate immune related predictive biomarkers of sensitivity or insensitivity to treatment with avelumab + SOC CRT in tumor specimens (eg, PD-L1 expression) after 1 dose of avelumab in patients who provide this optional biopsy.	• Tumor tissue biomarkers including but not limited to, PD-L1 expression and tumor infiltrating CD8+ T-lymphocytes.
Safety	• To evaluate the overall safety and tolerability profile of avelumab in combination with SOC CRT and placebo in combination with SOC CRT.	• AEs and laboratory abnormalities as graded by NCI-CTCAE v4.03.

Abbreviations: ADA = anti-drug antibodies; AE = adverse event; AUC_{inf} = area under the concentration-time curve extrapolated to infinity; CL = clearance; C_{max} = maximum observed concentration; CRT = chemoradiotherapy; C_{trough} = predose concentration during multiple dosing; PK = pharmacokinetics; NCI-CTCAE = National Cancer Institute common terminology criteria for adverse events; PD-L1 = programmed death-ligand 1; SOC = standard of care; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum plasma concentration; V_z = volume of distribution for extravascular dosing.

METHODS

Study Design: Study B9991016 was a Phase 3, international, multicenter, randomized, double-blind, parallel, 2-arm study in patients with previously untreated, histologically-confirmed locally advanced squamous cell carcinoma of the head and neck (LA SCCHN, including oral cavity, oropharynx, larynx, or hypopharynx) who were candidates for definitive CRT with cisplatin.

In this study, approximately 640 patients were to be randomized in a 1:1 ratio to either Arm A (avelumab + SOC CRT) or Arm B (placebo + SOC CRT). Randomization was stratified by tumor (T) stage (< T4 vs T4), nodal (N) stage (N0/N1/N2a/N2b vs N2c/N3), and human papilloma virus (HPV) status (positive vs negative) as measured by p16 expression by immunohistochemistry (IHC).

There were 3 treatment phases in this study:

CLINICAL STUDY REPORT SYNOPSIS

- Lead-in Phase: On Day 1 of the Lead-in Phase of the study, patients received a single dose of avelumab or matching placebo, administered 7 days prior to initiation of the CRT Phase;

- CRT Phase: Avelumab or matching placebo was administered on Days 8, 25, and 39 in conjunction with SOC CRT starting on Day 1 of the CRT phase;

- Maintenance Phase: Following completion of the CRT Phase, avelumab or matching placebo was administered every 2 weeks (Q2W) for 12 months during the Maintenance Phase.

Diagnosis and Main Criteria for Inclusion: Patients aged 18 years or above, with previously diagnosed and untreated advanced SCCHN, Stage III, IVa, IVb HPV-negative disease or Non-oropharyngeal HPV-positive disease, HPV-positive oropharyngeal disease were candidates for definitive CRT with cisplatin.

Study Treatment: The study treatments included the following:

Arm A: Avelumab + SOC CRT:

- Avelumab 10 mg/kg intravenous (IV): Day 1 of the Lead-in phase; Days 8, 25, and 39 of the CRT Phase; every 2 weeks (Q2W) for 12 months during the Maintenance Phase.

- Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.

- Intensity-modulated radiation therapy (IMRT) 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week for 7 weeks during the CRT Phase.

Arm B: Placebo + SOC CRT:

- Placebo IV matching avelumab: Day 1 of the Lead-in phase; Days 8, 25, and 39 of the CRT Phase; Q2W for 12 months during the Maintenance Phase.

- Cisplatin 100 mg/m^2 IV: Days 1, 22, and 43 of the CRT Phase.

- IMRT 70 Gy/35 fractions/7 weeks; 1 fraction/day, 5 fractions/week for 7 weeks during the CRT Phase.

Note: The Day 25 dose of avelumab/placebo during the CRT Phase may be administered between Day 24 and Day 29.

Efficacy Evaluations: Not applicable.

Pharmacokinetic, Immunogenicity, and Biomarker Evaluations:

CLINICAL STUDY REPORT SYNOPSIS

Pharmacokinetics: Blood samples of all patients were collected for pharmacokinetics (PK) analysis of avelumab. For the analysis of cisplatin blood samples were to be collected in a total of 24 patients (12 patients in avelumab + SOC CRT arm and 12 patients in placebo + SOC CRT arm) at selected sites. PK parameters analyzed included minimum plasma concentration (C_{trough}), maximum plasma concentration (C_{max}) for avelumab and area under the concentration-time curve extrapolated to infinity (AUC_{inf}), C_{max}, clearance (CL), time to maximum plasma concentration (T_{max}), elimination half-life ($t_{1/2}$), and volume of distribution (V_z) for cisplatin (total and free), as data permitted.

Immunogenicity: Blood samples were collected and assessed for development of avelumab anti-drug antibodies (ADAs). Samples that were positive for ADA were to undergo neutralizing antibody (nAb) characterization.

Biomarker: Tumor biospecimens representing tissue samples from tumor resection or biopsy were used to analyze programmed death-ligand 1 (PD-L1) expression and tumor infiltrating CD8+ T-lymphocytes by IHC. Samples obtained during the Lead-in Phase (optional), Maintenance Phase (in patients who undergo a clinically indicated tumor resection), and/or at the End of Treatment/Withdrawal visit (all patients) were assessed in parallel with the mandatory pretreatment biospecimens(s) to provide data on the changes in the tumor that accumulated over the course of therapy, including acquired mechanisms of resistance.

Safety Evaluations: Safety assessments included collection of adverse events (AEs), Serious Adverse Events (SAEs), vital signs, physical examination, electrocardiogram (ECG, 12-lead), and laboratory assessments (including pregnancy tests).

Statistical Methods:

Pharmacokinetics: C_{trough} and C_{max} for avelumab were to be summarized descriptively (n, mean, SD, CV, median, minimum, maximum, geometric mean, its associated CV, and 95% CI) by treatment phase, and day in Arm A. PK parameters for cisplatin (total and free) were to be estimated using noncompartmental and/or compartment methods. Analyses also included C_{max}, time to T_{max}, AUC_{inf}, $t_{½}$, CL, and V_z as data permitted.

Additionally, avelumab PK were to be evaluated following cisplatin dosing by comparing the overall geometric mean ratios of C_{max} and C_{trough} in only Arm A on Day 8 of the CRT Phase to Day 1 of the Lead-in Phase. Cisplatin PK (total and free) were evaluated following avelumab or placebo dosing by comparing the overall geometric mean ratios of C_{max} and AUC_{inf} on Day 1 of the CRT Phase in Arm A to Day 1 of the CRT Phase in Arm B.

Immunogenicity: The immunogenicity data were summarized as the percentage of patients with positive ADA and nAb.

Biomarker: Summary statistics for on-treatment biomarkers included the ratio to baseline for continuous biomarkers.

CLINICAL STUDY REPORT SYNOPSIS

Safety: All analyses were based on treatment-emergent adverse events (TEAEs) (started during the on-treatment period), if not otherwise specified. The AE listings included all AEs (whether treatment-emergent or not). AEs with onset outside the on-treatment period were flagged in the listings.

The frequency (number and percentage) of patients with SAEs by system organ class and preferred term (PT) and related SAEs by system organ class and PT were presented for treatment-emergent SAEs by treatment arm. Listings of all SAEs were also provided with the relevant information with a flag for SAEs with onset outside of the on-treatment period.

Laboratory results were classified according to the National Cancer Institute common terminology criteria for AEs (NCI-CTCAE) criteria version 4.03. Quantitative data of laboratory values and vital signs were summarized using simple descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from baseline for each nominal visit over time. End of Treatment visit laboratory results were summarized separately.

RESULTS

Subject Disposition and Demography: Table S2 presents a summary of patient disposition by study phase. A total of 697 patients were randomized. A smaller number of patients in the avelumab + SOC CRT group versus placebo + SOC CRT group completed the maintenance phase.

No patient discontinuations were reported as due to coronavirus disease 19 (COVID-19) related study disruptions.

Overall, demographic characteristics were balanced across treatment arms. Most enrolled patients were males, most were < 65 years old, and the majority were White. Refer to the B9991016 final study report dated 25 Jun 2020 for additional details on demographic and baseline characteristics.

Table S2. Subject Disposition by Study Phase - Full Analysis Set (Protocol B9991016)

	Avelumab + SOC CRT (N = 350) n (%)	Placebo + SOC CRT (N = 347) n (%)
Disposition : Lead-In phase		
Discontinued	5 (1.4)	4 (1.2)
Reason for discontinuation		
Death	0	1 (0.3)
Adverse event	3 (0.9)	0
No longer meets eligibility criteria	0	1 (0.3)

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Subject Disposition by Study Phase - Full Analysis Set (Protocol B9991016)

	Avelumab + SOC CRT (N = 350) n (%)	Placebo + SOC CRT (N = 347) n (%)
Withdrawal by subject	2 (0.6)	2 (0.6)
Completed	345 (98.6)	343 (98.8)
Ongoing	0	0
Disposition : CRT phase for Avelumab or Placebo		
Subjects entering CRT phase	345 (98.6)	340 (98.0)
Discontinued	33 (9.4)	27 (7.8)
Reason for discontinuation		
Death	5 (1.4)	8 (2.3)
Adverse event	12 (3.4)	12 (3.5)
Physician decision	2 (0.6)	1 (0.3)
Global deterioration of health status	1 (0.3)	0
Withdrawal by subject	10 (2.9)	4 (1.2)
Lost to follow-up	1 (0.3)	1 (0.3)
Other	2 (0.6)	1 (0.3)
Completed	312 (89.1)	313 (90.2)
Ongoing	0	0
Disposition : CRT phase for Cisplatin		
Subjects entering CRT phase	345 (98.6)	340 (98.0)
Discontinued	111 (31.7)	104 (30.0)
Reason for discontinuation		
Death	3 (0.9)	8 (2.3)
Adverse event	82 (23.4)	81 (23.3)
Physician decision	12 (3.4)	10 (2.9)
Global deterioration of health status	1 (0.3)	0
Withdrawal by subject	11 (3.1)	3 (0.9)
Lost to follow-up	1 (0.3)	1 (0.3)
Other	1 (0.3)	1 (0.3)
Completed	234 (66.9)	236 (68.0)
Ongoing	0	0
Disposition : CRT phase for IMRT		
Subjects entering CRT phase	345 (98.6)	340 (98.0)
Discontinued	23 (6.6)	20 (5.8)
Reason for discontinuation		
Death	5 (1.4)	8 (2.3)
Adverse event	5 (1.4)	5 (1.4)
Global deterioration of health status	1 (0.3)	0

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Subject Disposition by Study Phase - Full Analysis Set (Protocol B9991016)

	Avelumab + SOC CRT (N = 350) n (%)	Placebo + SOC CRT (N = 347) n (%)
Withdrawal by subject	10 (2.9)	6 (1.7)
Lost to follow-up	1 (0.3)	1 (0.3)
Other	1 (0.3)	0
Completed	322 (92.0)	320 (92.2)
Ongoing	0	0
Disposition : Maintenance phase		
Subjects entering Maintenance phase	291 (83.1)	304 (87.6)
Discontinued	152 (43.4)	127 (36.6)
Reason for discontinuation		
Death	17 (4.9)	11 (3.2)
Progressive disease	60 (17.1)	54 (15.6)
Adverse event	24 (6.9)	21 (6.1)
Non-compliance with study drug	1 (0.3)	1 (0.3)
Physician decision	1 (0.3)	1 (0.3)
Global deterioration of health status	14 (4.0)	5 (1.4)
Withdrawal by subject	31 (8.9)	25 (7.2)
Lost to follow-up	1 (0.3)	2 (0.6)
Study terminated by sponsor	1 (0.3)	6 (1.7)
Other	2 (0.6)	1 (0.3)
Completed	139 (39.7)	177 (51.0)
Ongoing	0	0
Disposition : Follow-Up phase		
Subjects entering Follow-Up	266 (76.0)	284 (81.8)
Discontinued	58 (16.6)	68 (19.6)
Reason for discontinuation		
Death	12 (3.4)	10 (2.9)
Withdrawal by subject	6 (1.7)	2 (0.6)
Lost to follow-up	1 (0.3)	1 (0.3)
Study terminated by sponsor	32 (9.1)	50 (14.4)
Other	7 (2.0)	5 (1.4)
Completed	208 (59.4)	216 (62.2)
Ongoing	0	0
Disposition : Long-Term Follow-Up phase		
Subjects entering Long-Term Follow-Up	247 (70.6)	237 (68.3)
Discontinued	247 (70.6)	237 (68.3)
Reason for discontinuation		

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Subject Disposition by Study Phase - Full Analysis Set (Protocol B9991016)

	Avelumab + SOC CRT (N = 350) n (%)	Placebo + SOC CRT (N = 347) n (%)
Death	51 (14.6)	31 (8.9)
Withdrawal by subject	7 (2.0)	1 (0.3)
Lost to follow-up	2 (0.6)	4 (1.2)
Study terminated by sponsor	187 (53.4)	201 (57.9)
Ongoing	0	0

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 02OCT2020 (14:21) Source Data: ADDS Output
File: ./B9991016/B9991016_sCSR/adds_s001a1 Date of Generation: 07OCT2020 (01:17) Snapshot Date: 02OCT2020
Table 14.1.1.2.2.1 is for Pfizer internal use.

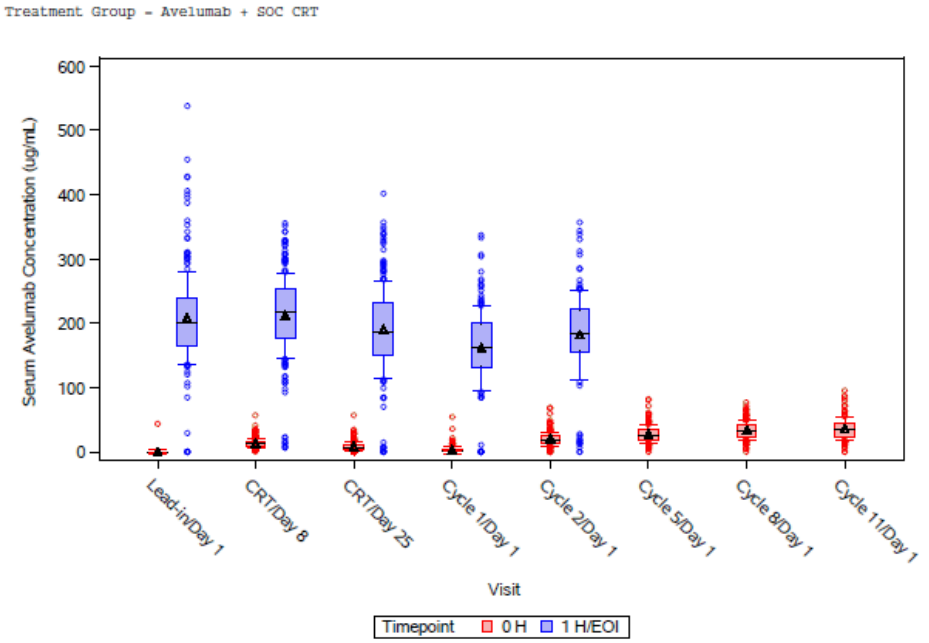
Efficacy Results: Refer to the B9991016 final study report dated 25 June 2020 for presentation of efficacy results.

Pharmacokinetic Results:

Avelumab: Serum avelumab C_{max} and C_{trough} concentrations are presented by study phase and visit in Figure S1. Mean serum avelumab concentrations were similar at 1 hour post infusion for each study phase and visit and C_{trough} increased over time even after reaching state steady.

CLINICAL STUDY REPORT SYNOPSIS

Figure S1 Box-Plots of Serum Trough and Maximum Concentration for Avelumab by Study Phase and Visit - Avelumab PK Concentration Analysis Set



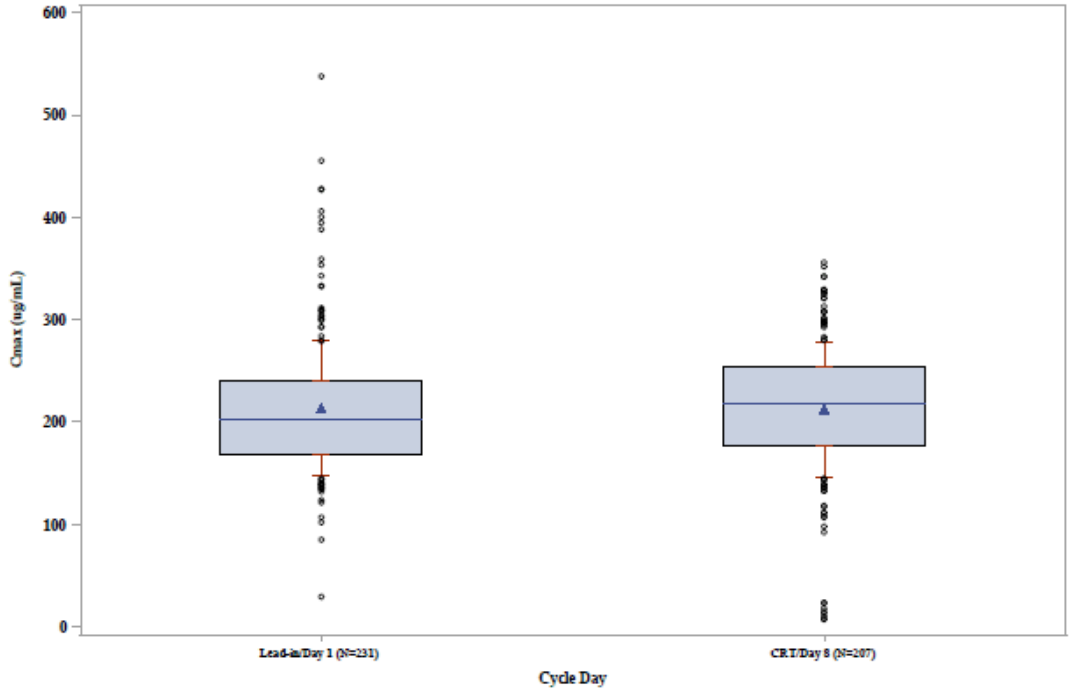
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.2 ug/mL.
0 H = predose; summary statistics include concentration values from samples collected within 2 hours prior to the start of infusion and following a prior dose that was within ±10% of 10 mg/kg and was administered within 14 ± 3 days of the prior dose for samples in maintenance phase.
1 H/EOI = end of infusion (i.e. 1 H assuming 1-hour duration of infusion)/Cmax; summary statistics include concentration values from samples collected within ±20% of the end of an uninterrupted infusion of between 50 min to 1 h 20 min in duration, with total dose administered within ±10% of 10 mg/kg.
Values from anomalous sample which are 3 SD above or below the mean concentration for the same visit and nominal time have been excluded from the presentation.
Symbol in the box interior = Mean. The horizontal line in the box interior = Median. Upper and lower box lines = 1st quantile and 3rd quantiles, respectively. End of vertical lines = 1 SD above and below the mean.
Symbols outside the box = measurements outside 1 SD from the mean.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2020 (21:04) Source Data: ADPC Output File: ./B9991016/B9991016_PK/pk_plot_1 Date of Generation: 11NOV2020 (22:02) Cutoff Date: 13MAR2020 Snapshot Date: 02OCT2020

Source: Figure 14.4.4.1.

The effect of cisplatin treatment on the avelumab PK parameter C_{max} on Day 8 of the CRT Phase compared to Day 1 of the Lead-in Phase is presented in Figure S2. The observed mean avelumab C_{max} values were similar at Day 1 and Day 8 of treatment, indicating no effect.

CLINICAL STUDY REPORT SYNOPSIS

Figure S2 Box-Plots of Avelumab Cmax in the Absence (Lead-in Day 1) and Presence of Cisplatin (CRT Day 8) - Avelumab PK Parameter Analysis Set - Treatment Group = Avelumab + SOC CRT



Summary statistics include concentration values from samples collected within ±20% of the end of an uninterrupted infusion of between 50 min to 1 h 20 min in duration, with total dose administered within ±10% of 10 mg/kg.
Values from anomalous sample which are 3 SD above or below the mean concentration for the same visit and nominal time have been excluded from the presentation.
Symbol in the box interior = Mean. The horizontal line in the box interior = Median. Upper and lower box lines = 1st quantiles and 3rd quantiles, respectively.
End of vertical lines = 1 SD above and below the mean.
Symbols outside the box = measurements outside 1 SD from the mean.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2020 (21:04) Source Data: ADPP2 Output File: ./B9991016/B9991016_PK/pk_plot_3 Date of Generation: 12NOV2020 (00:27)
Cutoff Date: 13MAR2020 Snapshot Date: 02OCT2020

Source: Figure 14.4.5.2.

Cisplatin: Cisplatin PK samples were collected from 12 patients in the avelumab + SOC CRT group and 23 patients in the placebo + SOC CRT group. Median total plasma cisplatin concentration and cisplatin PK parameters are presented in Figure S3 and Table S3, respectively. AUC_{last} is reported instead of AUC_{inf} because AUC_{inf} could not be calculated. The observed GM ratio of AUC_{last} for total cisplatin was numerically lower in the avelumab + SOC CRT group compared to the placebo + SOC CRT group, but is not considered meaningful as the 90% confidence intervals (CIs) overlap with 100 (geometric mean [GM] ratio = 89.90, 90% CI = 78.06, 103.55; Table S4).

CLINICAL STUDY REPORT SYNOPSIS

Table S3. Summary of Total Cisplatin Pharmacokinetics Parameters by Treatment Group on Day 1 of the CRT Phase - Cisplatin PK Parameter Analysis Set (Protocol B9991016)

	N	n	Avelumab + SOC CRT	N	n	Placebo + SOC CRT
AUC_{last} (ng.hr/mL)	12	10	44500(43)	23	20	51040(35)
$AUC_{last, dn}$ (ng.hr/mL/mg)	12	10	299.1(30)	23	20	332.7(17)
C_{max} (ng/mL)	12	12	3781(44)	23	23	4001(34)
$C_{max, dn}$ (ng/mL/mg)	12	12	26.23(36)	23	23	25.33(26)
T_{last} (hr)	12	10	22.10(19.9, 26.5)	23	20	23.95(20.8, 28.1)
T_{max} (hr)	12	12	1.000(0.500, 2.40)	23	23	1.170(0.983, 24.0)

Geometric mean (geometric %CV) for all except: median (range) for T_{last} and T_{max}.
N = Number of subjects in the treatment group.
n = Number of subjects contributing to the statistical summary.
PK parameters with zero values were excluded from the calculation of geometric means and its associated %CV.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2020 (21:04) Source Data: ADPP Output
File: ./B9991016/B9991016_PK/adpp_s002 Date of Generation: 05NOV2020 (23:11) Cutoff Date: 13MAR2020 Snapshot Date: 02OCT2020
Table 14.4.5.3 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

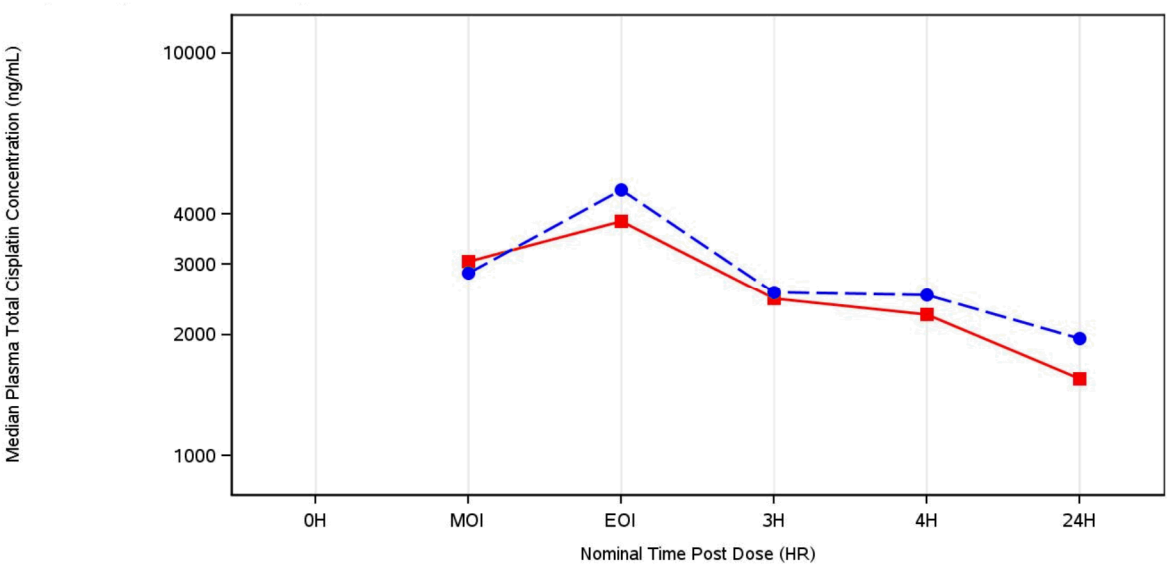
Table S4. Effect of Study Treatment on Total Cisplatin Pharmacokinetics Parameters ($C_{max, dn}$, $AUC_{last, dn}$) on Day 1 of the CRT Phase - Cisplatin PK Parameter Analysis Set (Protocol B9991016)

		$AUC_{last, dn}$, ng.hr/mL/mg	$C_{max, dn}$, ng/mL/mg
Avelumab + SOC CRT	n	10	12
	GM	299.1	26.23
	GM CV (%)	30	36
	GM 95% CI	(242.7, 368.5)	(21.05, 32.67)
Placebo + SOC CRT	n	20	23
	GM	332.7	25.33
	GM CV (%)	17	26
	GM 95% CI	(307.9, 359.4)	(22.71, 28.25)
Avelumab + SOC CRT vs Placebo + SOC CRT	n	30	35
	GM Ratio	89.90	103.53
	GM 90% CI	(78.06, 103.55)	(87.09, 123.07)

PK parameters with zero values were excluded from the calculation of geometric means and its associated %CV.
GM = Geometric mean.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2020 (21:04) Source Data: ADPP Output
File: ./B9991016/B9991016_PK/adpp_s003 Date of Generation: 06NOV2020 (03:35) Cutoff Date: 13MAR2020 Snapshot Date: 02OCT2020
Table 14.4.5.5 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

Figure S3 Median Plasma Total Cisplatin Concentrations by Treatment Group in the CRT Phase (Log Scale) - Cisplatin PK Concentration Analysis Set



Avelumab + SOC CRT [1]:	12	11	10	8	7	6
Placebo + SOC CRT [1]:	23	18	18	21	20	15

[1] Number of observations (non-missing concentrations).
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 40 ng/mL.
Summary statistics for the end of infusion (EOI) timepoint have been plotted versus the 1 H nominal time and mid-infusion (MOI) timepoint have been plotted versus the 30 MIN nominal time.
MOI and EOI correspond to mid and end of infusion nominal and both are dependent on the actual infusion duration (60-120 min).
0 H = predose/Ctrough; summary statistics include concentration values from samples collected on day of infusion and prior to or on infusion start time.
Other samples including EOI; summary statistics include concentration values from samples collected within ±10% of nominal time of an uninterrupted infusion of between 60 min to 2 h in duration.
PFIZER CONFIDENTIAL SDTM Creation: 14MAY2020 (22:45) Source Data: ADPC Output File: ./B9991016/B9991016_ADA/adpc_median Date of Generation: 15SEP2020 (02:11)
Cutoff Date: 31Mar2019 Snapshot Date: 11Feb2020

Source: Figure 14.4.4.4.

Immunogenicity Results:

Subject ADA categories are summarized in Table S5. Treatment-induced ADA responses occurred in 47 (15.3%) patients who received avelumab in combination with SOC CRT. No patients who were baseline ADA positive had treatment-boosted ADA.

Tests for nAbs were not performed.

CLINICAL STUDY REPORT SYNOPSIS

Table S5. Summary of Subject ADA Categories - Immunogenicity Analysis Set (Protocol B9991016)

	Avelumab + SOC CRT (N = 331) n (%)
Subjects with at least one valid ADA result at any time point (N0)	331 (100.0)
Subjects with valid baseline ADA result (N1)	324 (97.9)
Subjects with valid baseline ADA results and at least one valid post-baseline ADA result (N2)	313 (94.6)
Subjects with at least one valid post-baseline ADA result and without positive baseline ADA result (N3)	307 (92.7)
ADA never-positive (n/N0)	277 (83.7)
ADA ever-positive (n/N0)	54 (16.3)
Baseline ADA positive (n/N1)	7 (2.2)
Treatment-boosted ADA (n/N2)	0
Treatment-induced ADA (n/N3)	47 (15.3)
Transient ADA response (n/N3)	22 (7.2)
Persistent ADA response (n/N3)	25 (8.1)

Baseline is defined as the last assessment on or prior to the date/time of the first dose of avelumab.
The denominator to calculate percentages for N0, N1, N2, N3 is N, the number of subjects in the immunogenicity analysis set.
PFIZER CONFIDENTIAL SDTM Creation: 05NOV2020 (00:25) Source Data: ADIS Output
File: ./B9991016/B9991016_ADA/adis_s001 Date of Generation: 05NOV2020 (02:08) Cutoff Date: 13MAR2020 Snapshot Date: 02OCT2020
Table 14.4.9.1.1 is for Pfizer internal use.

Biomarker Results:

Pre-treatment PD-L1 expression based on immune cells and tumor cells and tumor infiltrating CD8+ T-lymphocytes as assessed by IHC were candidate predictive biomarkers in this study. The numbers of patients included in the analysis with both pre- and post-treatment biomarker data available were 36 patients for PD-L1 positive immune cells and PD-L1 tumor staining (13 patients and 23 patients from the avelumab + SOC CRT and placebo + SOC CRT arms, respectively), and 35 patients for CD8+ cells (13 patients and 22 patients from the avelumab + SOC CRT and placebo + SOC CRT arms, respectively). The median change in the number of PD-L1-positive immune cells from pre- to post-treatment was 0.0 and -3.0 for the avelumab + SOC CRT arm and placebo + SOC CRT arm, respectively. The median change in PD-L1-positive tumor cells from pre- to post-treatment was 0.0 for both the avelumab + SOC CRT arm and placebo + SOC CRT arm. The median change in CD8+ cells total area from pre- to post-treatment was 0.2 and 0.6 for the avelumab + SOC CRT arm and placebo + SOC CRT arm, respectively. No significant differences were detected between the treatment arms ($p = 0.141$, $p = 0.614$, and $p = 0.839$

CLINICAL STUDY REPORT SYNOPSIS

for change from baseline in PD-L1 positive immune cells, PD-L1 tumor staining, and CD8+ cells total area, respectively).

Additional biomarker data will be presented in a future report.

Safety Results:

Overall, the proportion of patients who reported AEs was similar across treatment arms except for a higher incidence (defined as ≥ 5% difference) of all-causality and treatment-related TEAEs of Grade ≥ 3 and TEAEs leading to dose interruption of avelumab or placebo in the avelumab + SOC CRT arm in comparison to the placebo + SOC CRT arm.

Relevant differences in the frequency of TEAEs were observed for the PTs of Constipation, Pyrexia, Leukopenia, Neutrophil count decreased, Odynophagia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Chills, and Pharyngeal inflammation (Table S6). Relevant differences in the frequency of treatment-related TEAEs were observed for the PTs of Weight decreased, Leukopenia, Neutrophil count decreased, Odynophagia, Pyrexia, Alanine aminotransferase increased, Aspartate aminotransferase increased, Chills, and Pharyngeal inflammation.

TEAEs leading to discontinuation of avelumab, cisplatin, or IMRT occurred at similar frequencies in both treatment arms. The most common TEAE leading to discontinuation of avelumab was Infusion-related reaction (IRR) and for cisplatin was Neutropenia and Blood creatinine increased. TEAEs leading to discontinuation of IMRT were all single occurrences.

Deaths occurred more frequently in the avelumab + SOC CRT arm and were most often due to disease progression. The most frequent TEAEs leading to death were those in the system organ class of Infections and infestations (5 patients [1.4%] in the avelumab + SOC CRT arm and no patients in the placebo + SOC CRT treatment arm).

A summary of serious TEAEs occurring in ≥2% subjects in any treatment group is presented in Table S7.

Refer to the B9991016 final study report dated 25 June 2020 for the presentation of immune-related AEs (irAEs) and IRRs in this study.

CLINICAL STUDY REPORT SYNOPSIS

Table S6. Summary of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 2% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set (Protocol B9991016)

Preferred Term	Avelumab + SOC CRT (N = 348)		Placebo + SOC CRT (N = 344)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Subjects with events	345 (99.1)	305 (87.6)	342 (99.4)	281 (81.7)
Nausea	210 (60.3)	23 (6.6)	201 (58.4)	17 (4.9)
Anaemia	206 (59.2)	52 (14.9)	193 (56.1)	56 (16.3)
Constipation	178 (51.1)	7 (2.0)	155 (45.1)	3 (0.9)
Weight decreased	160 (46.0)	28 (8.0)	172 (50.0)	28 (8.1)
Dry mouth	151 (43.4)	5 (1.4)	158 (45.9)	4 (1.2)
Dysphagia	146 (42.0)	58 (16.7)	155 (45.1)	54 (15.7)
Mucosal inflammation	146 (42.0)	50 (14.4)	131 (38.1)	47 (13.7)
Radiation skin injury	135 (38.8)	19 (5.5)	136 (39.5)	17 (4.9)
Decreased appetite	129 (37.1)	25 (7.2)	124 (36.0)	20 (5.8)
Fatigue	116 (33.3)	15 (4.3)	128 (37.2)	13 (3.8)
Vomiting	114 (32.8)	19 (5.5)	125 (36.3)	24 (7.0)
Dysgeusia	106 (30.5)	0	119 (34.6)	2 (0.6)
Neutropenia	106 (30.5)	58 (16.7)	100 (29.1)	53 (15.4)
Pyrexia	96 (27.6)	4 (1.1)	47 (13.7)	3 (0.9)
Stomatitis	96 (27.6)	25 (7.2)	97 (28.2)	26 (7.6)
Hypomagnesaemia	93 (26.7)	4 (1.1)	84 (24.4)	4 (1.2)
Hypokalaemia	89 (25.6)	34 (9.8)	73 (21.2)	30 (8.7)
Blood creatinine increased	88 (25.3)	7 (2.0)	73 (21.2)	5 (1.5)
Hyponatraemia	84 (24.1)	40 (11.5)	70 (20.3)	38 (11.0)
Diarrhoea	83 (23.9)	9 (2.6)	67 (19.5)	8 (2.3)
Oropharyngeal pain	75 (21.6)	14 (4.0)	92 (26.7)	8 (2.3)
Cough	74 (21.3)	2 (0.6)	64 (18.6)	0
White blood cell count decreased	69 (19.8)	34 (9.8)	64 (18.6)	28 (8.1)
Asthenia	65 (18.7)	15 (4.3)	62 (18.0)	11 (3.2)
Leukopenia	64 (18.4)	22 (6.3)	46 (13.4)	20 (5.8)
Neutrophil count decreased	64 (18.4)	41 (11.8)	60 (17.4)	31 (9.0)
Odynophagia	64 (18.4)	16 (4.6)	48 (14.0)	3 (0.9)
Tinnitus	59 (17.0)	0	67 (19.5)	0
Alanine aminotransferase increased	57 (16.4)	8 (2.3)	30 (8.7)	1 (0.3)
Insomnia	57 (16.4)	1 (0.3)	47 (13.7)	0

CLINICAL STUDY REPORT SYNOPSIS

Table S6. Summary of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 2% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set (Protocol B9991016)

Preferred Term	Avelumab + SOC CRT (N = 348)		Placebo + SOC CRT (N = 344)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)
Aspartate aminotransferase increased	55 (15.8)	3 (0.9)	26 (7.6)	3 (0.9)
Pneumonia	54 (15.5)	23 (6.6)	38 (11.0)	24 (7.0)
Dermatitis	52 (14.9)	4 (1.1)	42 (12.2)	4 (1.2)
Dysphonia	51 (14.7)	0	47 (13.7)	1 (0.3)
Hypothyroidism	51 (14.7)	0	45 (13.1)	0
Thrombocytopenia	46 (13.2)	4 (1.1)	41 (11.9)	5 (1.5)
Headache	45 (12.9)	2 (0.6)	41 (11.9)	2 (0.6)
Rash	43 (12.4)	3 (0.9)	36 (10.5)	0
Hypoalbuminaemia	42 (12.1)	3 (0.9)	37 (10.8)	3 (0.9)
Dizziness	41 (11.8)	1 (0.3)	33 (9.6)	0
Chills	40 (11.5)	1 (0.3)	7 (2.0)	0
Lymphocyte count decreased	40 (11.5)	31 (8.9)	42 (12.2)	32 (9.3)
Oral pain	40 (11.5)	10 (2.9)	44 (12.8)	12 (3.5)
Platelet count decreased	40 (11.5)	6 (1.7)	33 (9.6)	2 (0.6)
Productive cough	40 (11.5)	1 (0.3)	32 (9.3)	1 (0.3)
Dehydration	39 (11.2)	11 (3.2)	42 (12.2)	16 (4.7)
Pruritus	38 (10.9)	0	24 (7.0)	0
Dyspnoea	35 (10.1)	7 (2.0)	39 (11.3)	9 (2.6)
Hyperkalaemia	34 (9.8)	4 (1.1)	32 (9.3)	8 (2.3)
Lymphopenia	33 (9.5)	21 (6.0)	27 (7.8)	16 (4.7)
Hyperglycaemia	32 (9.2)	8 (2.3)	33 (9.6)	6 (1.7)
Hypertension	32 (9.2)	12 (3.4)	28 (8.1)	15 (4.4)
Acute kidney injury	27 (7.8)	10 (2.9)	30 (8.7)	8 (2.3)
Pharyngeal inflammation	24 (6.9)	9 (2.6)	23 (6.7)	2 (0.6)
Hypophosphataemia	23 (6.6)	9 (2.6)	32 (9.3)	9 (2.6)
Amylase increased	22 (6.3)	7 (2.0)	10 (2.9)	4 (1.2)
Lipase increased	14 (4.0)	7 (2.0)	9 (2.6)	1 (0.3)
Laryngeal oedema	13 (3.7)	7 (2.0)	11 (3.2)	5 (1.5)
Febrile neutropenia	11 (3.2)	7 (2.0)	9 (2.6)	9 (2.6)
Pneumonia aspiration	10 (2.9)	5 (1.4)	13 (3.8)	7 (2.0)

CLINICAL STUDY REPORT SYNOPSIS

Table S6. Summary of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 2% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - Safety Analysis Set (Protocol B9991016)

Preferred Term	Avelumab + SOC CRT (N = 348)		Placebo + SOC CRT (N = 344)	
	All Grades (n %)	Grade ≥ 3 (n %)	All Grades (n %)	Grade ≥ 3 (n %)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
MedDRA v23.0 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 02OCT2020 (12:54) Source Data: ADAE Output
File: ./B9991016/B9991016_sCSR/adae_s999a Date of Generation: 07OCT2020 (01:20) Snapshot Date: 02OCT2020
Table 14.3.1.3.1.17 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

Table S7. Summary of Most Common Serious TEAEs ≥ 2% Subjects in Any Treatment Group by PT During the On-Treatment Period - Safety Analysis Set (Protocol B9991016)

Preferred Term	Avelumab + SOC CRT (N = 348) All Grades (n %)	Placebo + SOC CRT (N = 344) All Grades (n %)
Subjects with events	184 (52.9)	177 (51.5)
Pneumonia	25 (7.2)	20 (5.8)
Dysphagia	15 (4.3)	13 (3.8)
Acute kidney injury	12 (3.4)	11 (3.2)
Pyrexia	12 (3.4)	3 (0.9)
Vomiting	11 (3.2)	13 (3.8)
Dehydration	9 (2.6)	15 (4.4)
Febrile neutropenia	9 (2.6)	5 (1.5)
Anaemia	8 (2.3)	12 (3.5)
Blood creatinine increased	7 (2.0)	6 (1.7)
Nausea	7 (2.0)	9 (2.6)
Sepsis	7 (2.0)	5 (1.5)
Stomatitis	7 (2.0)	4 (1.2)
Dyspnoea	5 (1.4)	7 (2.0)
Hyponatraemia	4 (1.1)	7 (2.0)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.
For subjects reporting more than one AE within a preferred term, the AE with maximum grade is included in the table.
MedDRA v23.0 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 02OCT2020 (12:54) Source Data: ADAE Output
File: ./B9991016/B9991016_sCSR/adae_s999c Date of Generation: 07OCT2020 (01:19) Snapshot Date: 02OCT2020
Table 14.3.1.3.1.19 is for Pfizer internal use.

CLINICAL STUDY REPORT SYNOPSIS

Conclusions:

- In general, PK results for avelumab were consistent with previously observed exposures in patients with SCCHN with no indication of drug interaction between avelumab and cisplatin.

- The observed incidence of ADA in patients treated with avelumab was consistent with the incidence of ADA in previous studies of avelumab.

- No significant differences were noted between treatment groups in change from baseline of PD-L1 expression or the presence of CD8+ cells following 1 dose of therapy.

- The safety profile of avelumab administered in combination with CRT was generally tolerable, manageable, and consistent with the known safety profiles of avelumab and chemotherapy when administered as monotherapies. No new important signals were noted in the updated safety data compared to data reported in the Final CSR.