10 December 2020
EMA/CHMP/3166/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bavencio

International non-proprietary name: avelumab

Procedure No. EMEA/H/C/004338/II/0018

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Term
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADR	adverse drug reaction
AE	adverse event
aRCC	advanced renal cell carcinoma
aUC	locally advanced or metastatic urothelial carcinoma
BICR	blinded independent central review
BLA	Biologics License Application
BOR	best overall response
BSC	best supportive care
BTD	Breakthrough Designation
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CL	total systemic clearance
CPK	creatinine phosphokinase
CO	Clinical Overview
CR	complete response
CSR	Clinical Study Report
C_{trough}	predose concentration
CV	coefficient of variation
eCRF	electronic case report form
DR	duration of response
DRS-P	Disease Related Symptoms – Physical
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 dimensions 5 levels
ESMO	European Society for Medical Oncology
EU	European Union
FACT	Functional Assessment of Cancer Therapy

FBlSI-18	FACT Bladder Symptom Index
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GMP	Good Manufacturing Practice
HR	hazard ratio
ICH	International Conference for Harmonisation
IHC	immunohistochemistry
Ig	Immunoglobulin
IND	Investigational New Drug
IR	Incident Rate per 100 patient months
irAE	immune-related adverse event
IRR	infusion related reaction
ISS	Integrated Summary of Safety
IV	intravenous
LLQ	lower limit of quantification
mAb	monoclonal antibody
MAH	Marketing Authorisation Holder
MCC	Merkel cell carcinoma
nAb	neutralizing antibody
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	not evaluable
OR(R)	objective response (rate)
OS	overall survival
PBRER	Periodic Benefit-Risk Evaluation Report
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed cell death protein-ligand 1
PFS	progression-free survival
PIPD	potentially important protocol deviation
PK	pharmacokinetics

PM	Patient Months of Exposure
PMAR	Population Modelling Analysis Report
popPK	population pharmacokinetics
PR	partial response
PRO	patient-reported outcomes
PT	preferred term
Q2W	every 2 weeks
RCC	renal cell carcinoma
RCI	repeated confidence interval
RECIST v1.1	Response Evaluation Criteria in Solid Tumours Version 1.1
RTOR	Real Time Oncology Review
SAP	statistical analysis plan
SAE	serious adverse event
SBS	Summary of Biopharmaceutics and Associated Analytical Methods
sBLA	Supplemental Biologics License Application
SCE	Summary of Clinical Efficacy
SCP	Summary of Clinical Pharmacology Studies
SCS	Summary of Clinical Safety
SD	stable disease
SmPC	Summary of Product Characteristics
TKI	tyrosine kinase inhibitor
TEAE	treatment-emergent adverse event
TTD	time to deterioration
UC	urothelial carcinoma
US	United States
VEGFR	vascular endothelial growth factor receptor

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Merck Europe B.V. submitted to the European Medicines Agency on 26 May 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include a new indication for Bavencio as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.3 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics, Annex II and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0242/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0242/2018 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice on 22 October 2015 (EMEA/H/SA/2771/5/2015/II) for the development programme supporting the indication granted by the CHMP.

Date	Reference	SAWP Co-ordinators
22/10/2015	EMEA/H/SA/2771/5/2015/II	*Dr Pierre Démolis and Dr Jens Ersbøll*

The Scientific Advice pertained to the following clinical aspects of the dossier:

- Discussion on the design of the pivotal study B9991001 (including study population, selection of comparator, safety monitoring, study design, endpoints, statistical plan, inclusion of patients reported outcome results in the SmPC).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson, Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	26 May 2020
Start of procedure:	20 June 2020
CHMP Rapporteur's preliminary assessment report circulated on:	21 August 2020
PRAC Rapporteur's preliminary assessment report circulated on:	24 August 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	3 September 2020
CHMP Rapporteur's updated assessment report circulated on:	10 September 2020
Request for supplementary information adopted by the CHMP on:	17 September 2020
MAH's responses submitted to the CHMP on:	9 October 2020
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	10 November 2020
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	13 November 2020
PRAC RMP advice and assessment overview adopted by PRAC on:	26 November 2020
CHMP Rapporteur's updated assessment report on the MAH's responses circulated on:	3 December 2020
CHMP opinion:	10 December 2020
The CHMP adopted a report on the novelty of the indication/significant clinical benefit for Bavencio in comparison with existing therapies	10 December 2020

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Urothelial Carcinoma (UC) includes tumours originating from the urothelial cells lining the bladder, renal pelvis, ureter, and urethra. Bladder cancer alone accounts for 90% of UC, with approximately 550,000 new cases and 200,000 deaths attributed to bladder cancer worldwide each year. In Europe, an estimated 151, 297 new cases of bladder cancer were diagnosed in 2012. In 2012, there were 52 395 deaths from bladder cancer with an annual crude mortality rate of 7.1/100 000. Approximately 70% of patients with bladder cancer are >65 years of age. (Bellmunt et al, 2014). The incidence of bladder cancer has remained unchanged over the last 25 years.

State the claimed therapeutic indication

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy.

Management

Platinum-based regimens are the standard-of-care first-line treatment for patients with locally advanced or metastatic urothelial carcinoma (aUC) and result in median OS ranging from 9-14 months (De Santis et al, 2012; Calabro et al, 2009). Despite initial high response rates, durations of PFS and OS are limited because of emergent chemotherapy resistance. Further, severe side effects limit long-term use of current chemotherapy agents. Following successful first-line treatment, patients are typically managed with BSC until disease progression. Most patients will experience disease progression within 9 months after the initiation of treatment (von der Maase et al, 2005).

Recently approved PD-L1 inhibitors are new systemic therapies for aUC, both for 1L treatment in cisplatin-ineligible patients for patients with tumours expressing ≥ 5% PD-L1 and for patients experiencing disease progression after platinum-based chemotherapy regardless of PD-L1-status.

Galsky et al evaluated PD-1 inhibitor pembrolizumab as a maintenance treatment versus placebo in a Phase 2 study in patients with metastatic UC (mUC) following first-line treatment. PFS according to irRECIST was significantly longer in patients randomized to pembrolizumab versus placebo (log-rank p=0.038; Galsky et al, 2019).

2.1.2. About the product

Avelumab is a human Ig G1 mAb directed against PD-L1, which is expressed by tumour cells, as well as by a number of immune cell types. Avelumab binds to PD-L1 and blocks the interaction between PD-L1 and its receptors PD-1 and B7.1. This removes the suppressive effects of PD-L1 on anti-tumour CD8+ T-cells, resulting in the restoration of a cytotoxic T-cell response. In vitro, avelumab is capable of stimulating an antibody-dependent cell-mediated cytotoxicity (ADCC) against PD-L1-positive tumour

cells.

Approved indications:

- Bavencio is indicated as monotherapy for the treatment of adult patients with metastatic Merkel cell carcinoma (MCC).
- Bavencio in combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

EMA Scientific advice (SA) was received by the Applicant on 22 October 2015 (EMEA/H/SA/2771/5/2015/II)

The scope of the SA was to discuss the overall study design of Study B9991001.

It was brought to the attention of the Applicant the importance of PFS2 in the interpretation of a PFS benefit. In addition, the PD-L1-negative subgroup of patients was pointed out as important to support a MA claim in the entire population regardless of PD-L1-status. The applicant was advised to at least formulate hypotheses in the PD-L1-negative subgroup.

Pre-submission meeting with the Rapporteur on 30 March 2020

The pre-submission meeting concerned a discussion on the acceptability of study B9991001 results for approval of Bavencio as monotherapy in the first-line maintenance setting of locally advanced or metastatic urothelial carcinoma (aUC).

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

2.2. Non-clinical aspects

No new non-clinical data have been submitted with this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Avelumab is a protein, which is expected to be metabolised in the body and biodegrade in the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), avelumab is exempt from the submission of an Environmental Risk Assessment as the product and excipients do not expect to pose a significant risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 1. Overview of clinical studies.

Study ID	Phase, Study design, control type	Population	Study Posology	Study Objective	Subjs by arm entered/ compl.
B9991001 [JAVELIN Bladder 100] EudraCT No. 2015- 003262-86	Phase 3, multicenter, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus BSC versus BSC alone as maintenance treatment.	Patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy.	Avelumab 10 mg/kg IV Q2W plus BSC	Primary objective: Demonstrate the benefit of avelumab plus BSC versus BSC alone in prolonging OS for patients with PD-L1 positive tumours and all randomized patients.	Total: Avelumab +BSC: ITT: n=350 BSC: ITT: n=350 PD-L1-positive tumours: Avelumab +BSC: ITT: n=189 BSC: ITT: n=169
EMR100070-001 EudraCT No. 2013- 002834-19	Phase 1, open-label, multiple-ascending dose trial.	Patients with metastatic or locally advanced solid tumours.	Dose escalation, 1.0 mg/kg, 3.0 mg/kg, 10.0 mg/kg.	Investigate the safety, tolerability, pharmaco-kinetics, biological and clinical activity	Total: N=1758 Dose Escalation Phase: n=61

	UC expansion cohort: Patients with Histologically or cytologically documented locally advanced or metastatic transitional cell carcinoma of the urothelium (including renal pelvis, ureters, urinary bladder, or urethra) with relapsed, refractory, or progressive disease following last line of treatment	of avelumab and expansion to selected indications.	Dose Expansion Phase: n=1697 • aUC secondary expansion cohort – n= 44 aUC efficacy expansion cohort – n=205

2.3.2. Pharmacokinetics

To support the proposed dosing regimen in the current aUC submission, the following clinical pharmacology analyses and evaluations were provided based on data from avelumab PK and ADA data from study B9991001:

- An assessment of the popPK of avelumab in patients with aUC to estimate avelumab exposures. This analysis employed the monotherapy avelumab steady-state popPK model from the previous submissions.
- The justification of the 800 mg IV Q2W flat-dosing regimen in the aUC analysis population.
- Evaluation of exposure-response relationships of avelumab with key safety and efficacy endpoints.
- The immunogenicity of avelumab where the incidence of ADA was evaluated (see section 4.5.1). Moreover, the influence of ADA on PK and safety was assessed.

A full characterisation of the avelumab PK properties was provided in the original marketing authorisation application. A summary of the avelumab PK characteristics is provided below.

Absorption

Bavencio is for intravenous infusion only.

Distribution

The volumes of the central and peripheral compartments, according to a population PK analysis, were 2.84 L and 1.21 L in the typical subject, respectively. The geometric mean Vss (calculated from individual V1 and V2 parameter values) for a subject receiving 10 mg/kg was 4.72 L.

Elimination

Following IV administration of a 10 mg/kg dose the mean clearance determined by non-compartmental analysis was 0.36 mL/h/kg. The corresponding mean half-life was 95 h (~4 days). From a population PK analysis, the estimated t½ was approximately 6 days in subjects receiving 10 mg/kg every 2 weeks. According to population PK analysis, estimated mean maximal reduction from baseline CL was 32% in the mMCC population and 28% in the head and neck population.

Dose proportionality and time dependencies

The dose-normalized C_{max} and AUC0-336hr after first dose were approximately similar across 3 to 20 mg/kg. C_{trough} increased proportionally with doses between 10 to 20 mg/kg, but more than proportionally for doses between 1 to 10 mg/kg.

Table 2 lists the single study contributing PK and ADA data in the aUC patient population.

Table 2. Clinical Study Providing Clinical Pharmacology Data

Protocol/Location/Cutoff date	Study population (N)	PK/ADA sampling	Treatments
B9991001 (Phase 3) Locations: North America, Central/South America, Asia-Pacific including Japan, and Europe Cutoff date: 21 Oct 2019 PK/ADA Cutoff date: 30 Jun 2019	Adult patients with aUC without progressive disease previously treated with platinum-based induction chemotherapy. N=700 randomized. • 350 in Arm A • 350 in Arm B	PK samples collected (Arm A only) Avelumab PK blood sample (3.5 mL) collected from all patients pre-dose and end of infusion (immediately before end of avelumab infusion) on Days 1 & 15 of Cycles 1-3, then pre-dose and at end of infusion (immediately before end of avelumab infusion) on Day 1 of Cycles 5, 7, 9, 11, & 13. • Avelumab PK (n=344) ADA samples collected (Arm A only) Blood sample (3.5 mL) for ADAs collected pre-dose on Day 1 & Day 15 of Cycles 1-3, and then on Day 1 of Cycles 5, 7, 9, 11, & 13. All samples drawn within 2 hrs before start of avelumab infusion. Samples that are positive for ADA may undergo characterization for neutralizing antibodies. • Avelumab ADA (n=344)	Avelumab 10 mg/kg on Day 1 & Day 15 of each 4-wk treatment cycle.

Analytical methods

Validated avelumab serum concentration analytical method and anti-drug antibody assay have been used.

Pharmacokinetic Analysis

Summary statistics of avelumab Ctrough and Cmax were provided for study B9991001. A population pharmacokinetic (popPK) analysis across studies was conducted to characterise the PK of avelumab in the aUC population. The popPK analysis is further described below.

Population Pharmacokinetic Analysis

The present popPK analysis included PK data from patients with aUC in study B9991001 and used the

based structural component of the pre-established steady-state popPK model (Modeling & Simulation PopPK Report, ver 1.0, March 2017, previously submitted).

To derive summary measures of avelumab exposure, first the PK from study B9991001 was fit using the base structural component (including body weight by allometric scaling) of the pre-established steady-state popPK model. The population PK analysis dataset included avelumab PK data from the pooled studies (studies EMR100070-001, EMR100070-002, and EMR100070-003), with the addition of avelumab PK data in the first-line maintenance aUC analysis population (study B9991001, Arm A). Individual empirical Bayes estimates of avelumab PK parameters were generated for the aUC analysis population from this popPK model, and subsequently used for deriving both single-dose and steady-state exposure metrics of Ctrough, Cmax, and AUC.

As a pre-established steady-state popPK structural model was used, traditional covariate screening was not conducted because covariate effects have been characterized in the general solid tumour population. However, study B9991001 specific covariate effects such as ADA and PD L1 $\geq$ 25% status (dichotomous, yes/no) were graphically explored and final model individual estimates of clearance were compared to evaluate their potential influence on avelumab PK.

Outliers were identified in an initial NONMEM run as observations having an absolute conditional weighted residuals (CWRES) value exceeding 4. These were permanently excluded from subsequent analysis.

Model adequacy and goodness of fit plots were assessed including scatterplots of observed concentrations versus population and individual predicted concentration, and scatterplots of conditional weighted residuals versus population predictions and versus time after dose.

The popPK analysis was performed using NONMEM version 7.4.3 (ICON Development Solutions, Dublin, Ireland), and post-processing was conducted using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2,171 patients receiving avelumab were included in the population PK analysis; 1,827 patients were from the avelumab monotherapy solid tumour popPK dataset previously reported and 344 patients were from the current study B9991001 in which avelumab was administered as first-line maintenance therapy to patients with aUC. In total there were 15,392 PK records with measurable avelumab concentration, 4,566 of which were from the UC first-line maintenance population. In the

344 patients with UC who received first-line maintenance treatment, 66 were ADA ever-positive and 278 were ADA never-positive. A 15% higher baseline clearance in ADA ever-positive patients versus ADA never-positive patients is consistent with the trend seen in patients with renal cell carcinoma. A total of 187 patients had PD-L1-positive tumours, 137 had PD-L1-negative tumours, and 20 patients were missing PD-L1 status. The baseline demographics and continuous variables are presented in Table 3.

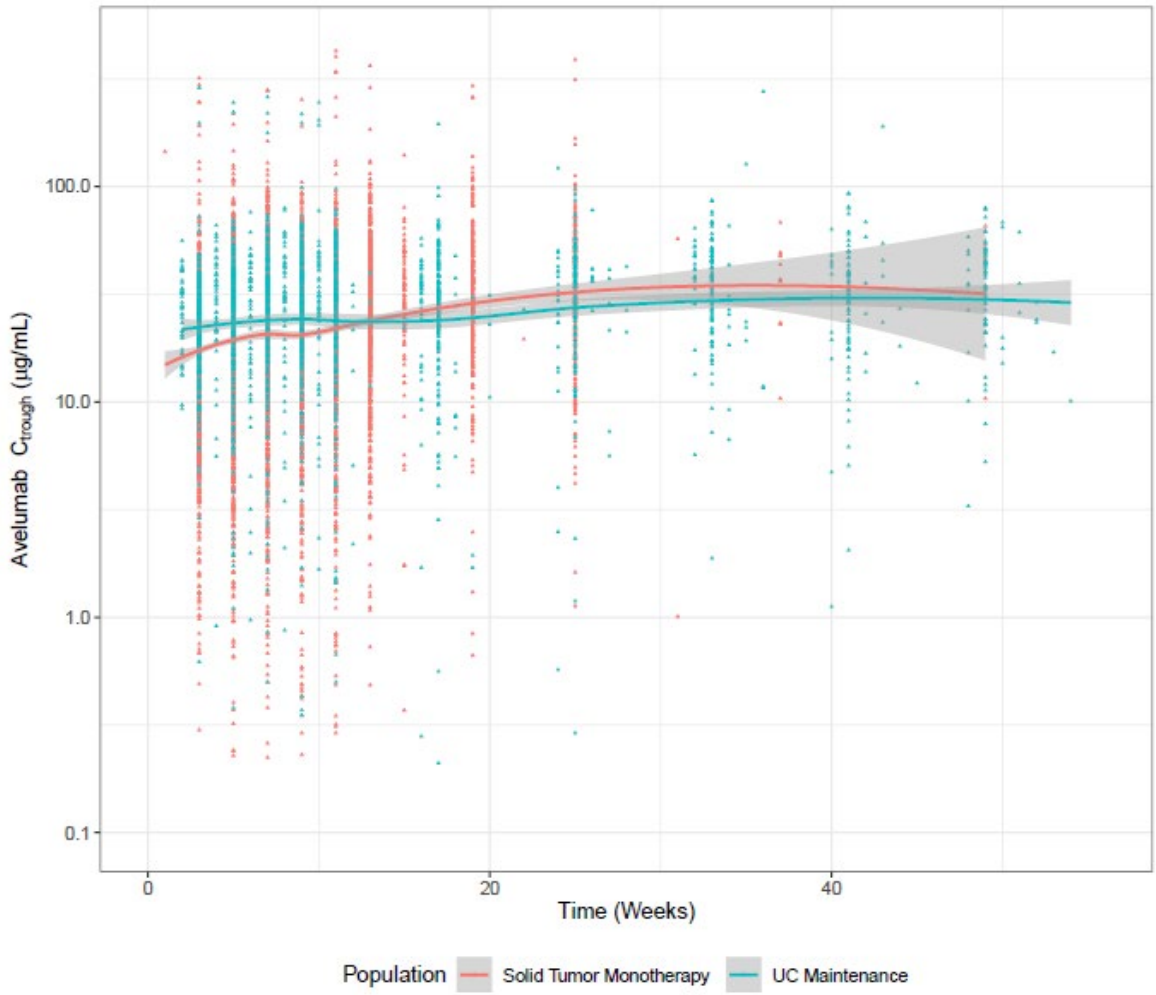
Table 3. Baseline Continuous Variables in UC First-line Maintenance Population

Exposure	N	Missing	Mean (SD)	Median (Range)
Age (yr)	344	0	67.2 (9.59)	68.5 (37-90)
Baseline Weight (kg)	344	0	75.2 (16.6)	72.4 (40-136)
Baseline Tumor Burden (mm)	344	115	29 (33.3)	19.9 (0-224)
Baseline Creatinine Clearance (mL/min)	344	0	66 (23.7)	62.1 (19.1-154)
Baseline eGFR (mL/min/1.73m^2	344	0	66.5 (21.4)	63.6 (29.7-171)
Baseline Albumin (g/L)	344	1	40.5 (4.43)	41 (19-51)
Baseline Bilirubin (μmol/L)	344	0	7.3 (3.59)	6.8 (0.2-23.9)
Baseline ALT (U/L)	344	0	19.1 (10.2)	16.8 (3-61.2)
Baseline AST (U/L)	344	0	22.1 (10)	19.8 (10.2-126)
Baseline Hemoglobin (g/dL)	344	0	11.9 (1.42)	11.8 (8.5-15.9)

Repository artifact ID FI-3199828. Line 1 substituted.
Baseline values were recorded after completing chemotherapy and prior to the first dose of avelumab.
UC=urothelial carcinoma; AST=aspartate aminotransferase; ALT=alanine aminotransferase; eGFR=estimated glomerular filtration rate; yr=year; kg=kilogram; U=unit; μmol=micromol; g=gram; mL=milliliter; min=minute; N=total number of patients; Missing=number of patients without a measurement; SD=standard deviation; L=liter.

The observed concentration data from the monotherapy studies in solid tumour patients (EMR100070-001, EMR100070-002 and EMR100070-003) were compared graphically to the observed data from the first-line maintenance aUC analysis population. The C_{trough} values were overlapping in both populations (Figure 1).

Figure 1 Plot of Observed Avelumab C_{trough} Over Time by Population



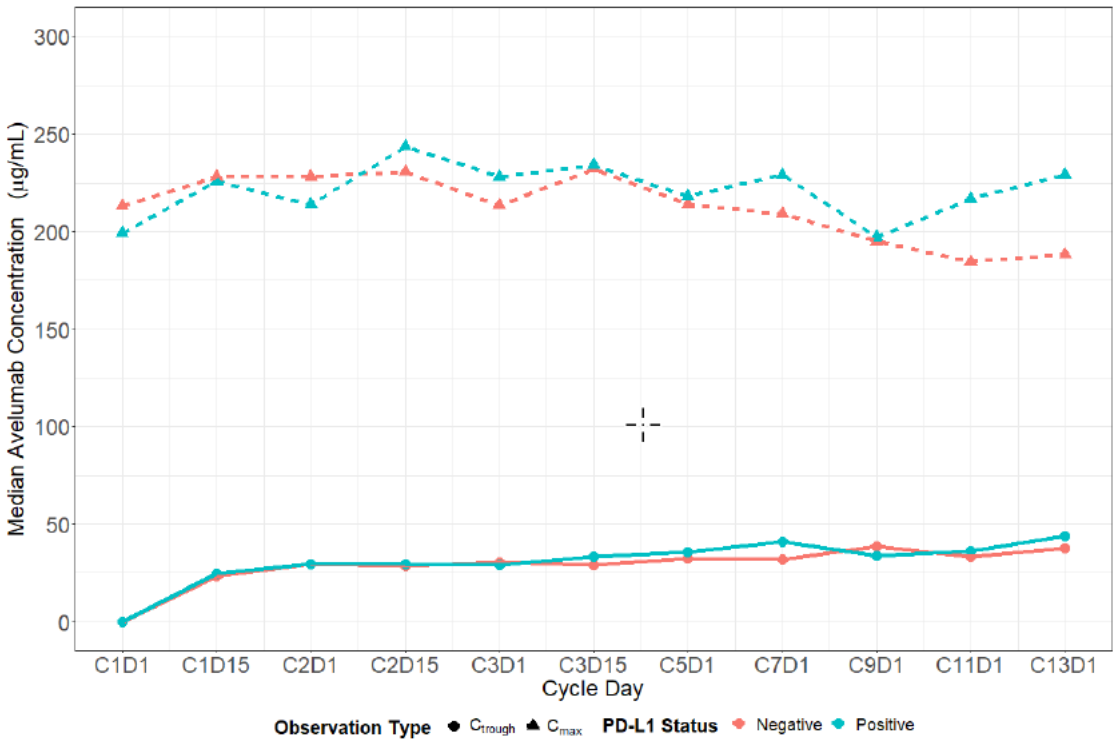
Repository artifact ID FI-12264413.

Concentrations are plotted out to 1 year after first dose. Solid Tumour Monotherapy represents the population included in previous popPK analysis and is presented in red; aUC Maintenance represents aUC first-line maintenance population treated with avelumab and is presented in blue. LOESS line is shown by population in same color. Shaded areas represent the 95% confidence intervals for the LOESS lines.

aUC=locally advanced or metastatic urothelial carcinoma; C_{trough}=trough concentration; mg=microgram; mL=milliliter; popPK=population pharmacokinetic

For the first-line maintenance aUC analysis population, the observed median avelumab C_{trough} and C_{max} values overlapped when grouped by PD-L1 status (Figure 2), indicating similar PK profiles between patients with PD-L1-positive tumours and those with PD-L1-negative tumours.

Figure 2. Plot of Median Observed Avelumab C_{trough} and C_{max} Over Time by PD-L1 Status for UC First-line Maintenance Population



Repository artifact ID FI-1880446.

C_{trough} and C_{max} are grouped by PD-L1 status and plotted out to Cycle 13 Day 1. Negative PD-L1 status represents patients with <25% PD-L1 immune cell expression by Ventana SP263 and is presented in red; Positive PD-L1 status represents patients with ≥25% PD-L1 immune cell expression by Ventana SP263 and is presented in blue. C_{max} observations are represented by dashed lines and C_{trough} are represented by solid lines.

UC=urothelial carcinoma; C_{trough}=trough concentration; C_{max}=maximum observed concentration; µg=microgram; mL=milliliter; popPK=population pharmacokinetic.

The final popPK model was a 2-compartment structural model with time-dependent clearance and fixed effects of baseline body weight on CL (baseline clearance), V1, V2, and Q, with exponents estimated on CL, V1, and V2. Final parameter estimates are presented in Table 4, model goodness-of-fit plots and visual predictive checks are presented in **Figure 3** and **Figure 4**, respectively.

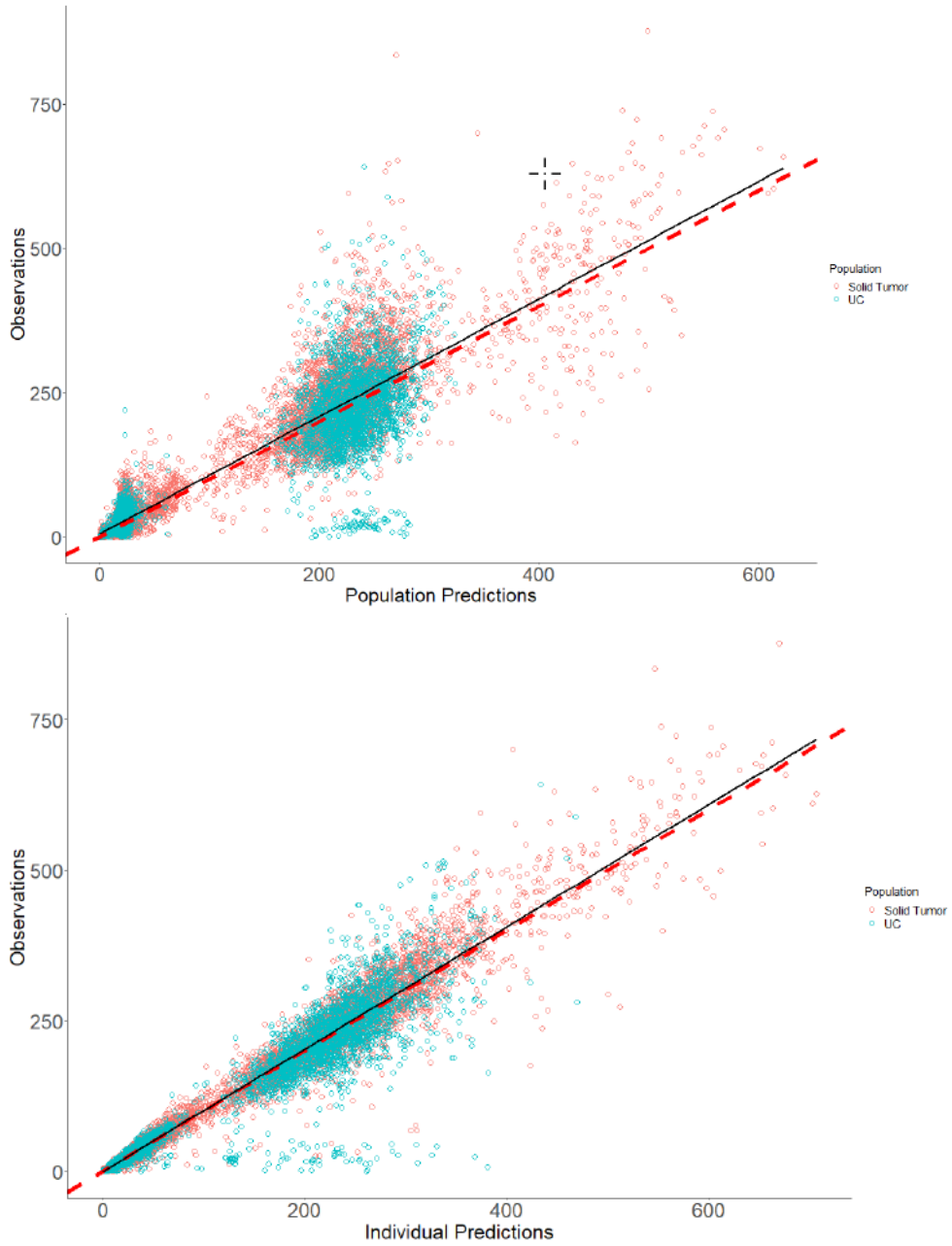
Table 4. Final Parameter Estimates Using Pooled PK Dataset Including Solid Tumour Monotherapy and UC First-Line Maintenance Populations

Parameter	Estimate	RSE (%)	95% CI	Shrinkage (%)[a]
θ_{CL} (L/h)	0.02731	1.02	0.02677 ; 0.02786	-
θ_{V_1} (L)	3.305	0.7822	3.254 ; 3.355	-
θ_{V_2} (L)	0.8147	6.305	0.714 ; 0.9153	-
θ_{Q} (L/h)	0.0288	13.83	0.02099 ; 0.03661	-
$\theta_{I_{max}}$	-0.01856	54.62	-0.03844 ; 0.00131	-
$\theta_{T_{50}}$ (days)	71.91	10.03	57.77 ; 86.06	-
θ_{γ}	2.319	16.27	1.579 ; 3.059	-
$\theta_{\text{weight on CL}}$	0.5358	6.659	0.4659 ; 0.6058	-
$\theta_{\text{weight on } V_1}$	0.5112	5.889	0.4522 ; 0.5702	-
$\theta_{\text{weight on } V_2}$	0.6775	23.38	0.3671 ; 0.9879	-
$\sigma_{\text{proportional error}}$	0.1976	2.868	0.1865 ; 0.2087	11.28
$\sigma_{\text{additive error}}$	1.747	9.462	1.423 ; 2.071	-
ω^2_{CL}	0.088	29.66	0.08 ; 0.09599	7.929
$\omega^2_{V_1}$	0.04769	21.84	0.03626 ; 0.05912	30.01
$\text{cov}_{CL - V_1}$	0.02956	17.19	0.02251 ; 0.03662	-
$\omega^2_{V_2}$	0	-	NA ; NA	-
$\omega^2_{I_{max}}$	0.0672	25.92	0.0391 ; 0.09531	33.25
$\text{OFV}_{\text{FOCE-I}}$	99460.8	-	NA ; NA	-

Repository artifact ID FI-1284907. Line 1 substituted.
Final model results are from model including all 2171 patients in popPK analysis dataset (solid tumor monotherapy and UC first-line maintenance treatment populations); CL represents baseline CL (at time of 0); fixed effect of body weight through allometric scaling of CL, V1, and V2 included estimated exponents (shown here as θs on the parameters); I_{max} is the maximal effect of time on CL; T_{50} is the time at which 50% of I_{max} is achieved; γ is the shape parameter; cov is the covariance between the IIV of the 2 parameters; IIV was incorporated as exponential random effect; RSE(%)=SE/estimate * 100%; 95% CI=estimate +/- 1.96 * SE. The 95%CI is calculated using the estimate and SE from the NONMEM output.
UC=urothelial carcinoma; CI=confidence interval; FOCE-I=first order conditional estimation method with interaction; h=hour; IIV=inter-individual variance; L=liter; popPK=population pharmacokinetic; RSE=relative standard error; SE=standard error.

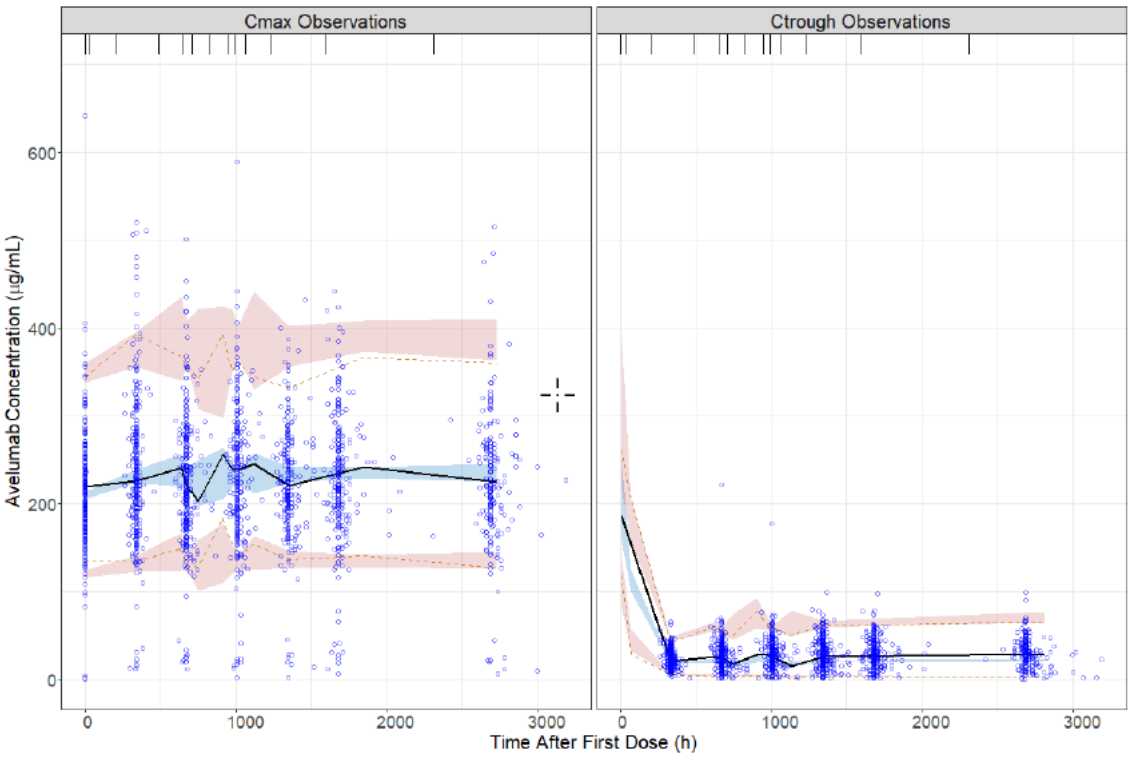
[a]Shrinkage reported in table row for proportional error is the shrinkage corresponding to both σs (proportional and additive)

Figure 3. Plot of Observed Avelumab Concentrations Versus Predicted Concentrations by Population



Repository artifact ID FI-1284344.
Solid tumor represents monotherapy population included in previous popPK analysis and is presented in red circles; UC represents UC first-line maintenance population and is presented in blue circles.
UC=urothelial carcinoma; popPK=population pharmacokinetic.

Figure 4. Visual Predictive Check for the Final PopPK Model for 3,200 Hour Time-course for Avelumab Overlaid with UC First-line Maintenance Population Observations



Repository artifact ID FI-1999710.
Figure shows time after first dose out to 3200 hours. The left panel displays C_{max} and the right panel displays C_{trough}. Shaded areas are the 90% confidence intervals around the simulated 5th, 50th, and 95th percentiles (from 100 simulated trials) and lines are the 5th, 50th, and 95th percentiles of the observed data, both from the entire model analysis population (avelumab solid tumor monotherapy and UC first-line maintenance population). Points display individual observations from the avelumab UC first-line maintenance population in blue.
UC=urothelial carcinoma; µg=microgram; Ctrough=trough concentration; Cmax=maximum concentration; h=hours; popPK=population pharmacokinetic.

Overall, the PK in the first-line maintenance aUC analysis population was consistent with the PK of the solid tumour population treated with monotherapy avelumab (Table 5). Furthermore, the η distribution in Imax across tumour type is visualised in **Figure 5**.

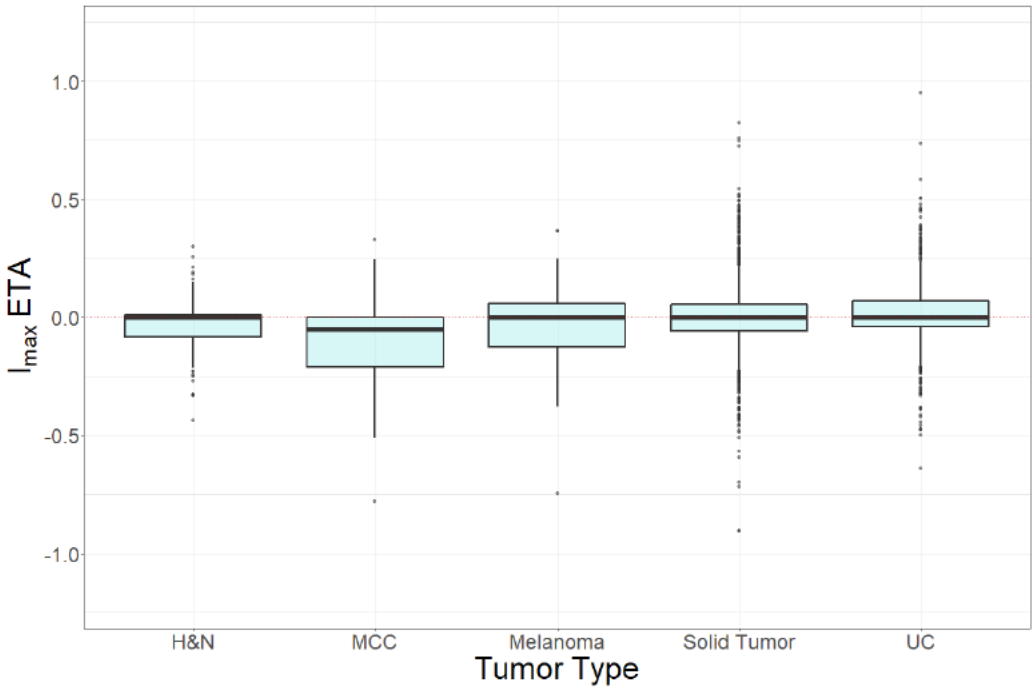
Table 5. Comparison of Parameter Estimates by Population From Current PopPK Model to Previous PopPK Model in Monotherapy

Parameter	Population	Geometric Mean	Lower 95% CI	Upper 95% CI	Mean (SD)	Median (Range)
$CL_{baseline}$ (L/h)	UC Maintenance	0.0264	0.0256	0.0272	0.0276 (0.00869)	0.0263 (0.00889-0.0819)
	Monotherapy Solid Tumor	0.0275	0.0272	0.0279	0.0287 (0.0087)	0.0274 (0.00994-0.0754)
	Combined Population	0.0274	0.027	0.0277	0.0285 (0.0087)	0.0272 (0.00889-0.0819)
	Previous Model	0.0278	0.0274	0.0281	0.0289 (0.00863)	0.0278 (0.00953-0.0718)
V_1 (L)	UC Maintenance	3.55	3.45	3.64	3.67 (1.25)	3.49 (1.9-20.7)
	Monotherapy Solid Tumor	3.25	3.23	3.28	3.3 (0.575)	3.26 (1.55-6.44)
	Combined Population	3.3	3.27	3.33	3.36 (0.736)	3.29 (1.55-20.7)
	Previous Model	3.1	3.07	3.13	3.15 (0.599)	3.11 (1.48-6.21)
V_2 (L)	UC Maintenance	0.833	0.82	0.846	0.842 (0.125)	0.825 (0.552-1.26)
	Monotherapy Solid Tumor	0.817	0.811	0.823	0.828 (0.14)	0.815 (0.458-1.66)
	Combined Population	0.819	0.814	0.825	0.831 (0.138)	0.816 (0.458-1.66)
	Previous Model	0.925	0.909	0.942	1.02 (0.759)	0.917 (0.214-16.3)
Q (L/h)	UC Maintenance	0.0297	0.0291	0.0304	0.0305 (0.00672)	0.0293 (0.0162-0.0551)
	Monotherapy Solid Tumor	0.0289	0.0286	0.0293	0.0298 (0.00755)	0.0288 (0.0123-0.0827)
	Combined Population	0.0291	0.0288	0.0293	0.0299 (0.00743)	0.0289 (0.0123-0.0827)
	Previous Model	0.0313	0.0313	0.0313	0.0313 (0)	0.0313 (0.0313-0.0313)
I_{max}[a]	UC Maintenance	NA	NA	NA	0.00735 (0.18)	-0.00741 (-0.659-0.931)
	Monotherapy Solid Tumor	NA	NA	NA	-0.0239 (0.158)	-0.0186 (-0.926-0.806)
	Combined Population	NA	NA	NA	-0.019 (0.162)	-0.0186 (-0.926-0.931)
	Previous Model	NA	NA	NA	-0.0417 (0.178)	0 (-0.984-0.661)
Max change in CL (%)[a]	UC Maintenance	NA	NA	NA	2.42 (19.8)	-0.739 (-48.3-154)
	Monotherapy Solid Tumor	NA	NA	NA	-1.14 (16.1)	-1.84 (-60.4-124)
	Combined Population	NA	NA	NA	-0.572 (16.8)	-1.84 (-60.4-154)
	Previous Model	NA	NA	NA	-2.6 (16.9)	0 (-62.6-93.6)
T_{50} (days)	UC Maintenance	71.9	71.9	71.9	71.9 (0)	71.9 (71.9-71.9)
	Monotherapy Solid Tumor	71.9	71.9	71.9	71.9 (0)	71.9 (71.9-71.9)
	Combined Population	71.9	71.9	71.9	71.9 (0)	71.9 (71.9-71.9)
	Previous Model	70.6	70.1	71	71.4 (13.4)	68.4 (68.4-131)
Gamma	UC Maintenance	2.32	2.32	2.32	2.32 (0)	2.32 (2.32-2.32)
	Monotherapy Solid Tumor	2.32	2.32	2.32	2.32 (0)	2.32 (2.32-2.32)
	Combined Population	2.32	2.32	2.32	2.32 (0)	2.32 (2.32-2.32)
	Previous Model	2.53	2.48	2.57	2.67 (0.643)	2.91 (0.73-2.91)
V_{ss} (L)	UC Maintenance	4.39	4.29	4.5	4.51 (1.3)	4.32 (2.64-21.7)
	Monotherapy Solid Tumor	4.08	4.05	4.11	4.13 (0.682)	4.08 (2.23-7.49)
	Combined Population	4.13	4.1	4.16	4.19 (0.823)	4.11 (2.23-21.7)
	Previous Model	4.1	4.06	4.13	4.18 (0.973)	4.08 (2.22-21.5)

Repository artifact ID FI-1284854. Line 1 substituted.
UC Maintenance=344 patients from Study B9991001 treated with avelumab for UC first-line maintenance, post-hoc individual estimates summarized descriptively here are from the current popPK model described within this report;
Monotherapy Solid Tumor=1,827 patients with solid tumors treated with monotherapy who were included in the report for the initial marketing applications (M & S PopPK Report [steady state data], version 1.0 MAR2017), post-hoc individual estimates summarized descriptively here are from the current popPK model described within this report;
Combined Population=2,171 patients in the current popPK analysis population (pooled dataset including aforementioned 344 patients from Study B9991001 and 1,827 patients with solid tumors treated with monotherapy), post-hoc individual estimates summarized descriptively here are from the current popPK model described within this report;
Previous Model=1,827 patients with solid tumors treated with monotherapy, post-hoc individual estimates summarized descriptively here are from the previous popPK model submitted for the initial marketing applications (M & S PopPK Report [steady state data], version 1.0 MAR2017).
Max change in CL from baseline (%) calculated as $(e^{I_{max}}-1)*100\%$.
UC=urothelial carcinoma; CI=confidence interval of the geometric mean; h=hour; L=liter; NA=not applicable; popPK=population pharmacokinetic; SD=standard deviation; CL represents clearance; $CL_{baseline}$ represents baseline CL (at time of 0); V_1 represents central volume; V_2 represents peripheral volume; Q represents intercompartmental clearance; I_{max} is the maximal effect of time on CL; T_{50} is the time at which 50% of I_{max} is achieved; Gamma is the shape parameter; V_{ss} represents the steady state volume of distribution

[a] Geometric mean and corresponding 95% CI not applicable as values can be negative for I_{max} and max change in CL (%).

Figure 5. Boxplot of ETA Distributions of Imax by Tumour Type From Final popPK Model



Repository artifact ID FI-2077266.
Solid Tumor population includes all patients who received avelumab monotherapy with tumor types that were not H&N, MCC, Melanoma, or UC (N=1286); UC population includes both solid tumor monotherapy and first-line maintenance patients (N=593)
H&N=Head and Neck; MCC=Merkel Cell Carcinoma; UC=urothelial carcinoma; popPK=population pharmacokinetic; I_{max} represents the maximal effect of time on CL.

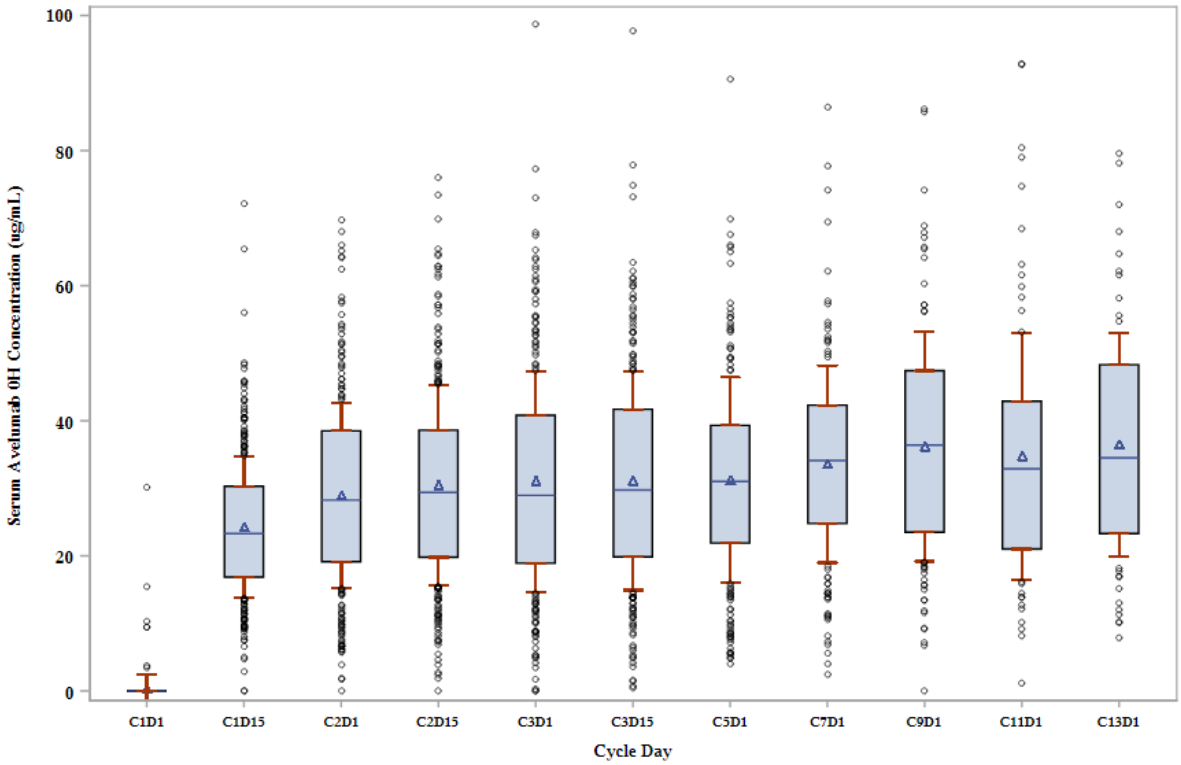
Pharmacokinetics in target population

In study B9991001, mean and median trough and maximum concentrations for avelumab were plotted using a box whisker plot by cycle and day. Avelumab C_{trough} (0H or prior to infusion) concentrations appeared to reach steady state at Cycle 2, the 3rd infusion of avelumab, and did not appear to increase over time (Figure 6). Study B9991001 employed the weight-based avelumab regimen of 10 mg/kg IV Q2W.

Geometric mean avelumab C_{trough} concentrations ranged from 22.2 µg/mL to 32.4 µg/mL between Cycle 1, Day 15 and the last planned collection on Cycle 13, Day 1. The variability in geometric mean C_{trough} (as geometric coefficient of variation, %) ranged from 48.6% to 85.2%, with overlapping distribution of concentration over time. Geometric mean avelumab C_{max} concentrations ranged from 168.9 µg/mL to 222.8 µg/mL between Cycle 1 Day 1 and Cycle 13 Day 1. The variability in geometric mean C_{max} (as geometric coefficient of variation, %) ranged from 30.3% to 86.2%, with overlapping distribution of concentration over time.

Figure 6. Box-Plots of Serum Avelumab 0H Concentration by Visit--Avelumab PK Concentration Analysis Set (Protocol B9991001)

Treatment Group=Avelumab+BSC



0H=prior to infusion or C_{trough}.
Summary statistics have been calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.20 ug/mL.
Values included are from samples collected on day of infusion on or prior to infusion start time and following a prior dose that was within ±10% of 10 mg/kg and was administered within 14±3 days of the sample in case of cycles 1 to 3.
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.
Symbol outside the box=measurements outside 1 SD from the mean.

Table 6 summarizes the exposure metrics, based on the current population PK model, derived for patients in study B9991001 who received at least 1 dose of avelumab (N=344 out of 350 in the avelumab+BSC arm).

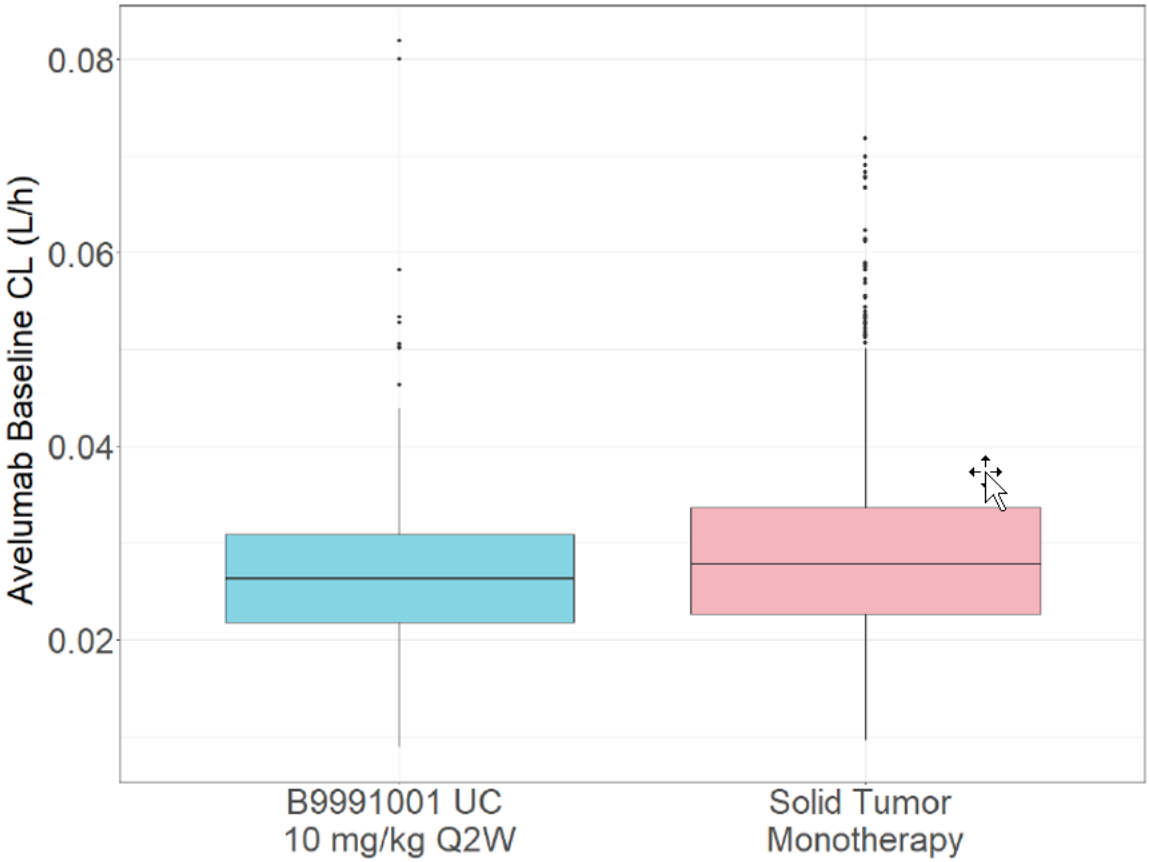
Table 6. Summary of Avelumab Exposure Metrics

Variable	N	Nm	Mean (Stdev)	Median (Max-Min)
First-dose CL (L/h)	344	0	0.028 (0.009)	0.026 (0.009-0.082)
First-dose AUC (μg.h/mL)	344	0	28655.142 (8123.010)	28348.339 (5499.360-92407.316)
Trough concentration Cycle 1 Day 15 (μg/mL)	344	0	23.215 (10.062)	22.690 (2.232-96.307)
First-dose Cmax (μg/mL)	344	0	209.469 (49.535)	204.675 (37.541-434.980)
First-dose amount (mg)	344	0	746.743 (170.872)	720.000 (126.000-1350.000)

Repository artifact ID FI-2148268.
Only patients who received at least one dose of avelumab are summarized in the table.
AUC=area under the avelumab concentration-time curve; BSC=best supportive care; CL=clearance; Cmax=maximum concentration; Max=maximum; Min=minimum value; N=number of patients; Nm=number of patients with missing observations; Stdev=standard deviation.

According to the population PK analysis, the geometric mean (95% CI) baseline CL of avelumab in the aUC population from study B9991001 was 0.0264 L/h (0.0256-0.0272), which was consistent with the baseline CL estimated with the previous pooled dataset of 0.0278 L/h (0.0274-0.0281). A comparison of avelumab baseline CL is represented in Figure 7. The change in CL over time of <5% in the aUC population indicates no change in avelumab clearance over time in patients with aUC.

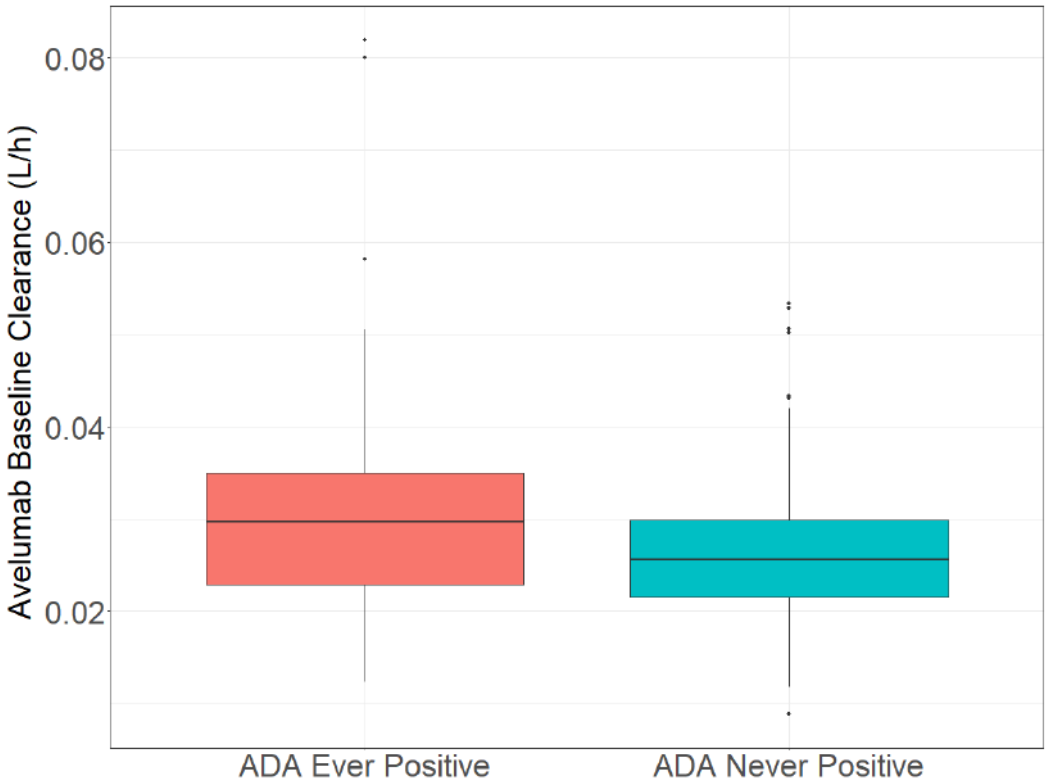
Figure 7. Boxplot Comparing Estimated Avelumab Baseline Clearance between aUC First-line Maintenance and Solid Tumour Monotherapy Populations



Repository artifact ID FI-2014170.
Blue boxplot is baseline clearance in aUC population of 344 patients receiving first-line maintenance treatment following 10 mg/kg Q2W using the popPK model as described within this report; pink boxplot is baseline clearance in Solid Tumor Monotherapy population of 1,827 patients from the previous submission (M & S PopPK Report [steady-state data], version 1.0 MAR2017).

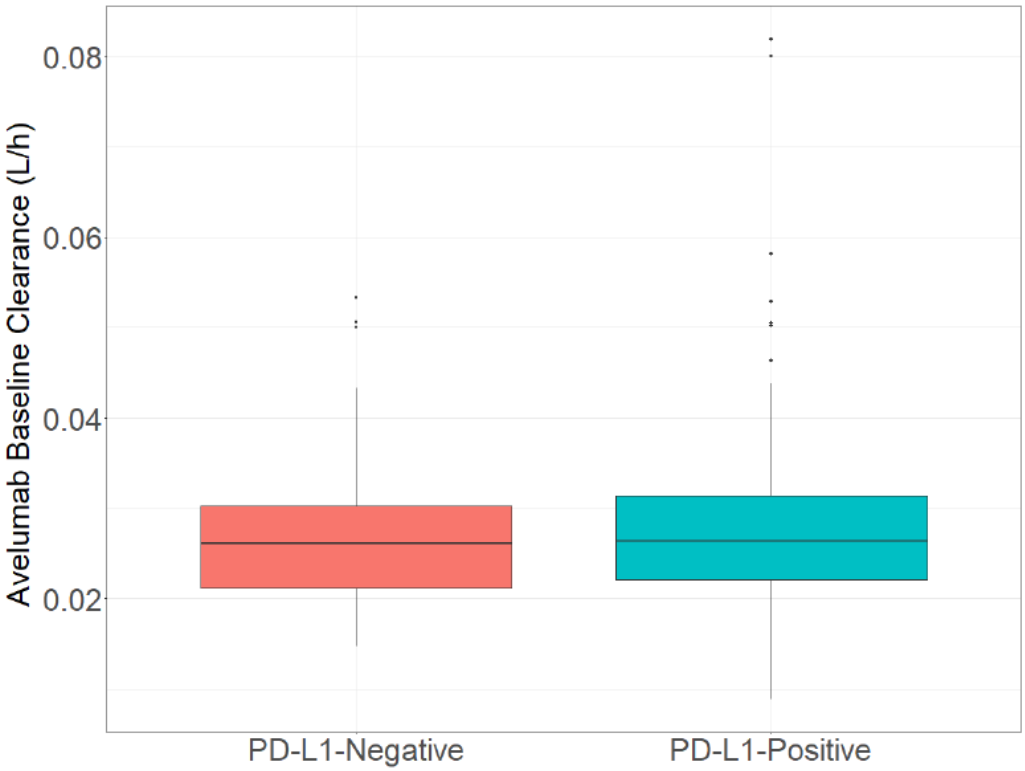
In the 344 patients with aUC who received first-line maintenance treatment, 66 were ADA ever-positive and 278 were ADA never-positive. Baseline CL and maximum change in CL from baseline were summarized by ADA status using the post-hoc estimates from the popPK model. Baseline CL was similar between the ADA status groups, with geometric mean (95% CI) of 0.0295 L/h (0.0271-0.0322) in ADA ever-positive patients, and 0.0257 (0.0249-0.0265) in ADA never-positive patients. Graphical comparison of avelumab baseline CL by ADA status is presented in **Figure 8** and shows overlap of CL distributions by ADA status.

Figure 8. Boxplot Comparing Estimated Avelumab Baseline Clearance for aUC First-line Maintenance Population from Study B9991001 by ADA Status



A total of 187 patients had PD-L1-positive tumours, 137 had PD-L1-negative tumours, and 20 patients were missing PD-L1 status. Avelumab baseline CL was similar between patients with PD L1 positive tumours and patients with PD-L1-negative tumours with geometric mean (95% CI) baseline CL of 0.0267 L/h (0.0256, 0.0279) in patients with PD-L1-positive tumours and 0.0259 L/h (0.0248, 0.0271) in patients with PD L1 negative tumours. Graphical comparison of avelumab baseline CL by PD-L1 status presented in **Figure 9** and shows overlap of CL distributions by PD-L1 status.

Figure 9. Boxplot Comparing Estimated Avelumab Baseline Clearance for UC First-line Maintenance Population from Study B9991001 by PD-L1 Status



Repository artifact ID FI-2000087.
Red boxplot represents baseline clearance in the PD-L1-Negative population (N=137); blue boxplot represents baseline clearance in the PD-L1-Positive population (N=187); patients with missing PD-L1 status (N=20) are not represented here.
UC=urothelial carcinoma; CL=clearance; L=liter; h=hour; PD-L1=Programmed Death Ligand-1.

Table 7 summarizes population PK predicted avelumab baseline CL by ADA status and PD-L1 status.

Table 7. Comparison of Baseline Clearance Estimates From Current PopPK Model by ADA Status and PD-L1 Status for UC First-line Maintenance Population

Parameter	Population	N	Geometric Mean	Lower 95% CI	Upper 95% CI	Mean (SD)	Median (Range)
$CL_{baseline}$ (L/h)	ADA Ever-Positive	66	0.0295	0.0271	0.0322	0.032 (0.013)	0.030 (0.012-0.082)
	ADA Never-Positive	278	0.0257	0.0249	0.0265	0.027 (0.007)	0.026 (0.009-0.053)
	PD-L1-Negative	137	0.0259	0.0248	0.0271	0.027 (0.008)	0.026 (0.015-0.053)
	PD-L1-Positive	187	0.0267	0.0256	0.0279	0.028 (0.010)	0.026 (0.009-0.082)
	PD-L1 Missing	20	0.0267	0.0245	0.0291	0.027 (0.006)	0.026 (0.019-0.040)

Repository artifact ID FI-2097927. Line 1 substituted.
UC first-line maintenance population includes 344 patients from Study B9991001 treated with avelumab, and post-hoc individual estimates summarized descriptively here are from the popPK model described within this report; ADA Ever-positive population includes patients who were ever-positive for ADA; ADA Never-positive population includes patients who never tested positive for ADA; PD-L1-Negative status represents patients with <25% PD-L1 immune cell expression by Ventana SP263; PD-L1-Positive status represents patients with ≥25% PD-L1 immune cell expression by Ventana SP263
UC=urothelial carcinoma; N=number of patients; ADA=anti-drug antibody; PD-L1= Programmed Death Ligand 1; CI=confidence interval of the geometric mean; h=hour; L=liter; NA=not applicable; popPK=population pharmacokinetic; SD=standard deviation.
[a] Geometric mean and geometric CI not applicable as values can be negative for I_{max}.

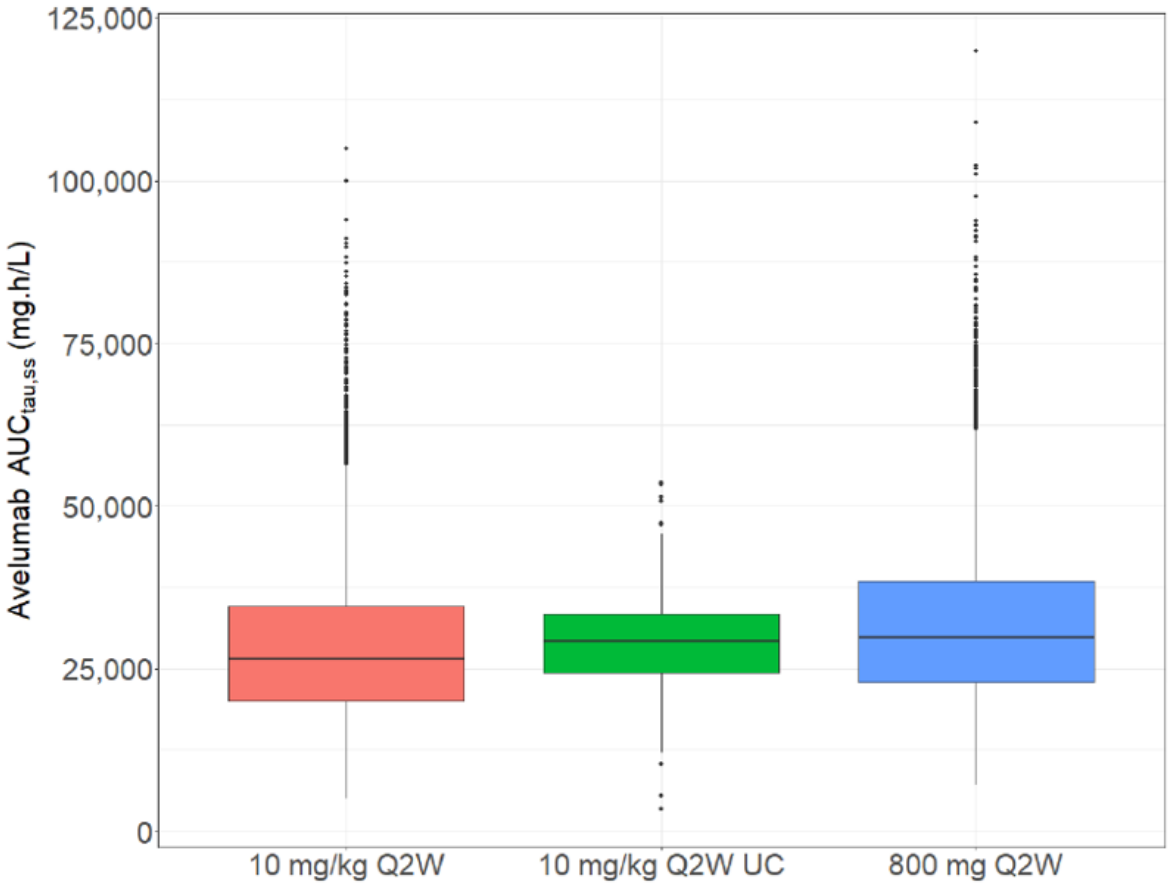
Flat-dose justification

The previous popPK model from avelumab monotherapy treatment of patients with solid tumours was used to derive single-dose and steady-state avelumab exposure metrics of AUC, Cmax, and Ctrough (Modeling and Simulation PopPK Report, version 1.0 March 2017, previously submitted). This previous popPK model utilized data from the pooled PK database of 1827 patients with solid tumours where the median baseline body weight was 70.6 kg (range: 30.4 to 204 kg). The simulated exposures for the 800 mg Q2W flat-dosing regimen from the previous popPK model served as the reference dataset and was imported into this current analysis.

For the first-line maintenance aUC analysis population, the same exposure metrics were derived from the final popPK model individual parameter estimates, and the predicted avelumab exposures were plotted alongside the exposure references of the previously simulated 800 mg Q2W exposure distributions.

Graphical comparison of avelumab exposures in patients with aUC from study B9991001 to those reference exposures simulated from the popPK model in patients with solid tumours with flat-dosing regimen are shown below in the form of boxplots for AUC at steady state ($AUC_{tau, ss}$) (Figure 10) and C_{trough} at steady state ($C_{trough, ss}$) (Figure 11). The exposures estimated in the first-line maintenance aUC analysis population were overlapping with those reference simulations presented previously for the 10 mg/kg Q2W regimen and the 800 mg Q2W flat dosing regimen from patients with various solid tumours.

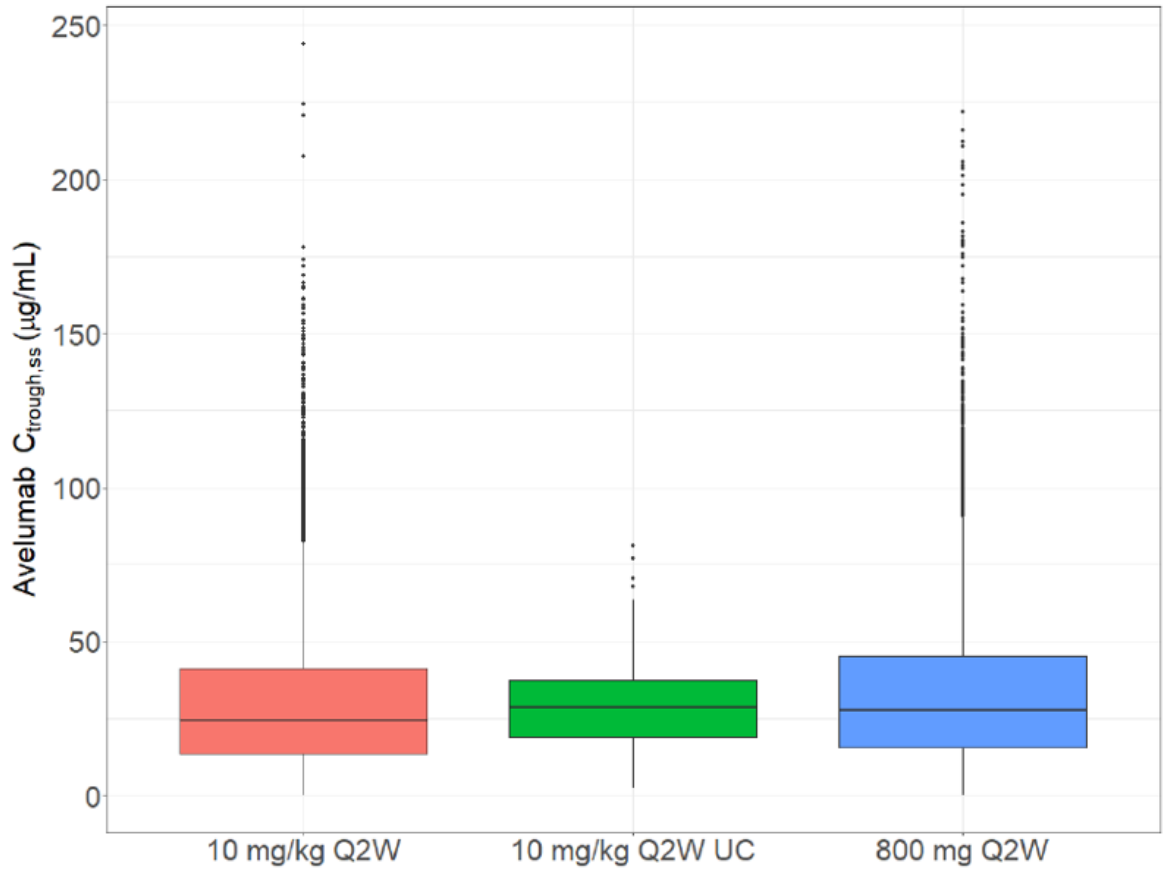
Figure 10. Boxplot for Derived Avelumab $AUC_{tau,ss}$ in aUC and Simulated Reference $AUC_{tau,ss}$ Following Weight-Based and Flat Dosing Regimens



Repository artifact ID FI-1578623.

Green boxplot is $AUC_{tau,ss}$ (derived from individual parameter estimates) in aUC population of 344 patients receiving first-line maintenance treatment with 10 mg/kg Q2W using the popPK model as described within this report; red boxplot and blue boxplot are previously-simulated $AUC_{tau,ss}$ following 10 mg/kg Q2W and 800 mg Q2W, respectively, using popPK model results in solid tumor monotherapy population, as performed in the flat dosing report (M & S Population Analysis Report for Flat Dosing, DEC2017, from previous submission).

Figure 11. Boxplot for Derived Avelumab $C_{trough,ss}$ in aUC and Simulated Reference $C_{trough,ss}$ Following Weight-Based and Flat Dosing Regimens



Repository artifact ID FI-1578627.
Green boxplot is $C_{trough,ss}$ (derived from individual parameter estimates) in aUC population of 344 patients receiving first-line maintenance treatment with 10 mg/kg Q2W using the popPK model as described within this report; red boxplot and blue boxplot are previously-simulated $C_{trough,ss}$ following 10 mg/kg Q2W and 800 mg Q2W, respectively, using popPK model results in solid tumor monotherapy population, as performed in the flat dosing report (M & S Population Analysis Report for Flat Dosing, DEC2017, from previous submission).

2.3.3. Pharmacodynamics

There are no new conclusions regarding pharmacodynamics since the original mMCC submission.

2.3.4. PK/PD modelling

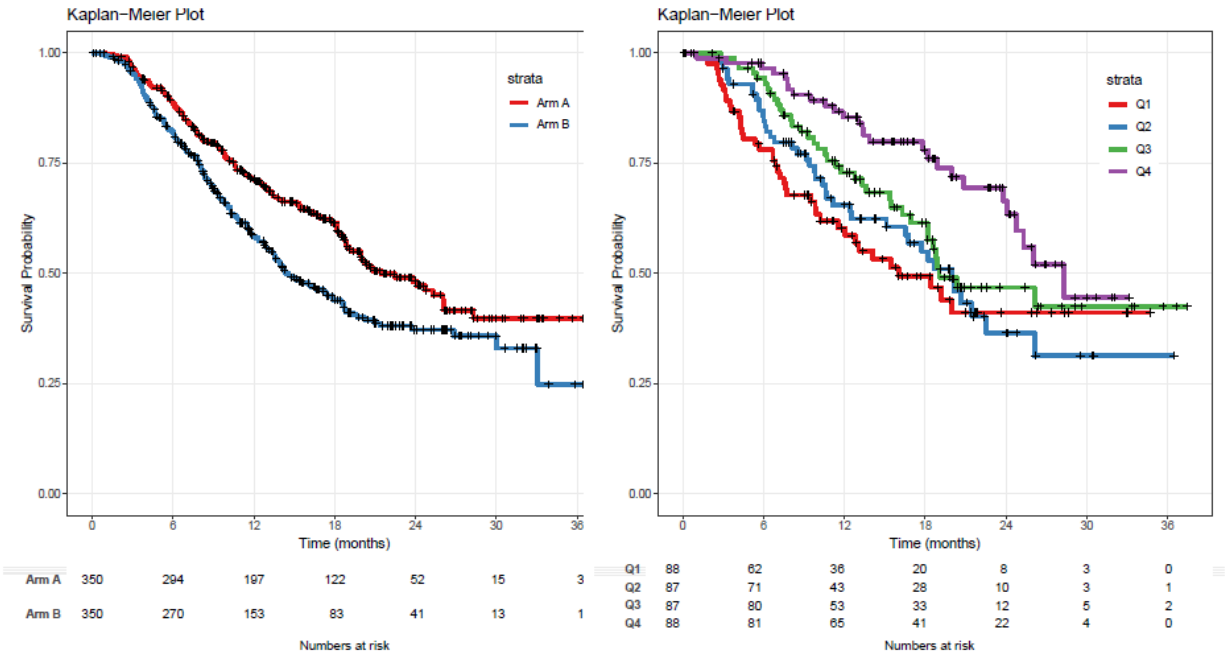
Exposure-Efficacy Analysis

The population PK/PD exposure- efficacy analysis, included data from patients with aUC in study B9991001 randomized to Arm A and used the derived avelumab exposure metrics from the popPK analysis.

The efficacy endpoint analyzed in the exposure-response analyses was overall survival (OS) in patients randomized to Arm A of study B9991001, irrespective of PD-L1 expression on their tumours (N=350) and in patients with PD-L1-positive tumours (N=189). The definition for OS is the same as that for the

analysis of clinical efficacy per study statistical analysis plan as reported in the CSR for B9991001. **Figure 12** shows the OS for patients in Study B9991001. The left panel shows the OS for all randomized patients by treatment Arm (avelumab+BSC Arm (red) versus BSC Arm (blue)), and the right panel shows the OS for patients in the avelumab+BSC Arm of study B999100 stratified by avelumab exposure quartiles (Cycle 1 Day 15 trough concentration): quartile 1 red, quartile 2 blue, quartile 3 green, and quartile 4 purple).

Figure 12. OS for Patients in Study B9991001 Irrespective of PD-L1 Expression.



(a) FI-3386337 **(b)** FI-3386341

Repository artifact IDs are shown in subfigure labels.
The left panel shows the OS for patients in Study B9991001 by treatment arm (Arm A versus Arm B) and the right panel shows the OS for patients in Study B9991001 Arm A only (avelumab+BSC), stratified by avelumab exposure (Cycle 1 Day 15 trough concentration) quartiles. Arm A=avelumab+BSC arm; AUC=area under the concentration-time curve; Arm B=BSC arm; BSC=best supportive care; OS=overall survival; PD-L1=Programmed Death Ligand-1; Q1=avelumab Cycle 1 Day 15 trough concentration, first quartile ; Q2=avelumab Cycle 1 Day 15 trough concentration, second quartile; Q3=avelumab Cycle 1 Day 15 trough concentration, third quartile; Q4=avelumab Cycle 1 Day 15 trough concentration, fourth quartile.

The exposure-efficacy data were evaluated using time-to-event analyses where the available data were fit to a survival function.

In order to minimize the potential impact of post-treatment effects on avelumab PK, avelumab single-dose exposure metrics (CL, AUC, C_{trough}, and C_{max}, and dose amount) were first evaluated in univariate analyses to assess the potential influence on the survival function.

A log-normal distribution best described the OS data based on likelihood ratio test and visual inspection of diagnostic plots. Avelumab single-dose Cycle 1 Day 15 C_{trough}, using a power model, was identified as the most significant exposure metric in patients with aUC randomized to Arm A, irrespective of PD-L1 expression. The final model parameter estimates are presented in Table 8.

Table 8. Final Model Parameter Estimates For OS Patients in the Avelumab+BSC Arm, Irrespective of PD-L1 Expression by PD-L1-Status

Parameter	Value	RSE (%)	95% CI
θ_σ	0.9525	6.02	(0.840 - 1.065)
θ_μ	6.5552	1.85	(6.318 - 6.793)
$\theta_{\text{Avelumab Cycle 1 Day 15 trough concentration on } \mu}$ (μg/mL)	0.0043	23.80	(0.002 - 0.006)
$\theta_{\text{Log of baseline LDH on } \mu}$	-0.0839	-32.16	(-0.137 - -0.031)
$\theta_{\text{Baseline metastasis on } \mu}(non-visceral)$	0.0552	38.56	(0.013 - 0.097)
$\theta_{\text{PDL1 on } \mu}$ (negative)	-0.0649	-28.63	(-0.101 - -0.028)
$\theta_{\text{PDL1 on } \mu}$ (missing)	-0.0396	-97.29	(-0.115 - 0.036)
$\theta_{\text{Baseline hemoglobin on } \mu}$ (g/L)	0.2298	36.71	(0.064 - 0.395)
OFV	2221.6239	-	-

Repository artifact ID FI-2989650. Line 1 substituted.
CI=confidence interval; μ_{OS}=location distribution parameter; σ_{OS}=scale distribution parameter; OFV=objective function value; OS=overall survival; PD-L1=Programmed Death Ligand-1; RSE=relative standard error.

Exposure-Safety Analysis

The population PK/PD exposure-safety analysis included data from patients with aUC in Study B9991001 and used the derived avelumab exposure metrics from the popPK analysis described above.

The safety analysis included all patients with aUC from study B9991001 who received at least one dose of avelumab. The analysis captured all types of adverse events (AEs) that occurred at least once in each patient. The safety event endpoints that were assessed were TEAEs Grade ≥ 3, irAEs Any Grade, and IRRs Any Grade. All AE grades were derived using the NCI CTCAE version 4.03 definitions. For each type of safety event, patients were classified as experiencing the AE in the applicable severity/Grade category at least once during the duration of the study, or never experiencing the AE. The incidence of all selected AEs endpoints is presented in Table 9.

Table 9. Incidence of Reported Safety Endpoints

Category	N (%)
Total Number of Patients	344 (100%)
irAE Any Grade	101 (29.4%)
irAE Grade ≥3	24 (7%)
TEAE Any Grade	337 (98%)
TEAE Grade ≥3	163 (47.4%)
IRR Any Grade	74 (21.5%)

Repository artifact ID FI-3199826.
Grades reported were based on CTCAE version 4.03 definitions. irAE Grade ≥3 and TEAE Any Grade were not modeled.
N=number of subjects; irAE=immune-related adverse event; TEAE=treatment-emergent adverse event; IRR=infusion-related reaction; CTCAE=Common Terminology Criteria for Adverse Events.

A base model was developed for each of the safety endpoints using a logistic regression model. Univariate screen of avelumab exposures of $AUC_{tau,sd}$, $C_{trough,sd}$, $C_{max,sd}$, and $C_{trough,ss}$ was performed to determine the exposure parameter with the largest change in deviance. The chosen exposure

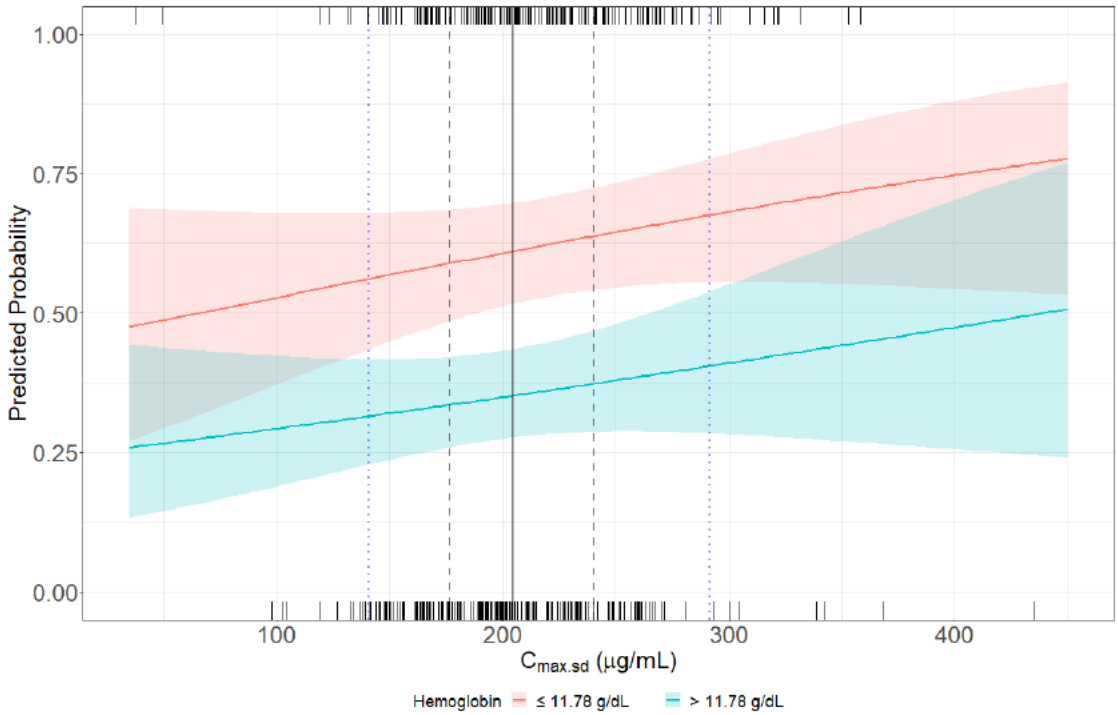
parameter was then selected for incorporation into the base model. The full model was comprised of the base model and all covariates of interest in scope. Covariates of interest included patient demographics, laboratory parameters, and disease-related values. Covariates were assessed for skewedness and collinearity and if two covariates were highly correlated (defined as $|r| \geq 0.6$), only one was selected for multivariate analysis based on clinical relevance. The final model included the avelumab exposure metric along with any covariate effects on regression parameters that were retained during the backward elimination step using a threshold of $\alpha < 0.01$. Model adequacy and goodness of fit was assessed by the Hosmer-Lemeshow test. Model predictive performance was based on the c-index (or area under the ROC curve).

The safety analysis was performed in R by binomial logistic regression using the glm function. R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was also used for data processing, all modeling analyses, post-processing, and generation of figures and tables.

Treatment-emergent Adverse Events of Grade ≥ 3

The final model for TEAEs Grade ≥ 3 included avelumab $C_{max,sd}$ (based on the largest change in deviance, p=0.07) and baseline hemoglobin. A relatively flat exposure-response relationship was observed, where the predicted probabilities of TEAEs Grade ≥ 3 appear greater in patients with aUC with high $C_{max,sd}$. Predicted probabilities of TEAE Grade ≥ 3 as a function of $C_{max,sd}$ and separated by median HGB (11.78 g/dL) are shown in Figure 13. For the 5th to 95th percentiles of $C_{max,sd}$ (140.9-291.5 µg/mL), the probabilities of TEAEs Grade ≥ 3 ranged from 0.560-0.675 for patients with baseline hemoglobin ≤ 11.78, and 0.314-0.404 for patients with baseline hemoglobin >11.78. The correlation between baseline hemoglobin and predicted probabilities of TEAEs Grade ≥ 3 is expected.

Figure 13. Predicted Probability of TEAE Grade ≥3 by Hemoglobin in Patients with UC

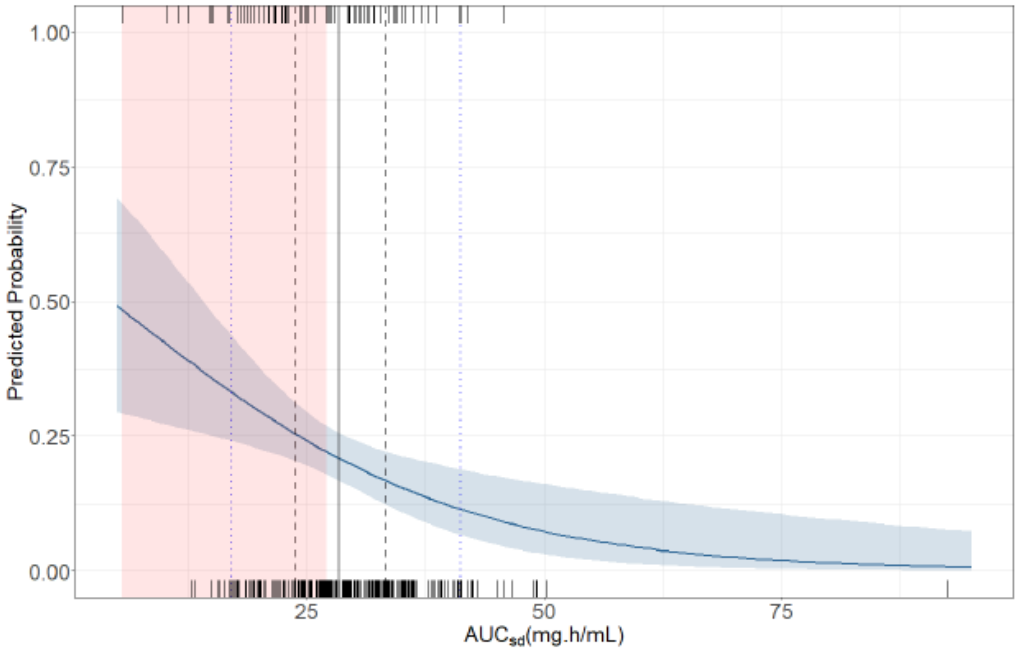


Repository artifact ID FI-3756699.
Red line and shaded region represent predicted probability of TEAE Grade ≥3 and 95% CI in patients with baseline hemoglobin ≤ 11.78 g/dL. Blue line and shaded region represent predicted probability of TEAE Grade ≥3 and 95% CI in patients with baseline hemoglobin > 11.78 g/dL. Dashed vertical lines represent the 25th and 75th percentiles of $C_{max,sd}$. Blue dotted vertical lines represent the 5th and 95th percentiles of $C_{max,sd}$. Derived $C_{max,sd}$ for patients with no TEAE Grade ≥3 event are marked on the bottom of the plot, while derived $C_{max,sd}$ for patients with at least one TEAE Grade ≥3 event are marked on the top of the plot.
TEAE=treatment-emergent adverse event; UC=urothelial carcinoma; $C_{max,sd}$=maximum observed concentration after single dose; µg=microgram; mL=milliliter; g=gram; dL=deciliter; CI=confidence interval.

Infusion-related Adverse Events of Any Grade

The final model for IRRs Any Grade included $AUC_{tau,sd}$ (based on the largest change in deviance, p=0.003). No other covariates were included based on backwards elimination threshold of α<0.01. An inverse exposure-response relationship was found, where the predicted probabilities of IRRs Any Grade are higher in patients with aUC with lower avelumab $AUC_{tau,sd}$ (Figure 14). This is likely confounded by dose interruptions as all of the patients who experienced a dose interruption when receiving the first infusion also had $AUC_{tau,sd}$ values below the population median (the range of exposures in these 8 patients is represented by the pink shaded region in Figure 14). Therefore, based on the shallow relationship and the direction of the effect, it is not considered meaningful.

Figure 14. Predicted Probability of IRR Any Grade in Patients with UC

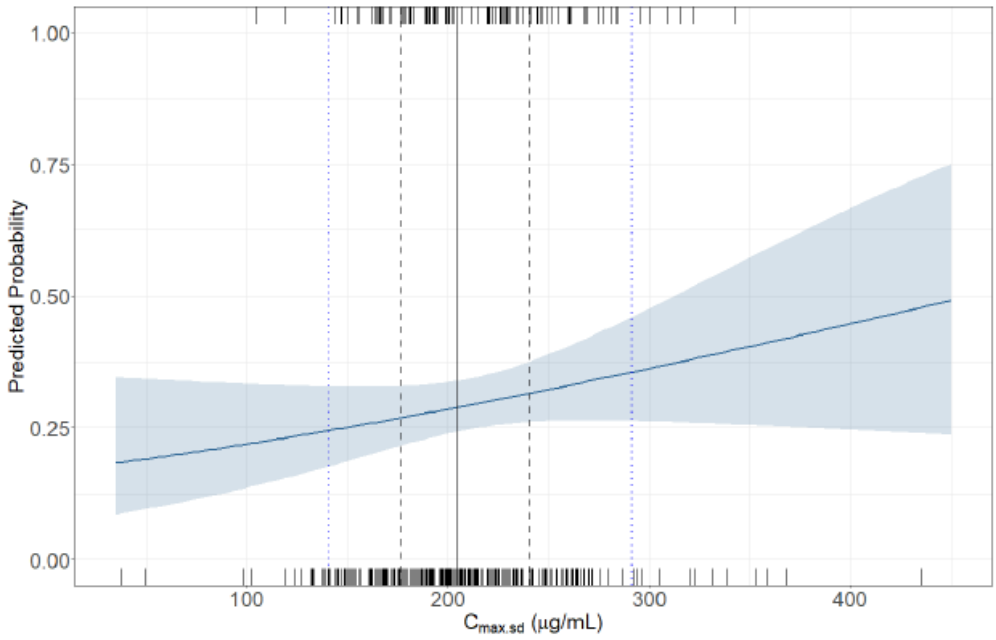


Repository artifact ID FI-3756698.
Blue line and shaded region represent predicted probability of IRR Any Grade and 95% CI. Dashed vertical lines represent the 25th and 75th percentiles of $AUC_{tau,sd}$. Blue dotted vertical lines represent the 5th and 95th percentiles of $AUC_{tau,sd}$. Red shaded region represent the range of $AUC_{tau,sd}$ (5.499-27.07 mg.h/mL) in patients who experienced a dose interruption when receiving their first infusion of avelumab. Derived $AUC_{tau,sd}$ for patients with no IRR Any Grade event are marked on the bottom of the plot, while derived $AUC_{tau,sd}$ for patients with at least one IRR Any Grade event are marked on the top of the plot.
IRR=infusion-related reaction; UC=urothelial carcinoma; $AUC_{tau,sd}$=area under the concentration-time profile of dosing interval after single dose; mg=milligram; h=hour; L=liter; g=gram; CI=confidence interval.

Immune-related Adverse Events of Any Grade

The final model for irAEs Any Grade included $C_{max,sd}$ (based on the largest change in deviance, p=0.14). No other covariates were included based on backwards elimination threshold of α<0.01. A relatively flat exposure-response relationship was observed, where the predicted probabilities of irAEs Any Grade appear higher in patients with aUC with higher $C_{max,sd}$, visualized in Figure 15. For the 5th to 95th percentiles of $C_{max,sd}$ (140.9-291.5 µg/mL), the predicted probabilities for irAEs Any Grade ranged from 0.244-0.355, which is considered low.

Figure 15. Predicted Probability of irAE Any Grade in Patients with UC



Repository artifact ID FI-3756619.
Blue line and shaded region represent predicted probability of irAE Any Grade and 95% CI. Dashed vertical lines represent the 25th and 75th percentiles of $C_{max,sd}$. Blue dotted vertical lines represent the 5th and 95th percentiles of $C_{max,sd}$. Derived $C_{max,sd}$ for patients with no irAE Any Grade event are marked on the bottom of the plot, while derived $C_{max,sd}$ for patients with at least one irAE Any Grade event are marked on the top of the plot.
irAE=immune-related adverse event; UC=urothelial carcinoma; $C_{max,sd}$=maximum observed concentration after single dose; µg=microgram; mL=milliliter; CI=confidence interval.

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

The avelumab PK in the aUC population was mainly evaluated through population PK. A previously submitted avelumab PK model (in the mMCC submission), based on several solid tumour indications, served as the basis of the popPK analysis in the aUC population. This approach is accepted and of note, the approach was also applied in the aRCC submission. The model development and the population PK model results are endorsed.

Overall, the PK of avelumab in the aUC population is similar to the avelumab PK in solid tumours. Exploratory graphical assessment of observed concentration as well as the population PK analysis, indicate that there is no change in avelumab clearance over time in the aUC patient population. The population PK parameters in the aUC population were consistent to the previous avelumab PK model. Furthermore, patient population specific covariates, ADA and PD-L1 status, do not seem to have a relevant effect on avelumab PK in the aUC population.

Flat-dose justification

The flat-dose justification is mainly based on the comparison between the expected (simulated) exposure range given the 10 mg/kg dose and the 800 mg flat-dose. In general, this approach is endorsed, and the objective is to ensure that the proposed flat-dose regimen results in a similar exposure range as the 10 mg/kg dosing regimen with the underlying assumption that the avelumab safety and efficacy profile remains the same. The comparison between simulated exposure range given 10 mg/kg Q2W or 800 mg Q2W, respectively, indicate that the 800 mg flat dose regimen in general

results in slightly higher exposure than for the per kg dosing (for all exposure metrics). As expected, the body weight relationship is reversed, with the lowest exposures for the patients with the highest body weights and a higher exposure for low body weight. Nevertheless, the expected exposure levels are within the reference exposure range and the new dosing regimen is expected to result in similar or slightly higher exposure compared to the 10 mg/kg dosing regimen. Hence, the 800 mg flat dose can be accepted for all patients regardless of body weight.

Exposure-response

It is important to note that several factors may limit the interpretation of the E-R modeling results. First, the range of data used in the analysis was limited to a single dose level (10 mg/kg IV Q2W), resulting in a narrow range of exposure evaluated (single-dose Cycle 1 Day 15 Ctrough ranged from 0 to 96 mg/L). In general, exposure-response analyses based on one dose level should be interpreted with caution since it is difficult to distinguish between effects of exposure and other variables that can confound the E-R relationship. Second, there was an imbalance of baseline health status across exposure quartiles, including more patients with ECOG=0 and higher body weight at baseline in higher exposure quartiles. As such, the E-R analyses should be considered exploratory only.

A univariate screen of avelumab exposures of AUCtau,sd, Ctrough,sd, Cmax,sd, and Ctrough,ss was performed to determine the most informative exposure parameter. As such, no mechanistic consideration has been made in the choice of exposure metric. For the exposure-efficacy analysis, only exposure metrics based on concentration samples from the first cycle were used in the analysis.

The exposure-OS results suggested that a higher exposure (Ctrough,sd) was associated with a higher probability of longer OS in the parametric survival models in patients irrespective of PD-L1 expression on their tumours and in patients with PDL1-positive tumours. The results are in line with the previously reported positive exposure-efficacy relationships for other indications of avelumab.

Models for safety endpoints TEAEs Grade ≥ 3 and irAEs Any Grade showed relatively shallow relationships between avelumab exposure (Cmax, sd) and safety events. The inverse relationship of avelumab AUCtau, sd and IRRs Any Grade is likely confounded by other factors, such as dose interruptions, hence the exposure cannot be considered an independent variable for infusion related response. Thus, the exposure-IRR relationship is not considered meaningful. In all models, ADA status and PD-L1 status were tested as covariates, but they were not significant for any safety endpoint and thus no associations were detected

Overall, the exposure-response relationships for safety endpoints were similar to those estimated previously for avelumab administered as monotherapy in patients with solid tumours and in combination with axitinib in patients with aRCC.

2.3.6. Conclusions on clinical pharmacology

In general, the clinical pharmacology documentation regarding the aUC indication is supported. Overall, the avelumab pharmacokinetics, PKPD and immunogenicity in the UC patient population is similar to what has been previously reported for solid state tumours and the aUC indication. The flat dose posology can be accepted.

2.4. Clinical efficacy

2.4.1. Main study

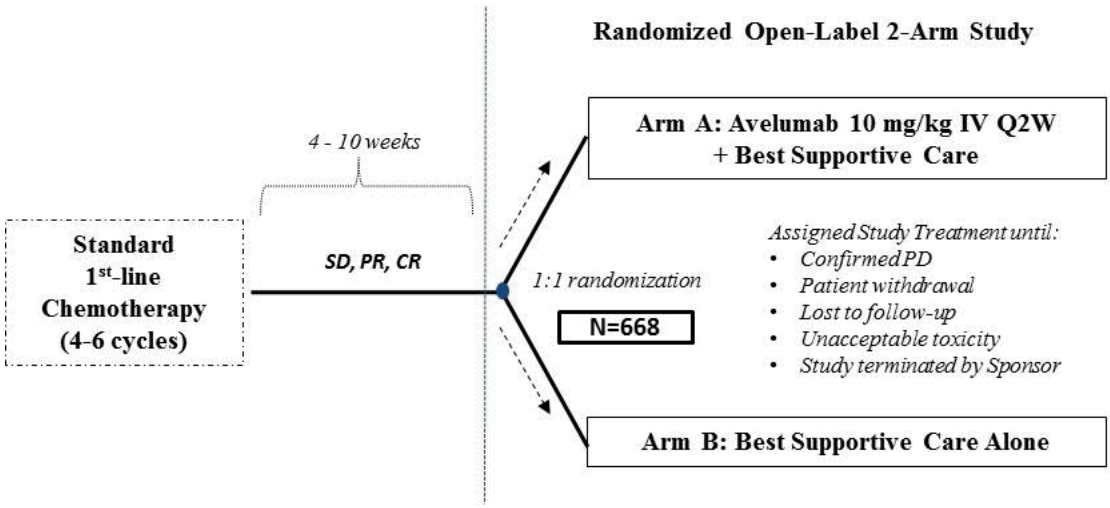
Title of Study

Study B9991001

A Phase 3, multicentre, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus BSC versus BSC alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy (JAVELIN Bladder 100).

Methods

Figure 16. Study B9991001 design



a. Allowed first-line chemotherapy regimens are gemcitabine + cisplatin or gemcitabine + carboplatin.
b. Randomization must occur at least 4 and not more than 10 weeks after the last dose of first-line chemotherapy and will be stratified by: best response on 1st-line therapy (CR or PR vs. SD) and metastatic disease site (visceral vs. non-visceral).

CR = complete response; IV = intravenous; PD = progressive disease; PR = partial response; Q2W = every 2 weeks; SD = stable disease

Study participants

Main inclusion criteria

- Diagnosis:
    a. Histologically confirmed, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium.
    b. Documented Stage IV disease (per American Joint Committee on Cancer/International Union for Cancer Control Tumour Node Metastasis (TNM) system, 7th edition) at the start of first-line chemotherapy.

c. Measurable disease prior to the start of first-line chemotherapy by RECIST v1.1.

- Prior first-line chemotherapy must have consisted of at least 4 cycles and no more than 6 cycles of gemcitabine + cisplatin and/or gemcitabine + carboplatin. No other chemotherapy regimens were allowed in this study.
    a. The last dose of first-line chemotherapy must have been received no less than 4 weeks, and no more than 10 weeks, prior to randomization in the present study.
- Patients without progressive disease as per RECIST v1.1 guideline (i.e., with an ongoing CR, PR, or SD) following completion of 4 to 6 cycles of first-line chemotherapy.
    a. Eligibility based on this criterion will be determined by investigator review of pre-chemotherapy and post-chemotherapy radiological assessments (CT/MRI scans).
- Provision of a recent formalin-fixed, paraffin-embedded (FFPE) tumour tissue block (or subsection thereof) from the most recent primary or metastatic tumour biopsy or resection obtained prior to treatment with first-line chemotherapy but within 24 months prior to randomization, with no intervening systemic anti-cancer therapy. If a FFPE tissue block cannot be provided, 15 freshly cut unstained slides (10 minimum) will be acceptable. If a suitable tissue sample is not otherwise available, then a de novo biopsy (core needle or excisional) must have been obtained for research purposes prior to randomization in this study. Note: tumour tissue from cytologic sampling (e.g., fine needle aspiration, including FFPE cell pellet material) or bone metastases are not acceptable and should not be submitted.
- Evidence of a signed and dated informed consent document indicating that the patient (or a legally acceptable representative, as allowed by local guideline/practice) has been informed of all pertinent aspects of the study.
- Age ≥18 years (≥20 years in Japan).
- Estimated life expectancy of at least 3 months.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1.
- Adequate bone marrow function, including:
    a. Absolute neutrophil count (ANC) ≥1,500/mm^3 or ≥1.5 x 10^9/L;
    b. Platelets ≥100,000/mm^3 or ≥100 x 10^9/L;
    c. Haemoglobin ≥9 g/dL (may have been transfused).
- Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min as calculated using the Cockcroft-Gault equation or by 24-hour urine collection for creatinine clearance or according to the local institutional standard method.
- Adequate liver function, including:
    a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN);
    b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 x ULN, or, for patients with documented metastatic disease to the liver, AST and ALT levels ≤5 × ULN.

Main exclusion criteria

- Patients whose disease progressed by RECIST v1.1 on or after first-line chemotherapy for urothelial cancer.

- Prior adjuvant or neoadjuvant systemic therapy within 12 months of randomization.
- Prior immunotherapy with IL-2, IFN-α, or an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or CTLA-4 antibody (including ipilimumab), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
- Major surgery ≤4 weeks or major radiation therapy ≤2 weeks prior to randomization. Prior palliative radiotherapy is permitted, provided it has been completed at least 48 hours prior to patient randomization.
- Patients with known symptomatic central nervous system (CNS) metastases requiring steroids. Patients with previously diagnosed CNS metastases are eligible if they have completed their treatment and have recovered from the acute effects of radiation therapy or surgery prior to randomization, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.
- Persisting toxicity related to prior therapy NCI CTCAE v4.0 Grade >1; however, alopecia, sensory neuropathy Grade ≤2 is acceptable, or other Grade ≤2 adverse events not constituting a safety risk based on the investigator's judgment are acceptable.
- Diagnosis of any other malignancy within 5 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the breast or of the cervix, low-grade (Gleason ≤6) prostate cancer on surveillance without any plans for treatment intervention (e.g., surgery, radiation, or castration), or prostate cancer that has been adequately treated with prostatectomy or radiotherapy and currently with no evidence of disease or symptoms.
- Participation in other studies involving investigational drug(s) within 4 weeks prior to randomization. Observational studies are permitted.
- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, or hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible.
- Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (<6 months prior to enrolment), myocardial infarction (<6 months prior to enrolment), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
- Active infection requiring systemic therapy.
- Known severe hypersensitivity reactions to monoclonal antibodies (Grade ≥3), any history of anaphylaxis, or uncontrolled asthma (i.e., 3 or more features of asthma symptom control per the Global Initiative for Asthma 2015).
- Current or prior use of immunosuppressive medication within 7 days prior to randomization, EXCEPT the following:
    c. Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra-articular injection);
    d. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent;
    e. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
- Positive test for human immunodeficiency virus (HIV) infection or known acquired immunodeficiency syndrome (AIDS).

- Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive).

In addition, the inclusion and exclusion criteria included restrictions regarding pregnancy, breastfeeding transplanted patients requiring immunosuppressive drugs, prior immunodeficiency, vaccinations within 4 weeks of study drug with non-inactive vaccines and other severe acute or chronic medical conditions.

Determination of PD-L1-status

The IUO-labelled VENTANA PD-L1 (SP263) Assay (Ventana Medical Systems, Inc., a member of the Roche Group) has been analytically validated in UC at a defined cut-off. For the purpose of this study, PD-L1 status is considered high if any of the following are met: ≥25% of tumour cells exhibit membrane staining; or, ICP >1% and tumour-associated immune cells with staining (IC+) ≥25%; or, ICP = 1% and IC+ = 100%. PD-L1 status is considered low/negative if none of the above criteria for PD-L1 high status are met. If PD-L1 status is interpreted as high the tumour will be defined as PD-L1-positive; PD-L1 low/negative status will be defined as PD-L1-negative.

Treatments

- Avelumab plus BSC; avelumab 10 mg/kg administered as 1-hour IV infusion Q2W
- BSC alone

BSC was prescribed and/or administered per current treatment practices at each investigational site and per individual patient needs and could include treatment with antibiotics, antiemetics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC did not include any active anti-tumour therapy.

In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab was mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids

For avelumab, no dose modifications were permitted in this study, but next infusion may be omitted based on persisting toxicity.

Treatment was to be continued until confirmed disease progression as assessed by BICR or unacceptable toxicity. Before amendment 4, in the absence of clinical deterioration, it was stipulated that the patient should remain on treatment until progression was confirmed by BICR at least 4 weeks after the first diagnosis of progression. However, avelumab could be continued at the investigator's discretion after discussion with the sponsor if the following criteria were met:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression;
- No decline in ECOG PS;
- Absence of rapid disease progression evident in radiographic imaging;
- Absence of progressive tumour at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Patients could be eligible for re-treatment at the discretion of the investigator and after discussion with the sponsor's medical monitor if the following criteria were met:

1) no cancer treatment was administered other than BSC since the last dose of avelumab,

2) the patient did not meet the safety withdrawal criteria,

3) the trial was still open.

Drug-related adverse reactions (excluding infusion-related reaction/hypersensitivity and immune-related AE) of Grade 3 severity required avelumab to be withheld until recovery to Grade ≤1 or baseline. Infusion -related reactions and irAEs were handled in agreement with 4.4 in SmPC.

Duration of on-treatment period was for safety endpoints defined as:

- Avelumab plus BSC: time from the first dose of study treatment through minimum (30 days + last dose of study treatment, start day of new anti-cancer drug therapy – 1 day)
- BSC: time from Cycle 1 Day 1 through minimum (30 days + end date of BSC, start day of new anti-cancer drug therapy – 1 day)

The MAH have proposed a different dosing regimen compared to what was used in the trial. The weight-based dosing regimen for avelumab (10 mg/kg IV Q2W) used in pivotal Phase 3 Study B9991001 was based on the dose identified in the Phase 1 Study EMR100070-001.

The recommended dosing regimen for the treatment of mMCC and aRCC is 800 mg of avelumab, given by IV infusion over 60 minutes Q2W, as summarized in the current SmPC. The proposed dosing regimen for avelumab for first-line maintenance treatment in patients with aUC is 800 mg IV Q2W.

Objectives

Primary Objectives

- To demonstrate the benefit of maintenance treatment with avelumab plus BSC vs. BSC alone in prolonging OS in patients with unresectable locally advanced or metastatic UC whose disease did not progress on or following completion of first-line platinum-containing chemotherapy in each co-primary aUC patient population:
    1. patients determined to have PD-L1-positive tumours (including infiltrating immune cells) by a verified Good Manufacturing Practice (GMP) PD-L1 immunohistochemistry (IHC) test,

and

    2. all randomized patients.

Secondary Objectives

- To compare the PFS of avelumab plus BSC vs. BSC alone in patients determined to have PD-L1-positive tumours (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and in all randomized patients.
- To evaluate the anti-tumour activity of avelumab plus BSC and BSC alone according to Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 in patients determined to have PD-L1-positive tumours (including infiltrating immune cells) by a verified GMP PD-L1 immunohistochemistry (IHC) test, and in all randomized patients.
- To evaluate the overall safety profile of avelumab plus BSC and BSC alone.

- To evaluate the PK of avelumab in each of the co-primary UC patient populations treated with avelumab.
- To assess the immunogenicity of avelumab in each of the co-primary UC patient populations treated with avelumab.
- To evaluate candidate predictive biomarkers of sensitivity or resistance to avelumab in pre-treatment tumour tissue in each of the co-primary UC patient populations treated with avelumab.
- To evaluate the effect of avelumab plus BSC and BSC alone on patient-reported outcomes (PROs) in each of the co-primary UC patient populations.

Exploratory Objectives

- To explore the predictive and/or pharmacodynamic (PD) characteristics of peripheral blood and additional tumour tissue biomarkers relevant to the mechanism of action of or resistance to avelumab.

Outcomes/endpoints

Table 10. Summary of key Efficacy endpoints: Definitions and Censoring Rules

Efficacy endpoint	Definition	Censoring/Handling of data
Primary endpoint		
Overall survival; PD-L1-positive tumours and All randomized patients Stratified by study stratification factors.	Time from the date of randomization to the date of death due to any cause.	Patients known to be alive will be censored at date of last contact. Other reasons for censoring include withdrawal of consent and lost to follow-up.
Secondary endpoint		
PFS based on BICR assessment per RECIST v1.1.[1]	Time from the date of randomization to the date of the first documentation of progressive disease (PD) or death due to any cause, whichever occurs first. For all patients, radiological tumour assessments will be performed every 8 weeks for up to a year and every 12 weeks thereafter until disease	Censoring: • On the date of the last adequate tumour assessment for patients who do not have an event (PD or death), or; • start a new anti-cancer therapy prior to an event, or;

[1] The FDA rules for censoring of PFS was applied. A sensitivity analysis according to the EMA guidelines (EMA/CHMP/27994/2008/Rev.1 (*Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man Methodological consideration for using progression-free survival (PFS) or disease-free survival (DFS) in confirmatory trials*) was therefore requested.

	progression regardless of initiation of subsequent anti-cancer therapy. Upon investigator-assessed disease progression, all radiographic images collected for a patient from baseline onwards was to be submitted to the BICR for expedited review.	• for patients with an event after 2 or more missing tumour assessments. Patients who do not have an adequate baseline tumour assessment or who do not have an adequate post-baseline tumour assessment will be censored on the date of randomization unless death occurred on or before the time of the second planned tumour assessment (i.e. ≤ 16 weeks after the date of randomization) in which case the death will be considered an event.
Objective Response (OR), as assessed per RECIST v1.1 by BICR and investigator.	Complete response (CR), or partial response (PR), according to RECIST v1.1, from the date of randomization, until the date of the first documentation of PD. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first met.	Patients who do not have a adequate radiographic tumour assessment (eg, no baseline assessment or no follow-up assessments) will be counted as non-responders in the assessment of OR.
Time to Tumour Response (TTR) as assessed per RECIST v1.1 by BICR and investigator.	For patients with an OR, as the time from the date of randomization to the first documentation of objective response (CR or PR) which is subsequently confirmed	
Duration of Response (DR) as assessed per RECIST v1.1 by BICR and investigator.	For patients with OR, as the time from the first documentation of objective response (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 is censored in the same way as the PFS endpoint, with the exception of no adequate baseline assessment.
Disease Control (DC) as assessed per RECIST v1.1 by BICR and investigator.	CR, PR, non-CR/non-PD or stable disease (SD). Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after the criteria for response are first	•

	met. Criteria for SD and non-CR/non-PD must have been met at least 6 weeks after the date of randomization.	

Patient Reported Outcomes endpoints

Patient reported bladder cancer symptom, functioning, global quality of life (QOL), and Time to Deterioration (TTD) using the NCCN-FACT FBlSI-18; and health status using the EQ-5D-5L.

The patients were to complete the questionnaires at the clinic at Day1 of each cycle (Q4W), at EOT/withdrawal and day 30, 60 and 90 after last dose of study drug. For the NCCN-FACT FBlSI-18 multi-item scales, the score may be imputed as the mean of the non- missing questions if at least half the questions in that scale are answered. For EQ-5D-5L, the entire score for that cycle is deemed missing if the answer to any one of the 5 dimensions is missing.

Exploratory Endpoints

Biomarkers: Peripheral blood and additional tumour tissue biomarkers consisting of the levels of cells, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), or proteins that may be related to anti-tumour immune response and/or response to or disease progression on avelumab, such as genes related to IFN-γ or transforming growth factor (TGF)-β.

Sample size

The study was designed to test the two primary populations in parallel.

Overall type I error rate was maintained at or below 1-sided 0.025 by allocating 0.015 alpha to the OS comparison for all randomized patients and 0.01 to the OS comparison for patients with PD-L1-positive tumours. The significance levels for each test also took into account the group-sequential nature of the design.

Approximately 668 patients were to be randomized to the treatment arms using a 1:1 randomization stratified by best response to first-line chemotherapy (CR or PR vs SD) and site of metastasis (visceral vs non-visceral) at time of initiating first-line chemotherapy. It was estimated that at least 50% of the randomized patients would be determined to have PD-L1-positive tumours.

The sample size for this study was determined based on the following assumptions:

- The median OS is 12 months for all patients and for patients with PD-L1-positive tumours, who receive BSC alone after first-line chemotherapy.
- The median OS was assumed to be 17.1 months for all patients receiving avelumab plus BSC after first-line chemotherapy.
- The median OS was assumed to be 18.5 months for patients with PD-L1-positive tumours, receiving avelumab plus BSC after first-line chemotherapy.
- 5% drop-out rate for OS within each treatment arm.

This corresponds to a hazard ratio (HR) of 0.7 for all patients and 0.65 for patients with PD-L1-positive tumours under the exponential model assumption.

For all patients, a total of 425 OS events were required to have 93% power to detect a HR of 0.7 using a one-sided log rank test at a significance level of 0.015 and a 2-look group sequential design.

For patients with PD-L1-positive tumours, a total of 219 OS events were required to have 80% power to detect a HR of 0.65 using a one-sided log rank test at a significance level of 0.01 and a 2-look group sequential design.

The study was considered positive if the stratified log rank test for OS is significant at the respective adjusted levels at the interim or at the final analyses, for either of the two co-primary populations.

Randomisation

Patients were randomized in a 1:1 ratio to receive avelumab plus BSC or BSC alone.

Randomization using web based IRT was stratified according to:

- Best response to first-line chemotherapy (CR/PR vs SD), and
- Metastatic disease site (visceral vs non-visceral) at the time of initiating first-line chemotherapy.
- Site of metastasis was defined at the time of initiation of the first-line chemotherapy. The "non-visceral" stratum includes patients with locally advanced disease as well as patients with only non-visceral disease. Patients with both visceral metastases and non-visceral sites of disease were categorized as "visceral".

Table 11. Disease Sites and Designation of Visceral vs Non-Visceral Site of Metastasis

Disease Site	Site of Metastasis = Visceral Disease
Bladder	Yes if the primary tumor did not arise in the bladder
Lung	Yes
Bone	No
Lymph node (any location)	No
Liver	Yes
Vagina	Yes
Urinary Tract	Yes if the lesion is distinct from the primary tumor
Prostate Gland	Yes
Uterus	Yes
Peritoneum	Yes
Kidney	Yes if it is not locally advanced disease (ie, an extension of a tumor that arose in the renal pelvis)
Renal Pelvis	Yes if the primary tumor did not arise in that renal pelvis
Adrenal	Yes if it is distinct from the primary tumor
Pleura	Yes
Pericardium	Yes
Brain	Yes
Heart	Yes

Study treatment (Cycle 1 Day 1) must start within 3 days after patient randomization.

Blinding (masking)

Study B9991001 was not blinded.

In the evaluation of imaging, all independent reviewers were blinded to subject name, date of birth, subject initials, treatment arm and investigator site identifiers.

Statistical methods

Analysis Sets

The analysis populations are defined as follows.

Full Analysis Set: All randomized patients. This set was used for Efficacy, PRO, patient characteristics endpoints.

Per Protocol Analysis Subset of FAS: Excludes from the FAS patients who did not receive the assigned treatment, patients with a baseline ECOG status 2 or higher, patients who did not meet inclusion criteria 1, 2, or 3, and patients who met exclusion criterion 1. This set was used for sensitivity analysis on the OS endpoint.

Primary Analysis Overall Survival

A 1-sided stratified log-rank test was used within each comparison at the interim and/or final analyses with the overall significance level preserved at its respective levels (1-sided 0.015 for all patients and

1-sided 0.01 for patients with PD-L1-positive tumours). OS time was summarized by treatment arm based on the FAS using the Kaplan-Meier method. The Cox proportional hazards model was fitted to compute the hazard ratios and the corresponding CIs. In order to account for the group-sequential design in this study, the RCI method was used to construct the 2-sided RCI for the hazard ratios.

Sensitivity Analyses Overall Survival

Sensitivity analyses were performed to explore robustness of primary analyses; the primary analyses (p-value, HR and 95% CIs) were repeated with Per protocol population and unstratified analysis.

Additionally, validity of proportional hazards assumptions was checked visually by plotting log(-log(OS)) versus log(time) within each randomization stratum and also by plotting Schoenfeld residuals for the stratified Cox proportional regression model. If the plots showed large departures from proportional hazards, OS assessment was to be analysed based on RMST differences.

Also, multivariable Cox regression analyses were performed to assess and adjust the treatment effect for relevant baseline factors of potential prognostic impact.

Progression-Free Survival

A stratified log-rank test (1-sided) was used to compare the PFS time between the experimental arm and the control arm. PFS time was summarized by treatment arm based on the FAS using the Kaplan-Meier method. The Cox proportional hazards model was fitted to compute the hazard ratios and the corresponding CIs.

A summary of PFS by the BICR assessment versus investigator assessment was provided. Measures of discordance were used to evaluate potential bias.

Objective Response

OR was defined as BOR of confirmed CR or PR according to RECIST v1.1 taking into account assessments performed from randomization until the first documentation of PD; only assessments performed on or before the start date of any further anti-cancer therapies were considered. ORR, the proportion of patients with OR, was calculated along with the 2-sided 95% CI using the Clopper-Pearson method for each treatment arm.

Patients with a CR after chemotherapy could only have a BOR of NE or PD after randomization.

A summary of BOR and OR by BICR assessment versus investigator assessment is provided along with concordance rates. Difference in concordance rates between treatment arms was used to evaluate potential evaluation bias.

Interim Analysis

Two analyses were planned for OS:

1) the IA, after all patients have been randomized, at least 315 of all randomized patients have died (74% of the target number of OS events for the 'all patients' population), and at least 146 patients with PD-L1-positive tumours have died (approximately 66.7% of the total OS events expected in the 'patients with PD-L1-positive tumours' population);

2) the final analysis after at least 425 of all randomized patients and at least 219 patients with PD-L1-positive tumours have died, and the last patient randomized in the study has been followed for at least 12 months after randomization.

To protect the integrity of the study and to preserve the type I error rate, a fraction of α for efficacy was planned to be spent at the IA and accounted for in the overall type I error rate (if the IA was

performed exactly at the planned number of OS events, α spent at IA is 0.005 for all patients and 0.002 for patients with PD-L1-positive tumours). The significance levels for the interim and final efficacy analyses of OS are determined by using the Lan-DeMets procedure with an O'Brien-Fleming stopping boundary. The overall significance level for the efficacy analysis of OS were preserved at (1-sided) 0.015 for all patients and 0.01 for patients with PD-L1-positive tumours.

The goals of the IA were to allow early stopping of treatment arm(s) for futility or efficacy and to potentially adjust the sample size. The study would have met its primary objective if the experimental arm was statistically significantly superior to the control arm for either one of the coprimary populations, either at the time of the IA or at the time of the final analysis.

Since the observed number of events at the IA was not exactly equal to the planned number of events, the efficacy and futility boundaries were determined based on the actual number of observed events using the pre-specified α-and β-spending functions.

Table 12. Efficacy and Futility Boundaries at Interim Analysis- Randomized Patients

	Population	
	All patients	**Patients with PD-L1-positive tumors**
Observed number of events	324 (76.2%)	143 (65.3%)
p-value (z-value) for efficacy	<0.0053 (<-2.553)	<0.0014 (<-2.981)
p-value (z-value) for futility[a]	>0.1849 (>-0.897)	>0.3718 (>-0.327)

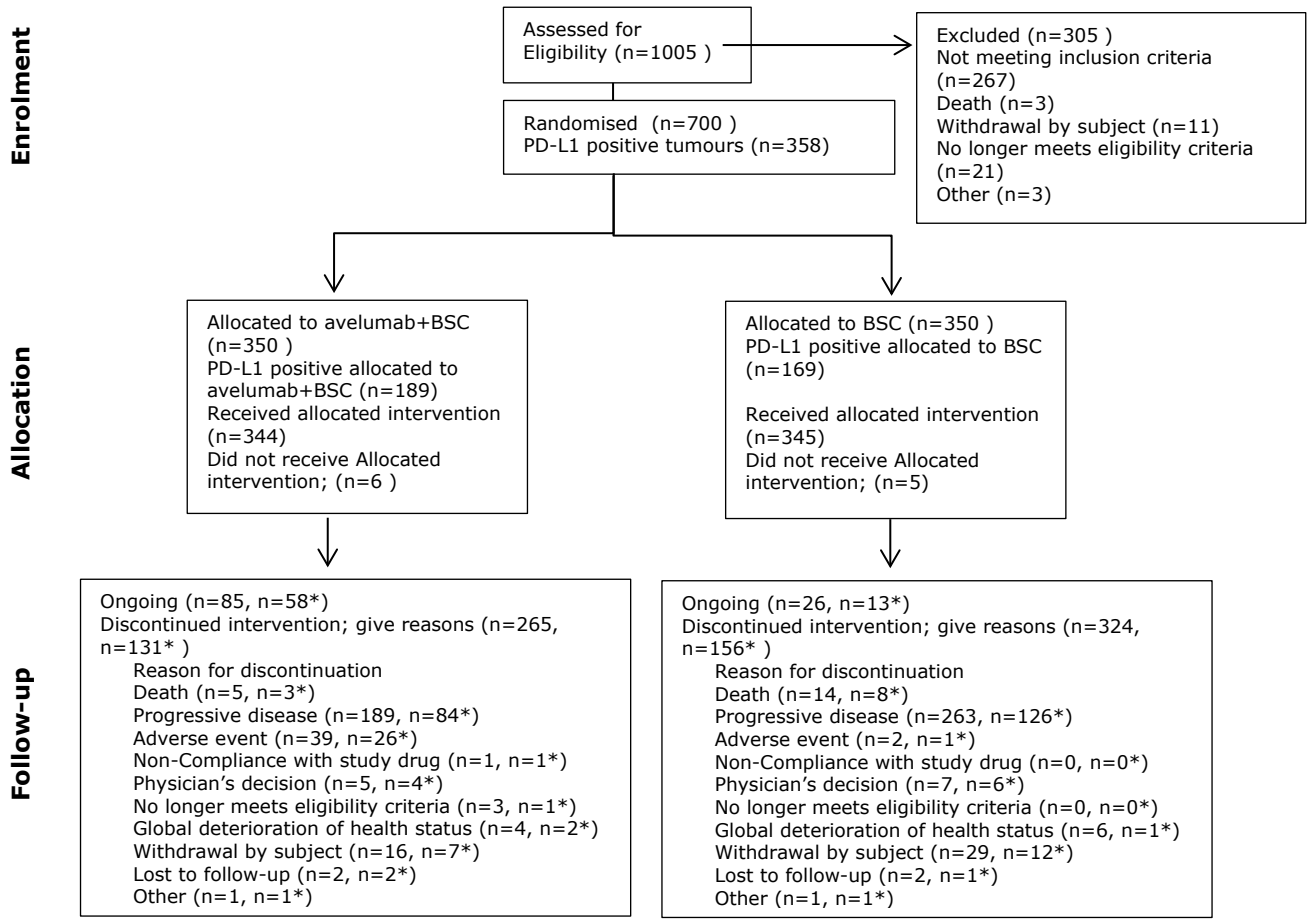
Source: Output from EAST®
[a] Non-binding.

No multiple testing procedure was used for secondary endpoints.

Results

Participant flow

Figure 17. Participant flow Study B9991001.



*patients with PD-L1-positive tumours.

Recruitment

The first patient was recruited in May 2016 (first subject visit 28 April 2016) and the last patient was recruited in June 2019. Data cut-off date for pre-specified interim analysis was 21 October 2019.

Patients were enrolled among 231 sites in 29 countries. The number of patients enrolled and randomized per country are summarized in descending order:

Spain 110, France 85, Japan 73, Italy 62, Australia 59, Republic of Korea 45, Greece 25, Belgium 24, Denmark 23, Taiwan 21, United Kingdom 19, United States 19, Russian Federation 17, Canada 15, Netherlands 15, Brazil 13, New Zealand 12, Serbia 10, Israel 7, Mexico 7, Norway 7, Sweden 7, India 6, Portugal 6, Poland 5, Argentina 4, Hong Kong 2, Czech Republic 1, Hungary 1.

The median duration of follow-up at the interim analysis for OS for all randomized patients was 19.6 months and 19.2 months for patients in the avelumab plus BSC arm and BSC alone arm, respectively. For patients with PD-L1-positive tumours, the median duration of follow-up for OS was 18.3 months and 20.0 months for avelumab plus BSC arm and the BSC alone arm, respectively.

Conduct of the study

Tumour assessments

For all patients, anti-tumour activity will be assessed through radiological tumour assessments conducted at baseline (including chest, abdomen, and pelvic CT or MRI scans), at 8 weeks after randomization, then every 8 weeks for up to 1 year from randomization, and every 12 weeks thereafter until documented disease progression as assessed by BICR regardless of initiation of subsequent anti-cancer therapy. Additional radiological tumour assessments should also be conducted whenever disease progression is suspected (e.g., symptomatic deterioration).

Protocol amendments

The Original Study B9991001 protocol was dated 29 October 2015. During the study, there were 4 protocol amendments (17 December 2015, 24 March 2016, 19 December 2016, 28 March 2019).

Key changes are summarized below:

Amendment 1, (17 December 2015)

Clarifications to the protocol were made, inclusion criteria were modified and a rule for discontinuation of treatment was added.

Amendment 2, 24 March 2016

Clarifications to the protocol were made and exclusion criteria were modified.

Amendment 3, 19 December 2016

Clarifications to the protocol were made, inclusion criteria regarding requirements for tumour tissue were modified, alternate methods for estimating creatinine clearance was added to the inclusion criteria 11, exceptions for exclusion criteria for persisting toxicity related to prior treatment and resected prostate cancer was added, AE collection period were extended, a higher eligibility limit for AST and ALT elevations in patients with liver metastases was added and the analysis of disease control was modified.

Amendment 4, 28 March 2019

Clarifications to the protocol were made, the exploratory endpoint of irRECIST was removed and associated elements were revised or removed accordingly and management of avelumab toxicity was updated to reflect current standards.

Amendment 1 and 2 were made before the first patient was recruited.

Protocol deviations

At least 1 potentially important protocol deviation (PIPD) was reported in 38.9% of all randomized patients (Table 13). The protocol deviation category with the highest frequency pertained to deviations from inclusion/exclusion criteria (12.0% in the avelumab plus BSC arm and 20.0% in the BSC alone arm). There were 9.6% patients with a PIPD associated with randomization in the IRT system under the wrong stratification value (Table 13).

Table 13. Potentially important protocol deviations, FAS

	Avelumab+BSC (N=350) n (%)	BSC (N=350) n (%)	Total (N=700) n (%)

Subjects with any potentially important deviations	145 (41.4)	127 (36.3)	272 (38.9)
CCMEDS	39 (11.1)	2 (0.6)	41 (5.9)
Inclusion/exclusion	42 (12.0)	70 (20.0)	112 (16.0)
Informed consent	52 (14.9)	38 (10.9)	90 (12.9)
Investigational product	14 (4.0)	0	14 (2.0)
Procedures/tests	9 (2.6)	9 (2.6)	18 (2.6)
Protocol specific discontinuation criteria	0	3 (0.9)	3 (0.4)
Randomization	32 (9.1)	35 (10.0)	67 (9.6)

10 patients treated with avelumab+BSC and 17 patients BSC arm did not meet inclusion criterion 03[2] according to PA3 and later. In the PA2 and earlier there was 1 patient treated with avelumab plus BSC that did not meet inclusion criterion 3[3].

Table 14. Subject disposition of actual treatment versus treatment assigned at randomization.

	As Randomized			
	Avelumab+BSC	**BSC**	**Not Randomized**	**Total**
As Treated				
Avelumab+BSC	344	0	0	344
% of As Randomized	98.3	0.0	0.0	
% of As Treated	100.0	0.0	0.0	
BSC	0	345	0	345
% of As Randomized	0.0	98.6	0.0	
% of As Treated	0.0	100.0	0.0	
Not Treated	6	5	0	11
% of As Randomized	1.7	1.4	0.0	
% of As Treated	54.5	45.5	0.0	
Total	350	350	0	700

[2] Inclusion criterion 3 according to PA3 and later: Patients without progressive disease as per RECIST v1.1 guideline following completion of first-line chemotherapy as determined by investigator review.
[3] Inclusion criterion 3 according to PA2 and earlier: Patients without progressive disease as per RECIST v1.1 guideline following completion of first-line chemotherapy as determined by independent central review.

Table 15. Specification of randomization deviations.

	Avelumab+BSC (N=350) n (%)	BSC (N=350) n (%)	Total (N=700) n (%)
RANDOMIZATION	32 (9.1)	35 (10.0)	67 (9.6)
Randomized under wrong stratification of CR/PR vs SD AND visceral vs non-visceral.	1 (0.3)	2 (0.6)	3 (0.4)
Randomized under wrong stratification of CR/PR vs SD.	23 (6.6)	22 (6.3)	45 (6.4)
Randomized under wrong stratification of visceral vs. non-visceral.	8 (2.3)	11 (3.1)	19 (2.7)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: DV Output File: ./B9991001/B9991001_CSR/addv_s001 Date of Generation: 14JAN2020 (08:13) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Table 16. Summary of overall survival considering actual strata – FAS

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Subjects with event, n (%)	145 (41.4)	179 (51.1)	61 (32.3)	82 (48.5)
Subjects censored, n (%)	205 (58.6)	171 (48.9)	128 (67.7)	87 (51.5)
Reason for censoring, n (%)				
Withdrawal of consent	16 (4.6)	22 (6.3)	8 (4.2)	8 (4.7)
Lost to follow-up [1]	5 (1.4)	6 (1.7)	3 (1.6)	2 (1.2)
Alive	184 (52.6)	143 (40.9)	117 (61.9)	77 (45.6)
Probability of being event-free (95% CI) [2]				
at 6 months	0.888 (0.849, 0.917)	0.822 (0.777, 0.859)	0.924 (0.875, 0.954)	0.824 (0.756, 0.874)
at 12 months	0.713 (0.660, 0.760)	0.584 (0.527, 0.637)	0.791 (0.721, 0.845)	0.604 (0.520, 0.677)
at 18 months	0.613 (0.554, 0.667)	0.438 (0.378, 0.497)	0.700 (0.619, 0.768)	0.478 (0.390, 0.561)
at 24 months	0.481 (0.413, 0.547)	0.372 (0.309, 0.434)	0.577 (0.481, 0.662)	0.405 (0.314, 0.494)
at 30 months	0.398 (0.318, 0.477)	0.330 (0.252, 0.411)	0.504 (0.386, 0.610)	0.405 (0.314, 0.494)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]				
Q1	10.5 (8.7, 12.5)	7.9 (6.5, 8.8)	13.8 (10.3, 18.2)	8.0 (6.0, 9.3)
Median	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)	NE (20.3, NE)	17.1 (13.5, 23.7)
Q3	NE (NE, NE)	33.0 (33.0, NE)	NE (NE, NE)	NE (33.0, NE)
Stratified analysis [4] Comparison vs BSC				
Hazard Ratio [5]	0.70		0.56	
95% CI [5]	0.560, 0.870		0.403, 0.786	
1-sided p-value [6]	0.0006		0.0003	
2-sided p-value [6]	0.0013		0.0006	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up > 16 weeks prior to data cutoff (21OCT2019).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral) based on CRF-derived stratification factors.
[5] Cox proportional hazard model used.
[6] Log-rank test is used.

Baseline data

Table 17. Demographic, baseline and disease characteristics - FAS

	All Subjects			Subjects with PD-L1-Positive Tumours		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Age (years), n (%)						
<65 years	129 (36.9)	107 (30.6)	236 (33.7)	62 (32.8)	49 (29.0)	111 (31.0)
≥65 years	221 (63.1)	243 (69.4)	464 (66.3)	127 (67.2)	120 (71.0)	247 (69.0)
65-<75 years	136 (38.9)	163 (46.6)	299 (42.7)	72 (38.1)	73 (43.2)	145 (40.5)
75-<85 years	80 (22.9)	78 (22.3)	158 (22.6)	51 (27.0)	47 (27.8)	98 (27.4)
≥85 years	5 (1.4)	2 (0.6)	7 (1.0)	4 (2.1)	0	4 (1.1)
n [1]	350	350	700	189	169	358
Mean (SD)	67.2 (9.52)	67.7 (9.20)	67.5 (9.36)	68.2 (9.87)	68.0 (9.71)	68.1 (9.78)
Q1	61.00	62.00	62.00	62.00	62.00	62.00
Median	68.00	69.00	69.00	70.00	70.00	70.00
Q3	74.00	74.00	74.00	75.00	75.00	75.00
Range (min, max)	(37.0, 90.0)	(32.0, 89.0)	(32.0, 90.0)	(37.0, 90.0)	(32.0, 84.0)	(32.0, 90.0)
Race, n (%)						
Black or African American	2 (0.6)	0	2 (0.3)	1 (0.5)	0	1 (0.3)
American Indian or Alaska Native	0	0	0	0	0	0
Asian	75 (21.4)	81 (23.1)	156 (22.3)	42 (22.2)	33 (19.5)	75 (20.9)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	232 (66.3)	238 (68.0)	470 (67.1)	121 (64.0)	119 (70.4)	240 (67.0)
Other	21 (6.0)	15 (4.3)	36 (5.1)	12 (6.3)	7 (4.1)	19 (5.3)
Unknown	20 (5.7)	16 (4.6)	36 (5.1)	13 (6.9)	10 (5.9)	23 (6.4)
Gender, n (%)						
Male	266 (76.0)	275 (78.6)	541 (77.3)	145 (76.7)	129 (76.3)	274 (76.5)
Female	84 (24.0)	75 (21.4)	159 (22.7)	44 (23.3)	40 (23.7)	84 (23.5)
Ethnicity, n (%)						
Hispanic or Latino	18 (5.1)	12 (3.4)	30 (4.3)	9 (4.8)	3 (1.8)	12 (3.4)
Not Hispanic or Latino	286 (81.7)	298 (85.1)	584 (83.4)	152 (80.4)	146 (86.4)	298 (83.2)
Not reported	42 (12.0)	36 (10.3)	78 (11.1)	24 (12.7)	18 (10.7)	42 (11.7)
Unknown	4 (1.1)	4 (1.1)	8 (1.1)	4 (2.1)	2 (1.2)	6 (1.7)

	All Subjects			Subjects with PD-L1-Positive Tumours		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Pooled Geographic Region, n (%)						
North America	12 (3.4)	22 (6.3)	34 (4.9)	8 (4.2)	8 (4.7)	16 (4.5)
Europe	214 (61.1)	203 (58.0)	417 (59.6)	110 (58.2)	102 (60.4)	212 (59.2)
Asia	73 (20.9)	74 (21.1)	147 (21.0)	40 (21.2)	31 (18.3)	71 (19.8)
Australasia	34 (9.7)	37 (10.6)	71 (10.1)	20 (10.6)	24 (14.2)	44 (12.3)
Rest of the World	17 (4.9)	14 (4.0)	31 (4.4)	11 (5.8)	4 (2.4)	15 (4.2)
Best response to first-line chemotherapy (IRT)						
CR or PR	253 (72.3)	252 (72.0)	505 (72.1)	139 (73.5)	128 (75.7)	267 (74.6)
SD	97 (27.7)	98 (28.0)	195 (27.9)	50 (26.5)	41 (24.3)	91 (25.4)
Site of metastasis (IRT)						
Visceral	191 (54.6)	191 (54.6)	382 (54.6)	88 (46.6)	79 (46.7)	167 (46.6)
Non-Visceral	159 (45.4)	159 (45.4)	318 (45.4)	101 (53.4)	90 (53.3)	191 (53.4)
Histopathological classification						
Carcinoma	306 (87.4)	292 (83.4)	598 (85.4)	163 (86.2)	137 (81.1)	300 (83.8)
Carcinoma with Squamous	16 (4.6)	26 (7.4)	42 (6.0)	8 (4.2)	13 (7.7)	21 (5.9)
Carcinoma with Glandular	6 (1.7)	9 (2.6)	15 (2.1)	3 (1.6)	6 (3.6)	9 (2.5)
Carcinoma with Variant	22 (6.3)	22 (6.3)	44 (6.3)	15 (7.9)	13 (7.7)	28 (7.8)
Other	0	1 (0.3)	1 (0.1)	0	0	0
ECOG performance status						
0	213 (60.9)	211 (60.3)	424 (60.6)	114 (60.3)	107 (63.3)	221 (61.7)
1	136 (38.9)	136 (38.9)	272 (38.9)	74 (39.2)	61 (36.1)	135 (37.7)
2	1 (0.3)	0	1 (0.1)	1 (0.5)	0	1 (0.3)
3	0	3 (0.9)	3 (0.4)	0	1 (0.6)	1 (0.3)
4	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
PD-L1 Status						
Positive	189 (54.0)	169 (48.3)	358 (51.1)	189 (100.0)	169 (100.0)	358 (100.0)
Negative	139 (39.7)	132 (37.7)	271 (38.7)	0	0	0
Unknown	22 (6.3)	49 (14.0)	71 (10.1)	0	0	0

	All Subjects			Subjects with PD-L1-Positive Tumours		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group. Baseline is defined as the last assessment on or prior to randomization for subjects randomized but not dosed, and the last assessment on or prior to first dose of
study treatment for subjects randomized and dosed.
[1] n is the number of subjects with non-missing age. Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
Cut-off date: 21OCT2019 Snapshot Date: 21NOV2019

Table 18 Demographic, Baseline and Disease Characteristics - Subjects with PD-L1-Negative Tumours and Subjects with PD-L1-Unknown Tumours in the Full Analysis Set (Protocol B9991001)

	Subjects with PD-L1-Negative Tumours			Subjects with PD-L1-Unknown Tumours		
	Avelumab +BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
Age (years), n (%)						
<65 years	55 (39.6)	40 (30.5)	95 (35.2)	12 (54.5)	18 (36.0)	30 (41.7)
≥65 years	84 (60.4)	91 (69.5)	175 (64.8)	10 (45.5)	32 (64.0)	42 (58.3)
65-<75 years	57 (41.0)	63 (48.1)	120 (44.4)	7 (31.8)	27 (54.0)	34 (47.2)
75-<85 years	26 (18.7)	26 (19.8)	52 (19.3)	3 (13.6)	5 (10.0)	8 (11.1)
≥85 years	1 (0.7)	2 (1.5)	3 (1.1)	0	0	0
n [1]	139	131	270	22	50	72
Mean (SD)	66.6 (8.80)	68.2 (8.64)	67.4 (8.75)	62.7 (9.57)	65.6 (8.71)	64.7 (9.01)
Q1	61.00	63.00	62.00	56.00	59.00	58.50
Median	68.00	69.00	68.00	62.50	67.50	66.50
Q3	73.00	74.00	73.00	69.00	72.00	72.00
Range (min, max)	(38.0, 86.0)	(43.0, 89.0)	(38.0, 89.0)	(39.0, 78.0)	(43.0, 82.0)	(39.0, 82.0)
Race, n (%)						
Black or African American	1 (0.7)	0	1 (0.4)	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Asian	27 (19.4)	30 (22.9)	57 (21.1)	6 (27.3)	18 (36.0)	24 (33.3)

	Subjects with PD-L1-Negative Tumours			Subjects with PD-L1-Unknown Tumours		
	Avelumab +BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	96 (69.1)	90 (68.7)	186 (68.9)	15 (68.2)	29 (58.0)	44 (61.1)
Other	8 (5.8)	6 (4.6)	14 (5.2)	1 (4.5)	2 (4.0)	3 (4.2)
Unknown	7 (5.0)	5 (3.8)	12 (4.4)	0	1 (2.0)	1 (1.4)
Gender, n (%)						
Male	103 (74.1)	108 (82.4)	211 (78.1)	18 (81.8)	38 (76.0)	56 (77.8)
Female	36 (25.9)	23 (17.6)	59 (21.9)	4 (18.2)	12 (24.0)	16 (22.2)
Ethnicity, n (%)						
Hispanic or Latino	7 (5.0)	4 (3.1)	11 (4.1)	2 (9.1)	5 (10.0)	7 (9.7)
Not Hispanic or Latino	115 (82.7)	110 (84.0)	225 (83.3)	19 (86.4)	42 (84.0)	61 (84.7)
Not reported	17 (12.2)	15 (11.5)	32 (11.9)	1 (4.5)	3 (6.0)	4 (5.6)
Unknown	0	2 (1.5)	2 (0.7)	0	0	0
Pooled Geographic Region, n (%)						
North America	4 (2.9)	11 (8.4)	15 (5.6)	0	3 (6.0)	3 (4.2)
Europe	92 (66.2)	79 (60.3)	171 (63.3)	12 (54.5)	22 (44.0)	34 (47.2)
Asia	27 (19.4)	26 (19.8)	53 (19.6)	6 (27.3)	17 (34.0)	23 (31.9)
Australasia	12 (8.6)	10 (7.6)	22 (8.1)	2 (9.1)	3 (6.0)	5 (6.9)
Rest of the World	4 (2.9)	5 (3.8)	9 (3.3)	2 (9.1)	5 (10.0)	7 (9.7)
Best response to first-line chemotherapy (IRT)						
CR or PR	101 (72.7)	91 (69.5)	192 (71.1)	13 (59.1)	33 (66.0)	46 (63.9)
SD	38 (27.3)	40 (30.5)	78 (28.9)	9 (40.9)	17 (34.0)	26 (36.1)
Site of metastasis (IRT)						
Visceral	90 (64.7)	82 (62.6)	172 (63.7)	13 (59.1)	30 (60.0)	43 (59.7)

	Subjects with PD-L1-Negative Tumours			Subjects with PD-L1-Unknown Tumours		
	Avelumab +BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
Non-Visceral	49 (35.3)	49 (37.4)	98 (36.3)	9 (40.9)	20 (40.0)	29 (40.3)
Histopathological classification						
Carcinoma	124 (89.2)	115 (87.8)	239 (88.5)	19 (86.4)	40 (80.0)	59 (81.9)
Carcinoma with Squamous	6 (4.3)	10 (7.6)	16 (5.9)	2 (9.1)	3 (6.0)	5 (6.9)
Carcinoma with Glandular	3 (2.2)	2 (1.5)	5 (1.9)	0	1 (2.0)	1 (1.4)
Carcinoma with Variant	6 (4.3)	4 (3.1)	10 (3.7)	1 (4.5)	5 (10.0)	6 (8.3)
Other	0	0	0	0	1 (2.0)	1 (1.4)
ECOG performance status						
0	84 (60.4)	71 (54.2)	155 (57.4)	15 (68.2)	33 (66.0)	48 (66.7)
1	55 (39.6)	58 (44.3)	113 (41.9)	7 (31.8)	17 (34.0)	24 (33.3)
2	0	0	0	0	0	0
3	0	2 (1.5)	2 (0.7)	0	0	0
4	0	0	0	0	0	0
Not reported	0	0	0	0	0	0
First-line chemotherapy regimen						
Cisplatin	0	0	0	0	0	0
Gemcitabine	0	0	0	0	0	0
Cisplatin+Gemcitabine	69 (49.6)	74 (56.5)	143 (53.0)	13 (59.1)	34 (68.0)	47 (65.3)
Carboplatin +Gemcitabine	65 (46.8)	53 (40.5)	118 (43.7)	8 (36.4)	15 (30.0)	23 (31.9)
Carboplatin +Cisplatin+Gemcitabine	5 (3.6)	4 (3.1)	9 (3.3)	1 (4.5)	1 (2.0)	2 (2.8)
Not reported	0	0	0	0	0	0
Creatinine clearance at baseline						
≥60 mL/min	60 (43.2)	70 (53.4)	130 (48.1)	17 (77.3)	29 (58.0)	46 (63.9)
<60 mL/min	79 (56.8)	57 (43.5)	136 (50.4)	5 (22.7)	21 (42.0)	26 (36.1)

	Subjects with PD-L1-Negative Tumours			Subjects with PD-L1-Unknown Tumours		
	Avelumab +BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
Unknown	0	4 (3.1)	4 (1.5)	0	0	0

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group. Baseline is defined as the last assessment on or prior to randomization for subjects randomized but not dosed, and the last assessment on or prior to first dose of study treatment for subjects randomized and dosed.
[1] n is the number of subjects with non-missing age. Age at Screening (years) = (date of given informed consent - date of birth + 1)/365.25.
Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Table 19. Disease characteristics: Primary diagnosis duration - FAS

	All Subjects			Subjects with PD-L1-Positive Tumors		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
Time since initial diagnosis (months) [1]						
n	350	350	700	189	169	358
Mean (SD)	23.9 (29.03)	27.4 (45.00)	25.7 (37.88)	25.1 (30.25)	22.4 (26.55)	23.9 (28.56)
Q1	7.0	7.1	7.1	7.1	6.7	7.0
Median	11.5	12.8	12.1	13.3	10.2	11.6
Q3	26.8	28.4	28.0	29.2	25.9	27.4
Range (min, max)	(2.4, 178.2)	(3.3, 448.0)	(2.4, 448.0)	(2.8, 178.2)	(3.3, 135.7)	(2.8, 178.2)

	Subjects with PD-L1-Negative Tumors			Subjects with PD-L1-Unknown Tumors		
	Avelumab+BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
Time since initial diagnosis (months) [1]						
n	139	131	270	22	50	72
Mean (SD)	22.2 (28.05)	35.0 (63.56)	28.4 (48.96)	24.0 (24.75)	24.2 (32.23)	24.1 (29.97)
Q1	6.7	7.2	7.0	8.5	7.5	7.5
Median	10.1	15.6	12.3	12.2	20.3	17.1
Q3	23.6	38.5	28.5	28.8	27.0	27.3
Range (min, max)	(2.4, 151.3)	(3.5, 448.0)	(2.4, 448.0)	(5.2, 84.2)	(5.3, 220.7)	(5.2, 220.7)

Table 20. Disease characteristics: Measurable disease at baseline by BICR - FAS

	All Subjects			Subjects with PD-L1-Positive Tumors		
	Avelumab+BSC (N=350)	BSC (N=350)	Total (N=700)	Avelumab+BSC (N=189)	BSC (N=169)	Total (N=358)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Measurable disease at baseline by BICR assessment [4]						
Yes	164 (46.9)	167 (47.7)	331 (47.3)	78 (41.3)	78 (46.2)	156 (43.6)
No	116 (33.1)	110 (31.4)	226 (32.3)	70 (37.0)	50 (29.6)	120 (33.5)
No disease	70 (20.0)	73 (20.9)	143 (20.4)	41 (21.7)	41 (24.3)	82 (22.9)

	Subjects with PD-L1-Negative Tumors			Subjects with PD-L1-Unknown Tumors		
	Avelumab+BSC (N=139)	BSC (N=131)	Total (N=270)	Avelumab+BSC (N=22)	BSC (N=50)	Total (N=72)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Measurable disease at baseline by BICR assessment [4]						
Yes	77 (55.4)	62 (47.3)	139 (51.5)	9 (40.9)	27 (54.0)	36 (50.0)
No	39 (28.1)	44 (33.6)	83 (30.7)	7 (31.8)	16 (32.0)	23 (31.9)
No disease	23 (16.5)	25 (19.1)	48 (17.8)	6 (27.3)	7 (14.0)	13 (18.1)

Table 21. Frequency of CR/PR/SD treated with avelumab + BSC or BSC by PD-L1-status

	All Subjects			Subjects with PD-L1-Positive Tumors		
CR	Avelumab+BSC (N=90)	BSC (N=89)	Total (N=179)	Avelumab+BSC (N=60)	BSC (N=53)	Total (N=113)
PR	Avelumab+BSC (N=163)	BSC (N=163)	Total (N=326)	Avelumab+BSC (N=79)	BSC (N=75)	Total (N=154)
SD	Avelumab+BSC (N=97)	BSC (N=98)	Total (N=195)	Avelumab+BSC (N=50)	BSC (N=41)	Total (N=91)

	Subjects with PD-L1-Negative Tumors			Subjects with PD-L1-Unknown Tumors		
CR	Avelumab+BSC (N=25)	BSC (N=25)	Total (N=50)	Avelumab+BSC (N=5)	BSC (N=11)	Total (N=16)
PR	Avelumab+BSC (N=76)	BSC (N=66)	Total (N=142)	Avelumab+BSC (N=8)	BSC (N=22)	Total (N=30)
SD	Avelumab+BSC (N=38)	BSC (N=40)	Total (N=78)	Avelumab+BSC (N=9)	BSC (N=17)	Total (N=26)

Numbers analysed

Table 22. Summary of analysis data sets - Number of participants

	Avelumab+BSC n (%)	BSC n (%)	Total n (%)
Screened			1005
Full analysis set [1]	350	350	700
Safety analysis set [2]	344 (98.3)	345 (98.6)	689 (98.4)
Per protocol analysis set [3]	316 (90.3)	310 (88.6)	626 (89.4)
PK concentration analysis set [4]	344 (98.3)	0	344 (49.1)
PK parameter analysis set [5]	344 (98.3)	0	344 (49.1)
Immunogenicity analysis set [6]	344 (98.3)	0	344 (49.1)
Biomarker analysis set [7]	324 (92.6)	299 (85.4)	623 (89.0)

The denominator to calculate percentages is the number of subjects in the full analysis set within each treatment group.
[1] Full analysis set: randomized subjects.
[2] Safety analysis set: subjects who received at least one dose of study drug on Avelumab+BSC or completed C1D1 visit on BSC.
[3] Per protocol analysis set: subjects in the full analysis set who do not meet any of the criteria that could impact the primary objectives of the study.
The criteria for excluding patients from Per Protocol Analysis Set are specified in SAP.
[4] PK concentration analysis set: subjects in the safety analysis set who have at least one post-dose concentration measurement above
the lower limit of quantitation (LLQ) for avelumab.
[5] PK parameter analysis set: subjects in the PK concentration analysis set who have at least one of the PK parameters of interest for avelumab.
[6] Immunogenicity analysis set: subjects in the safety analysis set who have at least one ADA/nAb sample collected for avelumab
[7] Biomarker Analysis Set: subjects in the safety analysis set who have at least one baseline biomarker assessment performed.
PFIZER CONFIDENTIAL SDTM Creation: 21DEC2019 (12:42) Source Data: ADSL Output File: ./B9991001_restricted/B9991001/adsl_s002 Date of Generation: 14JAN2020 (07:46) Cutoff Date: 21OCT2019; 30JUN2019 (PK and Immunogenicity) Snapshot Date: 21NOV2019; 24DEC2019 (Immunogenicity)
Table 14.1.1.1 is for Pfizer internal use.

Outcomes and estimation

Data from two data cut-offs are presented for the primary endpoint, overall survival; the pre-specified interim analysis (data cut-off date 21 October 2019), and an updated analysis performed at the request of the Agency (data cut-off date 19 January 2020). For all other endpoints only the interim analysis data cut-off date is used.

Primary endpoint of OS in co-primary analysis populations - all subjects and subjects with PD-L1-positive tumours

The primary endpoint OS (21 Oct 2019) was statistically significant improved for all patients (n=700) assigned to avelumab plus BSC compared with patients assigned to BSC (stratified HR 0.69; 95% CI 0.556, 0.863; 1-sided p-value 0.0005). The median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC arm. In patients with PD-L1-positive tumours (n=358) a statistically significant improvement in OS was also demonstrated for patients assigned to avelumab plus BSC compared with patients assigned to BSC (stratified HR 0.56; 95% CI: 0.404, 0.787; 1-sided p value 0.0003). The median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab plus BSC arm, and was 17.1 months (95% CI: 13.5, 23.7) in the BSC arm.

For all randomized patients, the median duration of follow-up for OS was more than 19 months and similar for both treatment arms.

Table 23. Overview of primary endpoint

Summary of Overall Survival (Primary Analysis) - All Subjects and Subjects with PD-L1-Positive Tumours in the Full Analysis Set (Protocol B9991001, data cut-off date 21 Oct. 2019)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Subjects with event, n (%)	145 (41.4)	179 (51.1)	61 (32.3)	82 (48.5)
Subjects censored, n (%)	205 (58.6)	171 (48.9)	128 (67.7)	87 (51.5)
Reason for censoring, n (%)				
Withdrawal of consent	16 (4.6)	22 (6.3)	8 (4.2)	8 (4.7)
Lost to follow-up [1]	5 (1.4)	6 (1.7)	3 (1.6)	2 (1.2)
Alive	184 (52.6)	143 (40.9)	117 (61.9)	77 (45.6)
Probability of being event-free (95% CI) [2]				
at 6 months	0.888 (0.849, 0.917)	0.822 (0.777, 0.859)	0.924 (0.875, 0.954)	0.824 (0.756, 0.874)
at 12 months	0.713 (0.660, 0.760)	0.584 (0.527, 0.637)	0.791 (0.721, 0.845)	0.604 (0.520, 0.677)
at 18 months	0.613 (0.554, 0.667)	0.438 (0.378, 0.497)	0.700 (0.619, 0.768)	0.478 (0.390, 0.561)
at 24 months	0.481 (0.413, 0.547)	0.372 (0.309, 0.434)	0.577 (0.481, 0.662)	0.405 (0.314, 0.494)
at 30 months	0.398 (0.318, 0.477)	0.330 (0.252, 0.411)	0.504 (0.386, 0.610)	0.405 (0.314, 0.494)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]				
Q1	10.5 (8.7, 12.5)	7.9 (6.5, 8.8)	13.8 (10.3, 18.2)	8.0 (6.0, 9.3)
Median	21.4 (18.9, 26.1)	14.3 (12.9, 17.9)	NE (20.3, NE)	17.1 (13.5, 23.7)
Q3	NE (NE, NE)	33.0 (33.0, NE)	NE (NE, NE)	NE (33.0, NE)
Stratified analysis [4] Comparison vs BSC				
Hazard Ratio [5]	0.69		0.56	
95% CI [5]	0.556, 0.863		0.404, 0.787	
RCI [6]	0.536, 0.923		0.388, 0.937	
1-sided p-value [7]	0.0005		0.0003	
2-sided p-value [7]	0.0010		0.0007	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up > 16 weeks prior to data cut-off (21OCT2019).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[5] Cox proportional hazard model used.
[6] Repeated confidence interval method used to take into account the group-sequential nature of the design.
[7] Log-rank test is used.
Cut-off date: 21OCT2019

Figure 18 Kaplan-Meier Plot of Overall Survival – FAS (Study B9991001, 21 Oct. 2019)

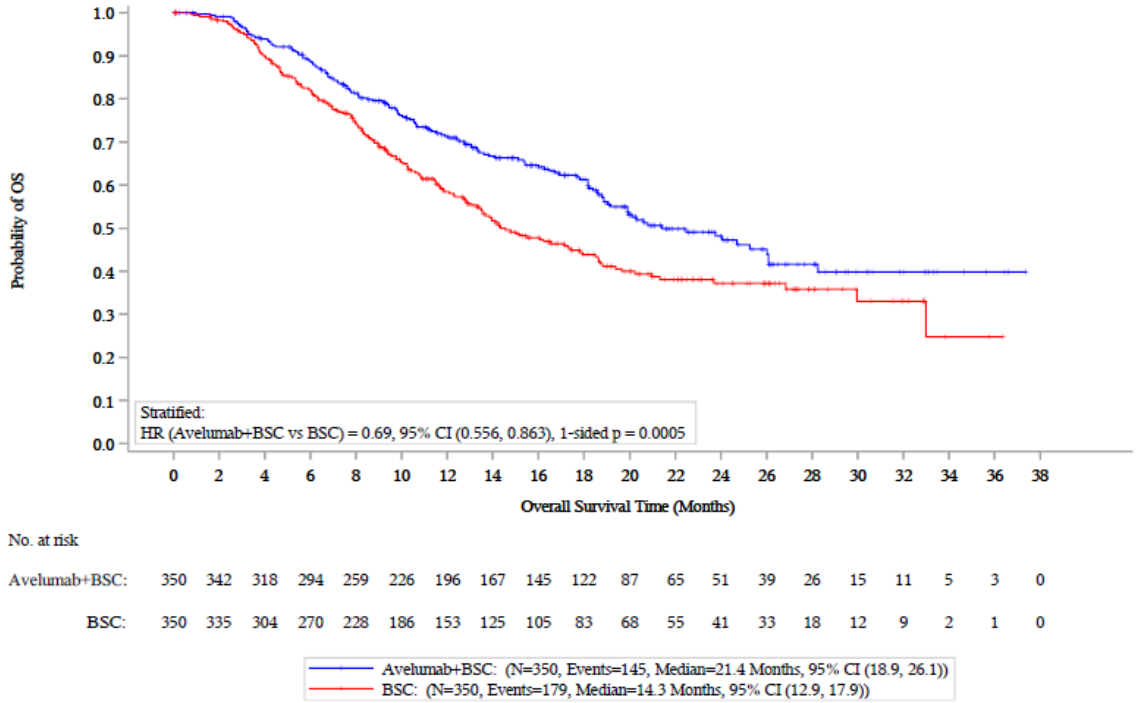
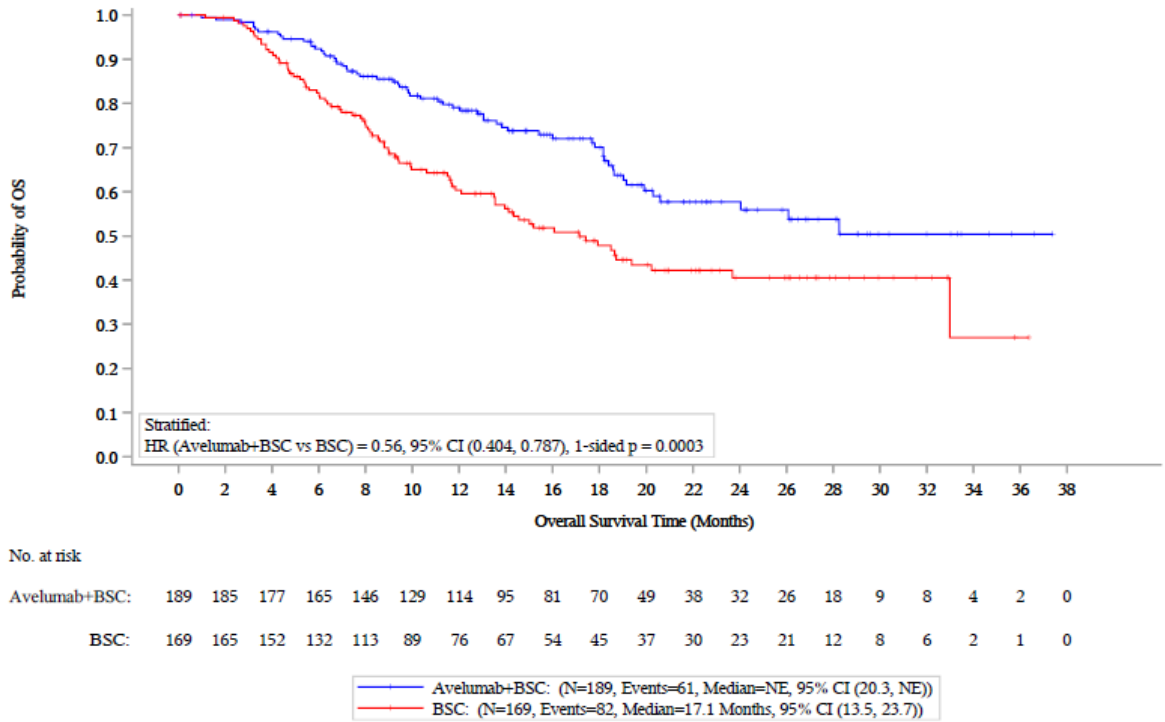


Figure 19 Kaplan-Meier Plot of Overall Survival - Subjects with PD-L1-Positive Tumours (Study B9991001, 21 Oct. 2019)



Updated OS data

A non pre-specified OS update was requested based on data from the safety database lock 19 January 2020, 90 days following the cut-off date of 21 October 2019.

For all randomized patients, the median duration of follow-up for OS was 21.9 months and 21 months for patients in the avelumab plus BSC arm and BSC alone arm, respectively. For patients with PD-L1-positive tumours, the median duration of follow-up for OS was 19.9 months and 21.9 months for patients in the avelumab plus BSC arm and BSC alone arm, respectively.

The updated OS data is similar to the OS from the interim analysis and confirms the conclusions drawn from the interim analysis.

The updated OS-data with an additional 90 days of follow-up with cut-off date 19 January 2020 rendered a median OS for all patients treated with avelumab and BSC of 22.1 months (95% CI 19.0, 26.1) and for patient treated with BSC 14.6 months (95% CI 12.8, 17.8) and HR 0.70 (95% CI 0.564, 0.862; 2 sided p value 0.0008). For patients with PD-L1-positive tumours the updated median OS was NE (95% CI 20.6, NE) for patients treated with avelumab and BSC and 17.5 months (95% CI 13.5, 31.6) for patients treated with BSC alone, HR 0.60 (95% CI 0.439, 0.833; 2 sided p value 0.0019).

OS for patients with PD-L1-negative patients was an exploratory analysis and part of the subgroup analysis. OS for patients with PD-L1-unknown tumours was not a prespecified endpoint. Using the updated OS-data with an additional 90 days of follow-up with cut-off date 19 January 2020, the median OS for patients with PD-L1-negative tumours was 18.9 months (95% CI 13.3, 22.1) for patients treated with avelumab and BSC and 13.4 months (95% CI 10.4, 17.3) for patients treated with BSC alone, HR 0.83 (95% CI 0.603, 1.131). For patients with PD-L1-unknown tumours the updated median OS was 20.1 months (95% CI 10.6, NE) for patients treated with avelumab and BSC and 13.0 months (95% CI 9.6, NE) for patients treated with BSC alone, HR 0.69 (95% CI 0.306, 1.550). The subgroup of patients with PD-L1-unknown tumours was small and hence no firm conclusions have been drawn from the data. However, data is presented for completeness.

OS in all patients and patients with PD-L1-positive tumours (not prespecified analysis, data cut-off date 19 Jan 2020)

Table 24. Summary of Overall Survival (Primary Analysis) - All Subjects and Subjects with PD-L1-Positive Tumours in the Full Analysis Set (Protocol B9991001, 19 Jan. 2020)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Subjects with event, n (%)	156 (44.6)	190 (54.3)	68 (36.0)	85 (50.3)
Subjects censored, n (%)	194 (55.4)	160 (45.7)	121 (64.0)	84 (49.7)
Reason for censoring, n (%)				
Withdrawal of consent	17 (4.9)	21 (6.0)	9 (4.8)	8 (4.7)
Lost to follow-up [1]	6 (1.7)	7 (2.0)	4 (2.1)	3 (1.8)
Alive	171 (48.9)	132 (37.7)	108 (57.1)	73 (43.2)
Probability of being event-free (95% CI) [2]				
at 6 months	0.888 (0.850, 0.917)	0.822 (0.777, 0.859)	0.924 (0.875, 0.954)	0.824 (0.756, 0.874)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
at 12 months	0.719 (0.667, 0.764)	0.577 (0.521, 0.630)	0.793 (0.725, 0.845)	0.607 (0.525, 0.679)
at 18 months	0.614 (0.556, 0.666)	0.439 (0.381, 0.495)	0.685 (0.607, 0.752)	0.483 (0.398, 0.563)
at 24 months	0.478 (0.414, 0.539)	0.380 (0.321, 0.439)	0.560 (0.469, 0.641)	0.418 (0.331, 0.504)
at 30 months	0.410 (0.340, 0.479)	0.337 (0.271, 0.405)	0.507 (0.407, 0.599)	0.418 (0.331, 0.504)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]				
Q1	10.5 (9.2, 12.7)	7.9 (6.5, 8.7)	13.6 (10.3, 18.2)	8.0 (6.0, 9.3)
Median	22.1 (19.0, 26.1)	14.6 (12.8, 17.8)	NE (20.6, NE)	17.5 (13.5, 31.6)
Q3	NE (NE, NE)	NE (31.6, NE)	NE (NE, NE)	NE (33.0, NE)
Stratified analysis [4] Comparison vs BSC				
Hazard Ratio [5]	0.70		0.60	
95% CI [5]	0.564, 0.862		0.439, 0.833	
1-sided p-value [6]	0.0004		0.0010	
2-sided p-value [6]	0.0008		0.0019	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] Includes subjects deemed to be lost to follow-up by the Investigator and subjects with last follow-up > 16 weeks prior to data cutoff (19JAN2020).
[2] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[3] CIs are calculated using Brookmeyer and Crowley method.
[4] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[5] Cox proportional hazard model used.
[6] Log-rank test is used.
Cutoff date: 19JAN2020.

Figure 20. Kaplan-Meier Plot of Overall Survival--FAS (Protocol B9991001) - Updated analysis (19 Jan. 2020)

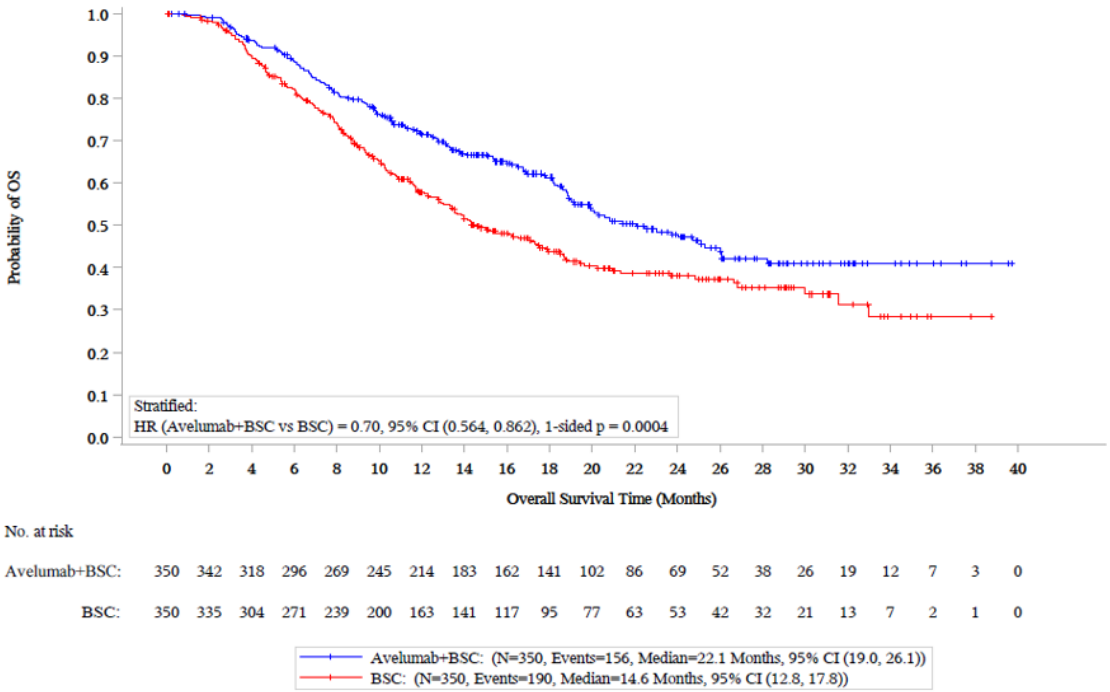
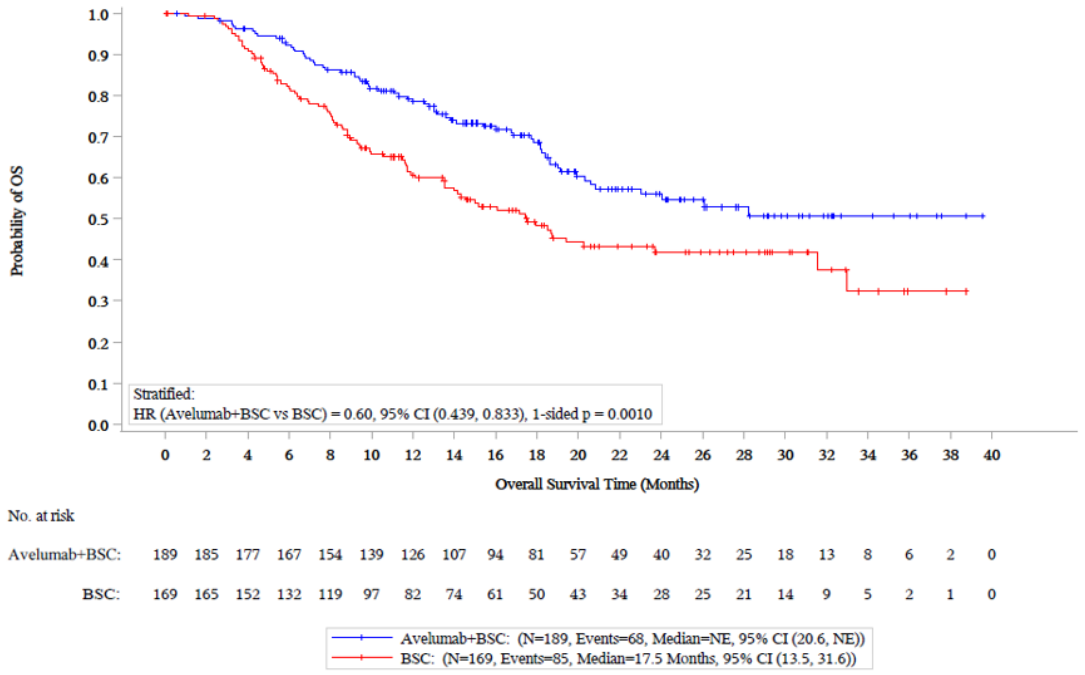


Figure 21. Kaplan-Meier Plot of Overall Survival--Subjects with PD-L1-Positive Tumours in the FAS (Protocol B9991001)--Updated analysis (19 Jan. 2020)



OS in patients with PD-L1-negative (exploratory analysis) and PD-L1-unknown tumours (not prespecified analysis, data cut-off date 19 Jan. 2020)

Table 25 Summary of Overall Survival - patients with PD-L1-Negative (exploratory analysis) and PD-L1-Unknown tumours in the Full Analysis Set (Protocol B9991001, not prespecified analysis, 19 Jan. 2020)

	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=139)	BSC (N=131)	Avelumab+BSC (N=22)	BSC (N=50)
Subjects with event, n (%)	80 (57.6)	80 (61.1)	8 (36.4)	25 (50.0)
Subjects censored, n (%)	59 (42.4)	51 (38.9)	14 (63.6)	25 (50.0)
Reason for censoring, n (%)				
Withdrawal of consent	5 (3.6)	5 (3.8)	3 (13.6)	8 (16.0)
Lost to follow-up [1]	1 (0.7)	2 (1.5)	1 (4.5)	2 (4.0)
Alive	53 (38.1)	44 (33.6)	10 (45.5)	15 (30.0)
Probability of being event-free (95% CI) [2]				
at 6 months	0.832 (0.758, 0.885)	0.821 (0.743, 0.877)	0.944 (0.666, 0.992)	0.818 (0.669, 0.905)
at 12 months	0.621 (0.533, 0.697)	0.547 (0.454, 0.630)	0.705 (0.428, 0.866)	0.557 (0.397, 0.691)
at 18 months	0.525 (0.434, 0.607)	0.388 (0.297, 0.478)	0.555 (0.279, 0.763)	0.421 (0.267, 0.567)
at 24 months	0.378 (0.285, 0.470)	0.315 (0.224, 0.410)	0.463 (0.195, 0.695)	0.421 (0.267, 0.567)
at 30 months	0.284 (0.189, 0.386)	0.234 (0.137, 0.346)	0.463 (0.195, 0.695)	0.281 (0.079, 0.530)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [3]				
Q1	7.8 (6.1, 10.0)	7.8 (5.7, 9.0)	11.5 (5.5, 20.1)	6.8 (3.7, 10.3)
Median	18.9 (13.3, 22.1)	13.4 (10.4, 17.3)	20.1 (10.6, NE)	13.0 (9.6, NE)
Q3	NE (25.1, NE)	26.8 (21.0, NE)	NE (20.1, NE)	NE (30.0, NE)
Stratified analysis [4] Comparison vs BSC				
Hazard Ratio [5]	0.83		0.69	
95% CI [5]	0.603, 1.131		0.306, 1.550	

Figure 22 Kaplan-Meier Plot of Overall Survival - Patients with PD-L1-Negative Tumours FAS (19 Jan. 2020)

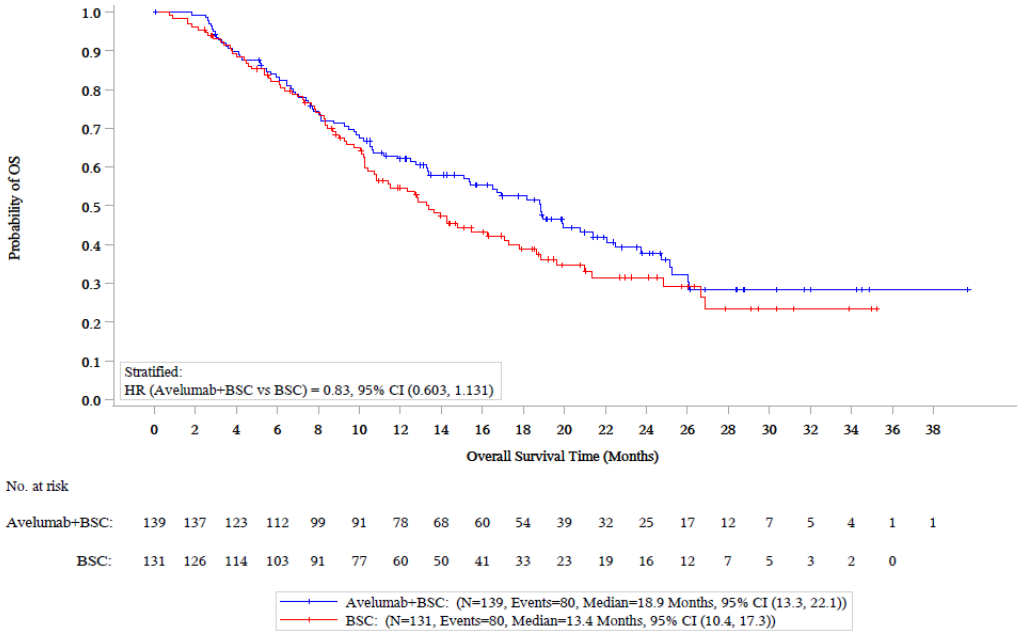
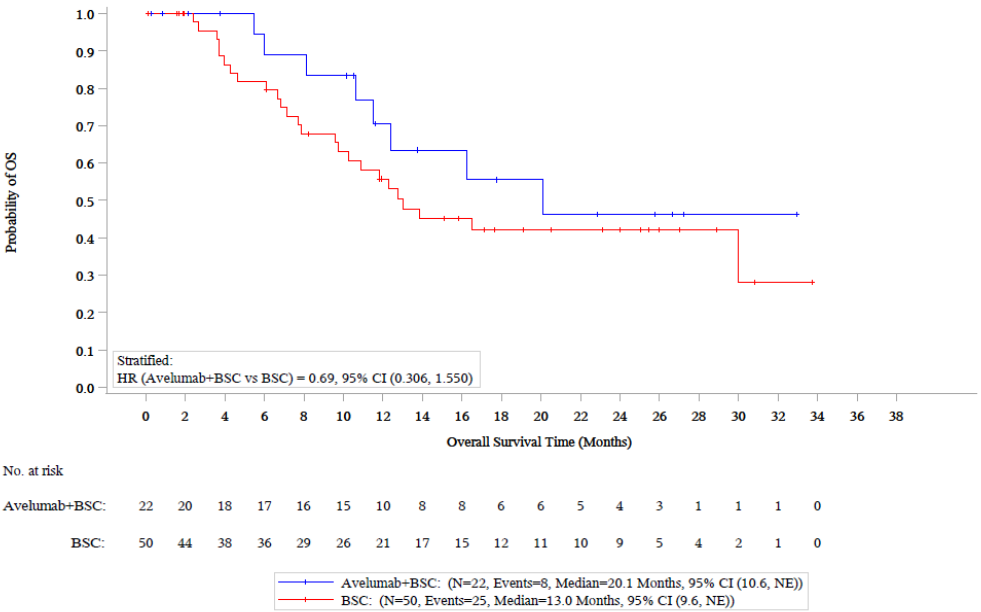


Figure 23 Kaplan-Meier Plot of Overall Survival - Patients with PD-L1-Unknown Tumours (19 Jan. 2020)

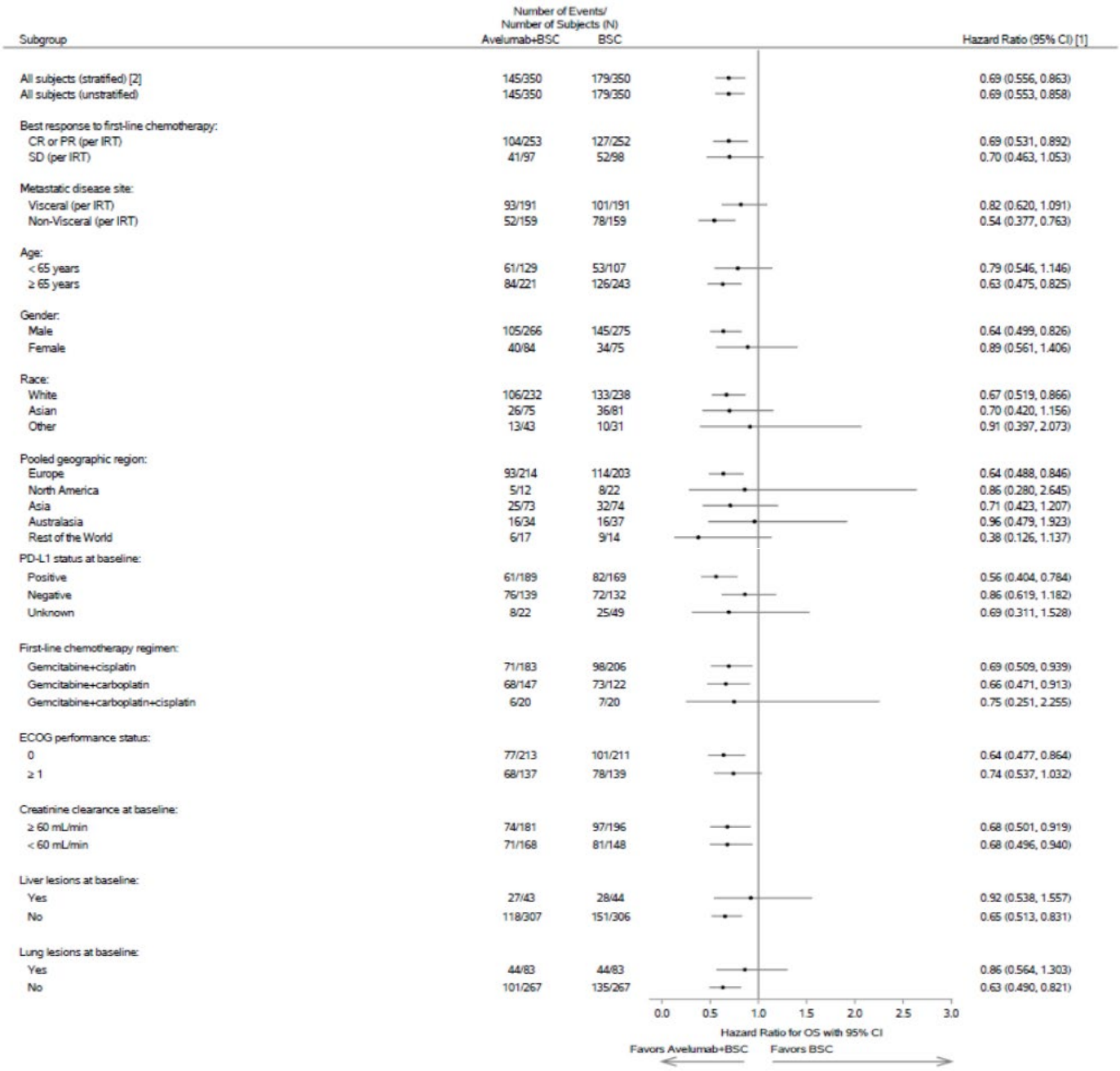


OS in subgroups

Subgroup analysis of OS for all patients and for patients with PD-L1-positive tumours display no detrimental effect in any subgroup of reasonable size.

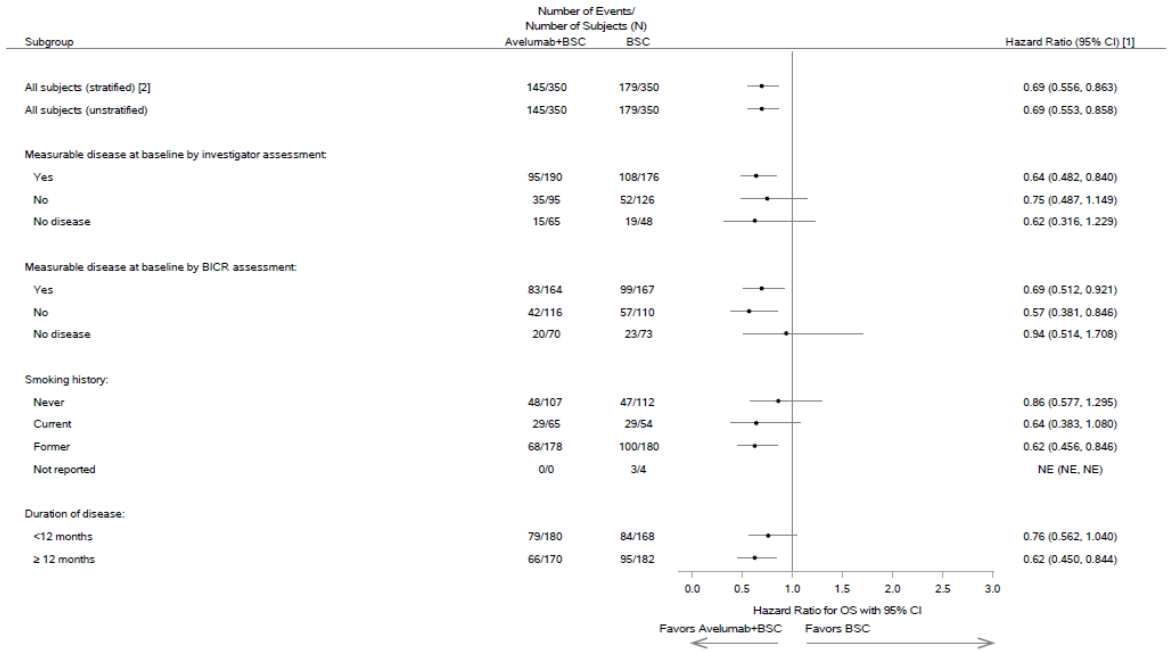
Subgroup analysis of OS for patients with PD-L1-negative tumours (data not shown) generally present with HR of ≤1, albeit with large confidence intervals due to small patient samples and more heterogeneity compared to the PFS subgroup results.

Figure 24. Forest Plot of Overall Survival by Subgroups – FAS (Study B9991001, 21 Oct. 2019)



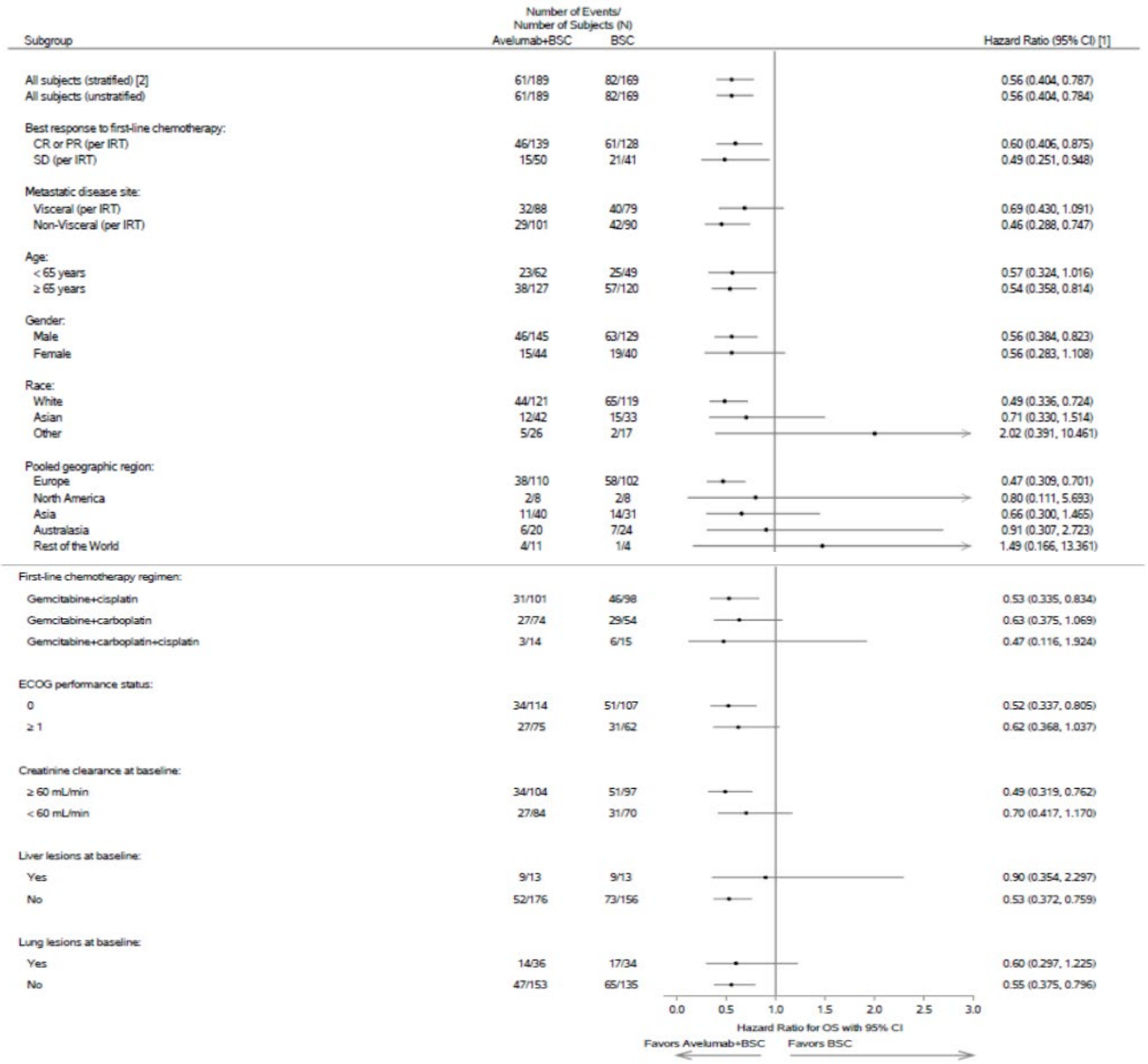
N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: /B9991001/B9991001_CSR/adtte_os_f003 Date of Generation: 14JAN2020 (13:45) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 25. Forest Plot of Overall Survival by Subgroups – FAS (Study B9991001, non prespecified subgroups, 21 Oct. 2019)



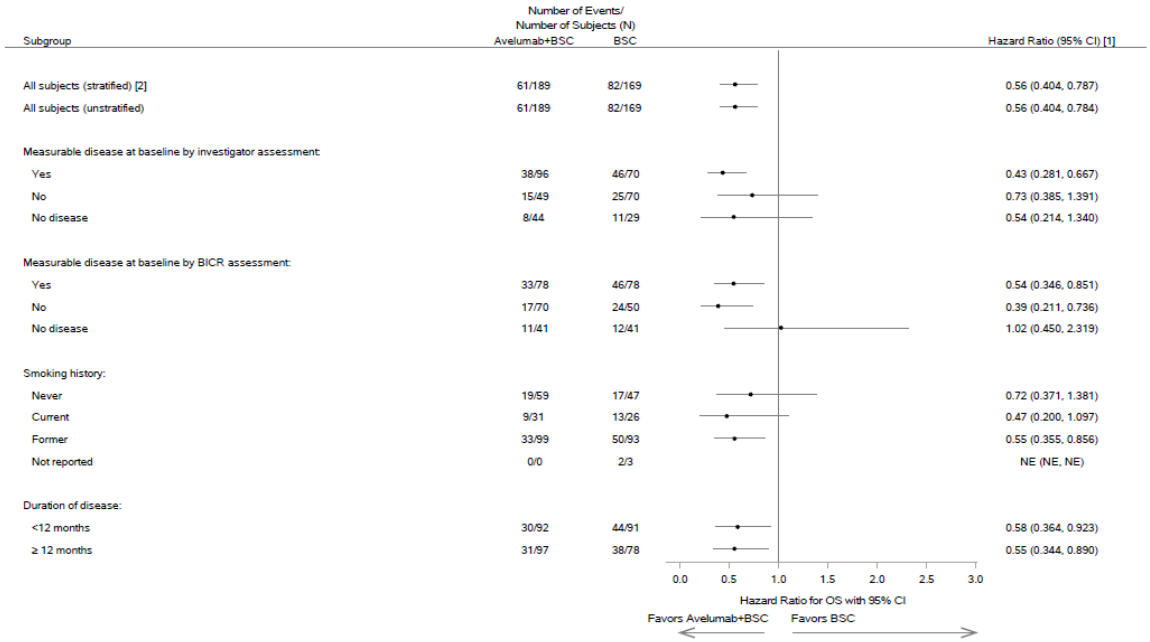
N is the number of subjects in the full analysis set in each treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Output File: /B9991001/CHMP_IA/adtte_os_f003_OC_F12 Date of Generation: 21SEP2020 (11:03) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 26. Forest Plot of Overall Survival by Subgroups – Subjects with PD-L1-Positive (Study B9991001, 21 Oct 2019)



N is the number of subjects with PD-L1-positive tumors in the full analysis set in each treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: ./B9991001/B9991001_CSR/adtte_os_f003_pdlpop Date of Generation: 14JAN2020 (13:49) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 27. Forest Plot of Overall Survival by Subgroups – Subjects with PD-L1-Positive (Study B9991001, non prespecified subgroups, 21 Oct 2019)



N is the number of subjects with PD-L1-positive tumors in the full analysis set in each treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the primary analysis presented which takes into account stratification factors, all other analyses are unstratified.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Output File: /B9991001/CHMP_IA/adtte_os_f003_OC_P12 Date of Generation: 21SEP2020 (11:37) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Sensitivity analyses of OS

Only minor differences for the subgroup analyses per protocol and actual strata were detected for all subjects and each PD-L1-strata. Detected differences are of no clinical relevance.

Ancillary analyses

Secondary endpoints

Progression Free Survival

The median PFS for avelumab plus BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC was 2.0 months (95% CI: 1.9, 2.7) for all patients. The median PFS for avelumab plus BSC was 5.7 months (95% CI: 3.7, 7.4) and for BSC was 2.1 months (95% CI: 1.9, 3.5) for patients with PD-L1-positive tumours and 3.0 months (95% CI 2.0, 3.7) for avelumab plus BSC and 1.9 months (95% CI 1.9, 2.1) for BSC for patients with PD-L1-negative tumours. Median PFS was 3.6 months (95% CI 1.9, 16.7) for avelumab plus BSC and 2.1 months (95% CI 1.9, 6.8) for BSC for patients with PD-L1-unknown tumours.

Table 26. Summary of Progression Free Survival Based on BICR Assessment (RECIST v1.1, 21 Oct. 2019).

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Subjects with event, n (%)	225 (64.3)	260 (74.3)	109 (57.7)	130 (76.9)
Type of event, n (%)				
Progressive disease	216 (61.7)	251 (71.7)	105 (55.6)	127 (75.1)
Death	9 (2.6)	9 (2.6)	4 (2.1)	3 (1.8)
Subjects censored, n (%)	125 (35.7)	90 (25.7)	80 (42.3)	39 (23.1)
Reason for censoring, n (%)				
No adequate baseline assessment	11 (3.1)	1 (0.3)	5 (2.6)	1 (0.6)
Start of new anti-cancer therapy	17 (4.9)	44 (12.6)	11 (5.8)	19 (11.2)
Event after ≥ 2 missing or inadequate post-baseline assessments	4 (1.1)	8 (2.3)	2 (1.1)	1 (0.6)
Withdrawal of consent	8 (2.3)	9 (2.6)	5 (2.6)	3 (1.8)
Lost to follow-up	0	1 (0.3)	0	0
No adequate post-baseline tumor assessment	1 (0.3)	0	0	0
Ongoing without an event	84 (24.0)	27 (7.7)	57 (30.2)	15 (8.9)
Probability of being event-free (95% CI) [1]				
at 3 months	0.581 (0.525, 0.634)	0.427 (0.371, 0.481)	0.649 (0.572, 0.716)	0.436 (0.357, 0.511)
at 6 months	0.407 (0.352, 0.461)	0.218 (0.172, 0.267)	0.481 (0.403, 0.555)	0.229 (0.165, 0.300)
at 9 months	0.330 (0.278, 0.384)	0.184 (0.140, 0.232)	0.384 (0.308, 0.459)	0.204 (0.142, 0.274)
at 12 months	0.296 (0.244, 0.350)	0.131 (0.092, 0.178)	0.356 (0.280, 0.433)	0.148 (0.092, 0.218)
at 15 months	0.269 (0.218, 0.323)	0.119 (0.081, 0.165)	0.325 (0.249, 0.403)	0.137 (0.082, 0.206)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]				
Q1	1.9 (1.8, 1.9)	1.8 (1.8, 1.8)	1.9 (1.9, 2.0)	1.8 (1.8, 1.9)
Median	3.7 (3.5, 5.5)	2.0 (1.9, 2.7)	5.7 (3.7, 7.4)	2.1 (1.9, 3.5)
Q3	17.9 (11.3, NE)	5.5 (4.1, 7.2)	25.0 (13.8, NE)	5.6 (4.1, 11.1)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.62		0.56	
95% CI [4]	0.519, 0.751		0.431, 0.728	
1-sided p-value [5]	<.0001		<.0001	
2-sided p-value [5]	<.0001		<.0001	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: ./B9991001/B9991001_CSR/adtteb_pfs_s001_pdl1_cp Date of Generation: 14JAN2020 (16:10) Cutoff date:21OCT2019 Snapshot Date:21NOV2019
Table 14.2.4.2 is for Pfizer internal use.

Table 27 Summary of Progression Free Survival Based on BICR Assessment (RECIST v1.1) – Subjects with PD-L1-negative (exploratory analysis) and PD-L1-unknown (not prespecified) tumours (21 Oct. 2019).

	Subjects with PD-L1-Negative Tumours		Subjects with PD-L1-Unknown Tumours	
	Avelumab+BSC (N=139)	BSC (N=131)	Avelumab+BSC (N=22)	BSC (N=50)
Subjects with event, n (%)	103 (74.1)	99 (75.6)	13 (59.1)	31 (62.0)
Type of event, n (%)				
Progressive disease	98 (70.5)	95 (72.5)	13 (59.1)	29 (58.0)
Death	5 (3.6)	4 (3.1)	0	2 (4.0)
Subjects censored, n (%)	36 (25.9)	32 (24.4)	9 (40.9)	19 (38.0)
Reason for censoring, n (%)				
No adequate baseline assessment	6 (4.3)	0	0	0
Start of new anti-cancer therapy	5 (3.6)	17 (13.0)	1 (4.5)	8 (16.0)
Event after≥ 2 missing or inadequate post-baseline assessments	2 (1.4)	6 (4.6)	0	1 (2.0)
Withdrawal of consent	1 (0.7)	1 (0.8)	2 (9.1)	5 (10.0)
Lost to follow-up	0	1 (0.8)	0	0
No adequate post-baseline tumour assessment	0	0	1 (4.5)	0
Ongoing without an event	22 (15.8)	7 (5.3)	5 (22.7)	5 (10.0)
Probability of being event-free (95% CI) [1]				
at 3 months	0.502 (0.413, 0.585)	0.394 (0.304, 0.483)	0.517 (0.275, 0.713)	0.488 (0.328, 0.630)
at 6 months	0.311 (0.233, 0.393)	0.146 (0.085, 0.223)	0.402 (0.184, 0.612)	0.373 (0.224, 0.522)
at 9 months	0.253 (0.180, 0.331)	0.098 (0.048, 0.169)	0.402 (0.184, 0.612)	0.342 (0.197, 0.492)
at 12 months	0.216 (0.148, 0.293)	0.071 (0.029, 0.138)	0.322 (0.119, 0.546)	0.239 (0.113, 0.391)
at 15 months	0.193 (0.127, 0.270)	0.071 (0.029, 0.138)	0.322 (0.119, 0.546)	0.199 (0.083, 0.352)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]				
Q1	1.8 (1.8, 1.9)	1.8 (1.7, 1.8)	1.9 (1.1, 2.4)	1.8 (1.2, 1.9)
Median	3.0 (2.0, 3.7)	1.9 (1.9, 2.1)	3.6 (1.9, 16.7)	2.1 (1.9, 6.8)
Q3	9.2 (5.7, 25.3)	3.8 (3.6, 5.6)	16.7 (3.6, NE)	10.3 (3.8, NE)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.63		0.97	
95% CI [4]	0.474, 0.847		0.488, 1.914	

	Subjects with PD-L1-Negative Tumours		Subjects with PD-L1-Unknown Tumours	
	Avelumab+BSC (N=139)	BSC (N=131)	Avelumab+BSC (N=22)	BSC (N=50)

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[4] Cox proportional hazard model used.
Cutoff date: 21OCT2019

Table 28. Summary of Progression Free Survival Based on Investigator Assessment (RECIST v1.1).

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Subjects with event, n (%)	235 (67.1)	277 (79.1)	111 (58.7)	138 (81.7)
Type of event, n (%)				
Progressive disease	225 (64.3)	271 (77.4)	105 (55.6)	135 (79.9)
Death	10 (2.9)	6 (1.7)	6 (3.2)	3 (1.8)
Subjects censored, n (%)	115 (32.9)	73 (20.9)	78 (41.3)	31 (18.3)
Reason for censoring, n (%)				
No adequate baseline assessment	9 (2.6)	10 (2.9)	4 (2.1)	6 (3.6)
Start of new anti-cancer therapy	9 (2.6)	21 (6.0)	6 (3.2)	6 (3.6)
Event after ≥ 2 missing or inadequate post-baseline assessments	1 (0.3)	5 (1.4)	0	1 (0.6)
Withdrawal of consent	7 (2.0)	9 (2.6)	4 (2.1)	4 (2.4)
Lost to follow-up	1 (0.3)	1 (0.3)	1 (0.5)	0
No adequate post-baseline tumor assessment	0	0	0	0
Ongoing without an event	88 (25.1)	27 (7.7)	63 (33.3)	14 (8.3)
Probability of being event-free (95% CI) [1]				
at 3 months	0.682 (0.629, 0.729)	0.445 (0.390, 0.500)	0.747 (0.677, 0.804)	0.479 (0.398, 0.555)
at 6 months	0.460 (0.406, 0.513)	0.234 (0.188, 0.283)	0.554 (0.478, 0.623)	0.260 (0.193, 0.331)
at 9 months	0.387 (0.334, 0.440)	0.167 (0.127, 0.212)	0.486 (0.410, 0.558)	0.168 (0.113, 0.233)
at 12 months	0.341 (0.288, 0.394)	0.116 (0.081, 0.157)	0.411 (0.335, 0.486)	0.102 (0.058, 0.160)
at 15 months	0.304 (0.252, 0.358)	0.092 (0.061, 0.131)	0.376 (0.299, 0.452)	0.085 (0.045, 0.141)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]				
Q1	1.9 (1.9, 2.2)	1.8 (1.8, 1.9)	2.8 (1.9, 3.7)	1.9 (1.8, 1.9)
Median	5.5 (4.2, 7.2)	2.1 (1.9, 3.0)	7.5 (5.5, 11.2)	2.8 (2.0, 3.7)
Q3	19.4 (15.1, NE)	5.7 (5.5, 7.2)	NE (18.3, NE)	6.0 (5.5, 8.3)
Stratified analysis [3] Comparison vs BSC				
Hazard Ratio [4]	0.52		0.43	
95% CI [4]	0.437, 0.625		0.329, 0.552	
1-sided p-value [5]	<.0001		<.0001	
2-sided p-value [5]	<.0001		<.0001	

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] CIs are derived using the log-log transformation with back transformation to untransformed scale.
[2] CIs are calculated using Brookmeyer and Crowley method.
[3] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
[4] Cox proportional hazard model used.
[5] Log-rank test is used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: ./B9991001/B9991001_CSR/adtte_pfs_s001_pdl1_cp Date of Generation: 14JAN2020 (15:07) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 28. Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) – FAS (Study B9991001 21 Oct. 2019)

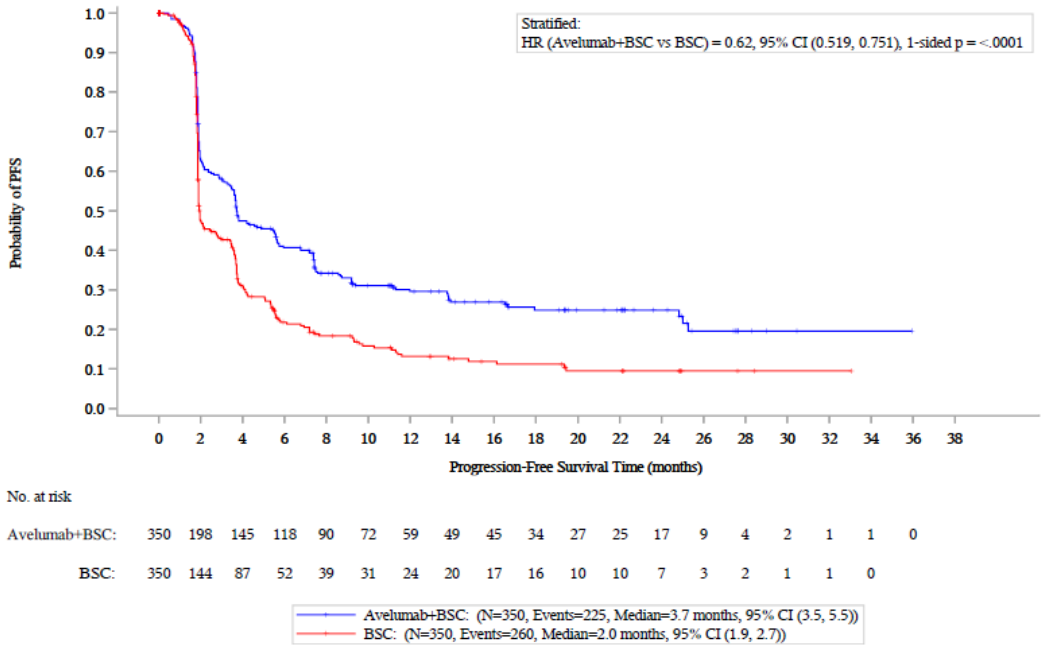


Figure 29 Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Subjects with PD-L1-Positive Tumours (Study B9991001 21 Oct. 2019)

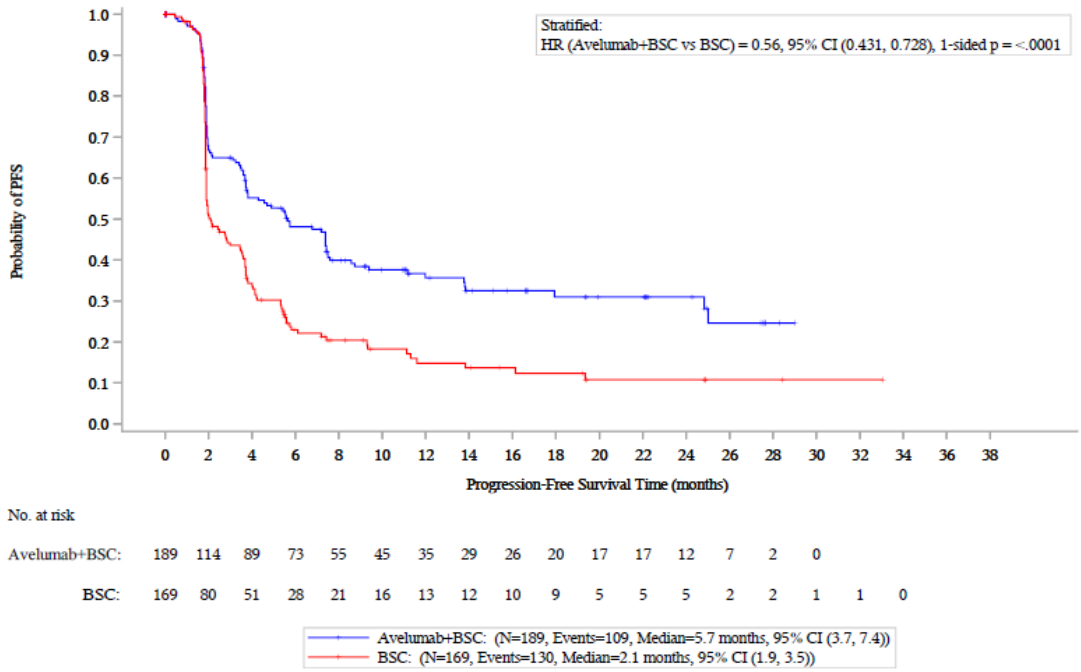


Figure 30. Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Subjects with PD-L1-Negative Tumours (Study B9991001, exploratory analysis, 21 Oct. 2019))

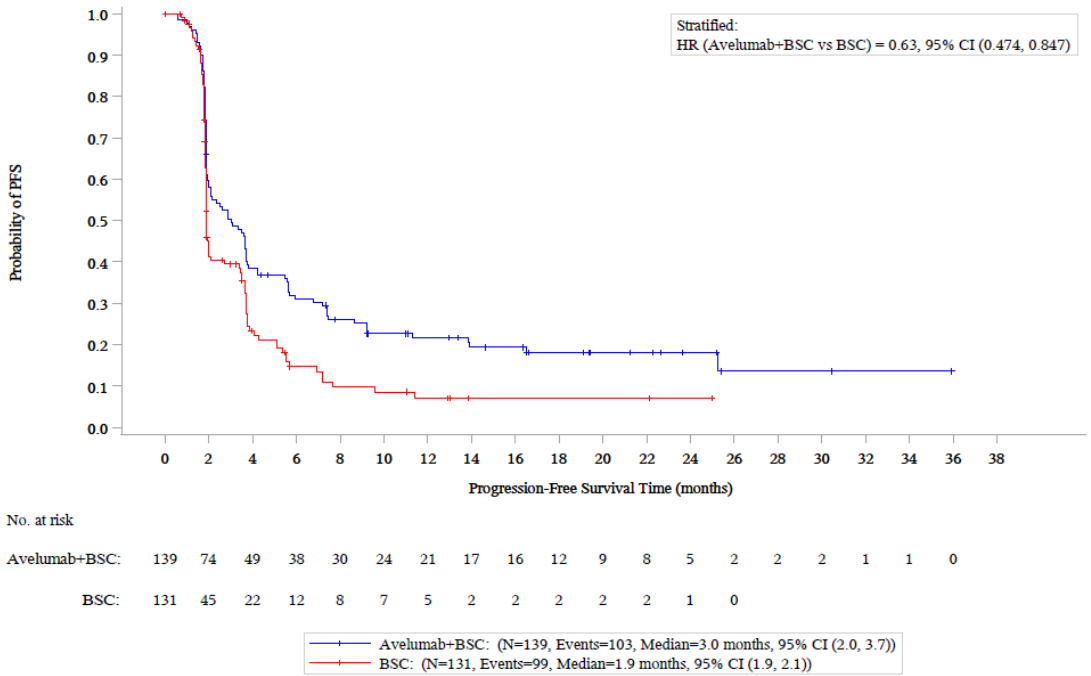
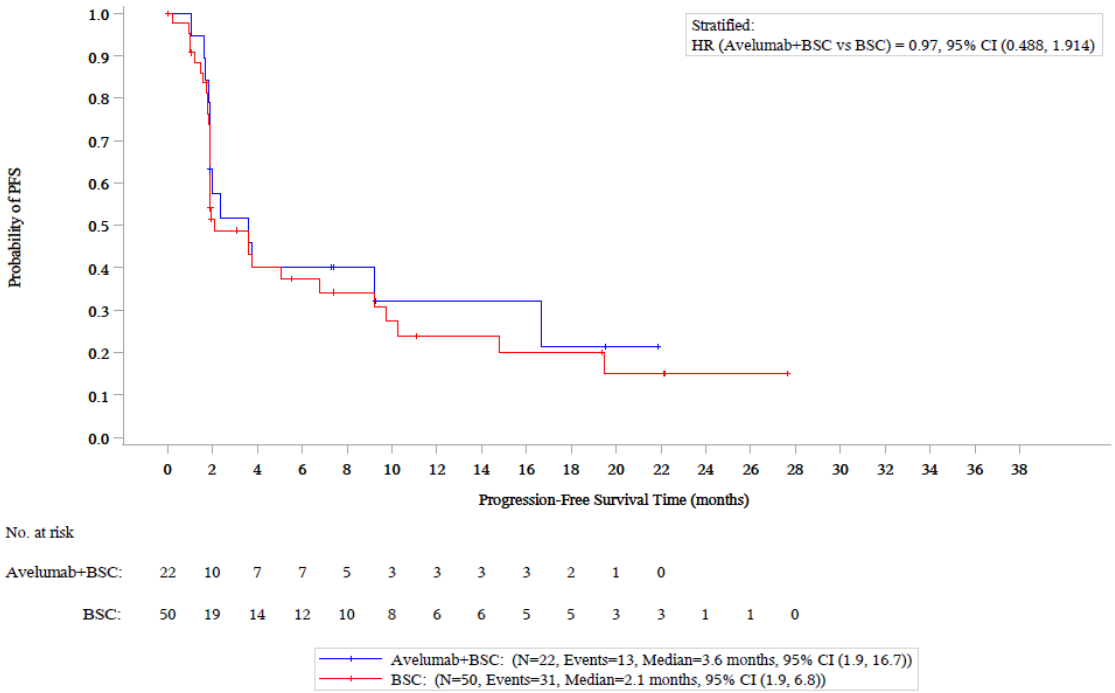
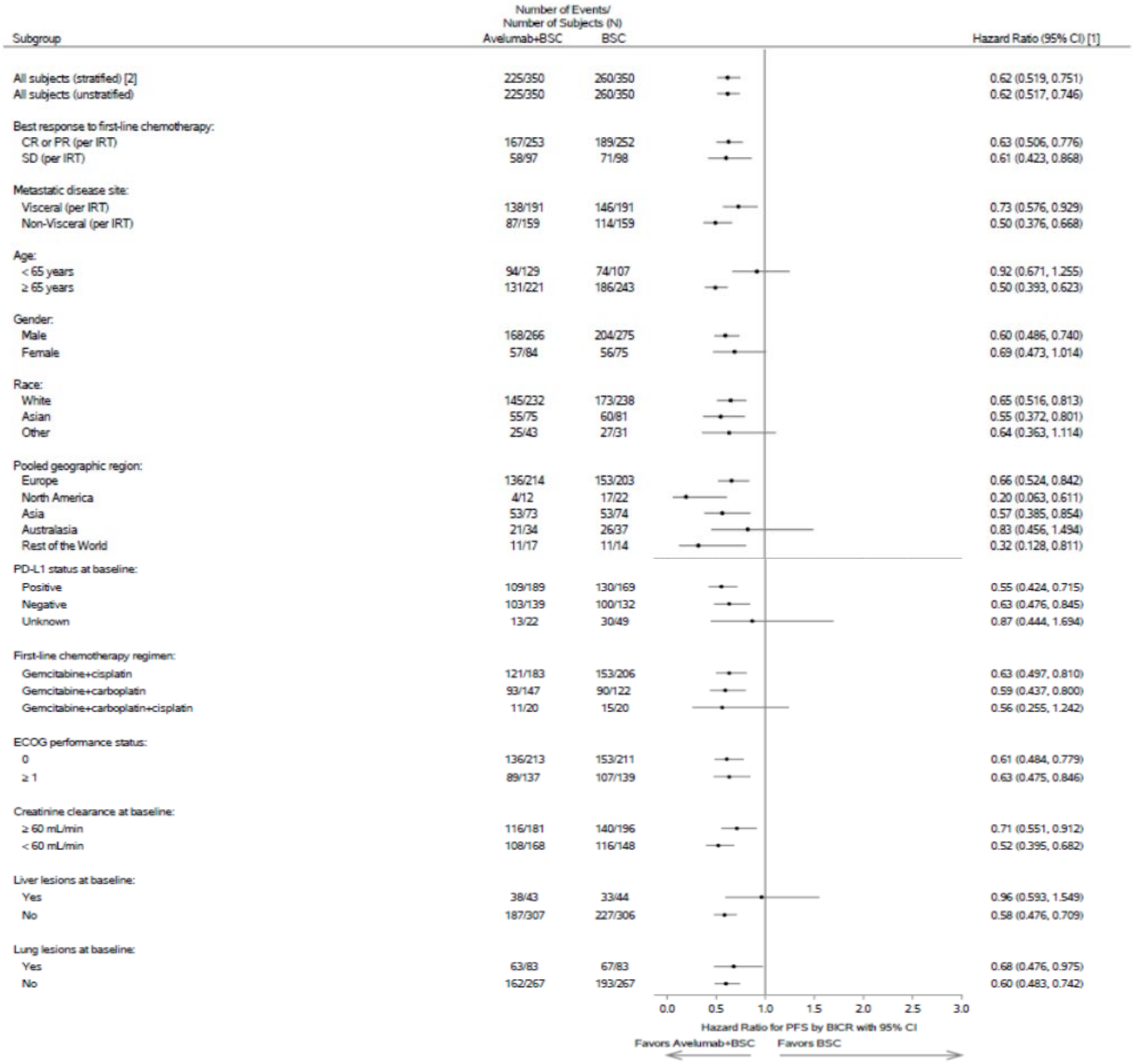


Figure 31. Kaplan-Meier Plot of Progression-Free Survival Based on BICR Assessment (RECIST v1.1) - Subjects with PD-L1-Unknown Tumours (Study B9991001, not prespecified endpoint)



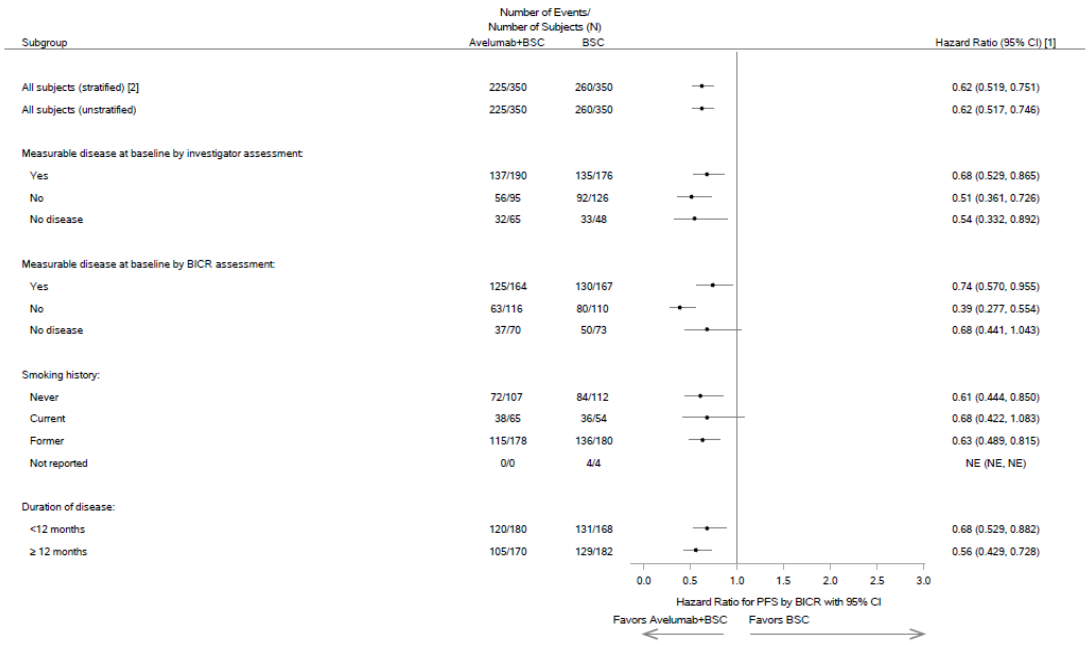
Subgroup Analysis of PFS

Figure 32. Forest Plot of Progression Free Survival by Subgroups Based on BICR Assessment – FAS (Study B9991001, 21 Oct. 2019)



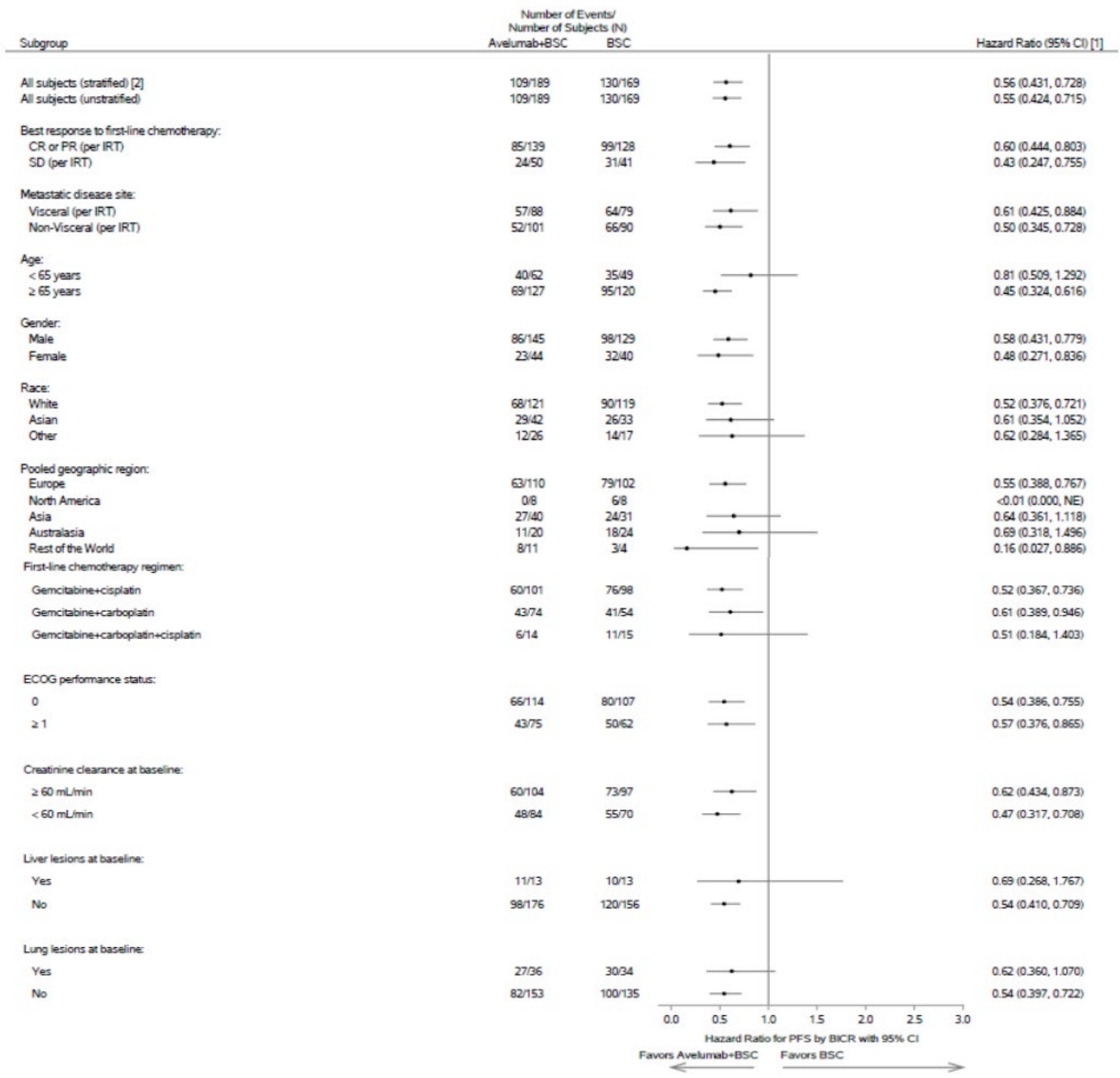
N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the analysis for all subjects which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: /B9991001/B9991001_CSR/adtteb_pfs_f003 Date of Generation: 14JAN2020 (15:56) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 33. Forest Plot of Progression Free Survival by Subgroups Based on BICR Assessment – FAS (Study B9991001, non prespecified subgroups, 21 Oct. 2019)



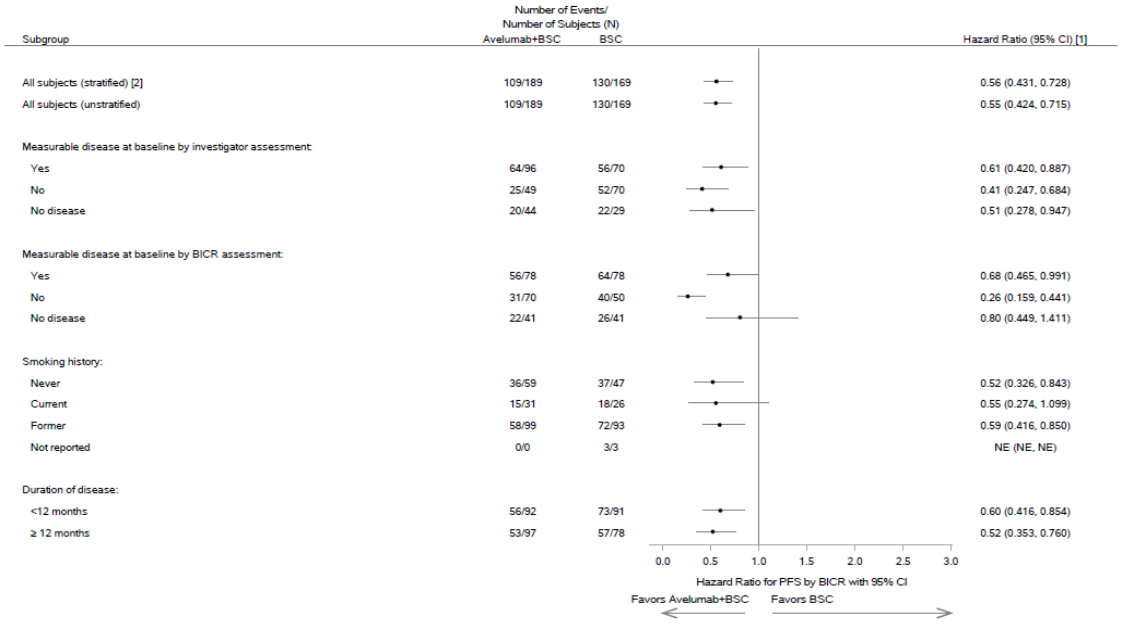
N is the number of subjects in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the analysis for all subjects which takes into account stratification factors, all other analyses are unstratified.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Output File: /B9991001/CHMP_IA/adtteb_pfs_f003_OC_F12 Date of Generation: 21SEP2020 (12:15) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 34. Forest Plot of Progression Free Survival by Subgroups Based on BICR Assessment – Subjects with PD-L1-Positive Tumours (Study B9991001, 21 Oct 2019)



N is the number of subjects with PD-L1-positive tumors in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the analysis for all subjects which takes into account stratification factors, all other analyses are unstratified.
Subgroups with <5% of the patient population were pooled (Race: Black/African American and Other) or not presented (Ethnicity since only two subgroups and Hispanic/Latino is <5% of the patient population).
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Output File: /B9991001/B9991001_CSR/adtteb_pfs_f003_pdl1 Date of Generation: 14JAN2020 (16:01) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Figure 35 Forest Plot of Progression Free Survival by Subgroups Based on BICR Assessment – Subjects with PD-L1-Positive Tumours (Study B9991001, non prespecified subgroups, 21 Oct 2019)



N is the number of subjects with PD-L1-positive tumors in the full analysis set within each subgroup and treatment group.
[1] Hazard ratios and associated CIs are calculated using Cox proportional hazard model.
[2] Stratified by best response to first-line chemotherapy (CR or PR vs. SD), metastatic disease site (visceral vs. non-visceral). IRT stratification values used.
Other than the analysis for all subjects which takes into account stratification factors, all other analyses are unstratified.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Output File: /B9991001/CHMP_IA/adtteb_pfs_f003_OC_P12 Date of Generation: 21SEP2020 (14:07) Cutoff date:21OCT2019 Snapshot Date:21NOV2019

Best Overall Response and Objective Response

Table 29. Summary of Best Overall Response and Objective Response (Confirmed) based on BICR Assessment (RECIST v1.1, 21 Oct. 2019)).

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Confirmed Best Overall Response, n (%)				
Complete response (CR)	21 (6.0)	3 (0.9)	18 (9.5)	1 (0.6)
Partial response (PR)	13 (3.7)	2 (0.6)	8 (4.2)	1 (0.6)
Stable disease (SD)	44 (12.6)	46 (13.1)	19 (10.1)	23 (13.6)
Non-CR/Non-PD	66 (18.9)	45 (12.9)	38 (20.1)	22 (13.0)
Progressive disease (PD)	130 (37.1)	169 (48.3)	59 (31.2)	82 (48.5)
Not evaluable (NE)	76 (21.7)	85 (24.3)	47 (24.9)	40 (23.7)
Reason for NE, n (%)				
No evidence of disease at baseline	52 (14.9)	50 (14.3)	31 (16.4)	28 (16.6)
No post-baseline assessments due to early death	1 (0.3)	4 (1.1)	1 (0.5)	1 (0.6)
No post-baseline assessments due to other reasons	18 (5.1)	17 (4.9)	12 (6.3)	5 (3.0)
All post-baseline assessments have overall response of NE	0	1 (0.3)	0	0
New anti-cancer therapy started before first post-baseline assessment	1 (0.3)	3 (0.9)	1 (0.5)	1 (0.6)
SD too early (<6 weeks after Randomization date)	2 (0.6)	8 (2.3)	1 (0.5)	3 (1.8)
PD too late (>12 weeks after Randomization date)	2 (0.6)	2 (0.6)	1 (0.5)	2 (1.2)
Objective Response (CR+PR), n (%)	34 (9.7)	5 (1.4)	26 (13.8)	2 (1.2)
95% CI [1]	6.8, 13.3	0.5, 3.3	9.2, 19.5	0.1, 4.2
Disease Control (CR+PR+SD+Non-CR/Non-PD), n (%)	144 (41.1)	96 (27.4)	83 (43.9)	47 (27.8)
95% CI [1]	35.9, 46.5	22.8, 32.4	36.7, 51.3	21.2, 35.2

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADRSB Output File: ./B9991001/B9991001_CSR/adrsb_borc_s001b_pdl_cp Date of Generation: 04FEB2020 (11:42) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.2.1.2.1.1 is for Pfizer internal use.

Table 30 Summary of Best Overall Response and Objective Response (Confirmed) based on BICR Assessment (RECIST v1.1) – Subjects with PD-L1-Negative (exploratory analysis) and PD-L1-Unknown tumours (not prespecified endpoint) (21 Oct. 2019)

	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=139)	BSC (N=131)	Avelumab+BSC (N=22)	BSC (N=50)
Confirmed Best Overall Response, n (%)				
Complete response (CR)	3 (2.2)	1 (0.8)	0	1 (2.0)
Partial response (PR)	5 (3.6)	0	0	1 (2.0)
Stable disease (SD)	24 (17.3)	14 (10.7)	1 (4.5)	9 (18.0)
Non-CR/Non-PD	24 (17.3)	19 (14.5)	4 (18.2)	4 (8.0)
Progressive disease (PD)	62 (44.6)	66 (50.4)	9 (40.9)	21 (42.0)
Not evaluable (NE)	21 (15.1)	31 (23.7)	8 (36.4)	14 (28.0)
Reason for NE, n (%)				
No evidence of disease at baseline	15 (10.8)	16 (12.2)	6 (27.3)	6 (12.0)
No post-baseline assessments due to early death	0	3 (2.3)	0	0
No post-baseline assessments due to other reasons	4 (2.9)	5 (3.8)	2 (9.1)	7 (14.0)
All post-baseline assessments have overall response of NE	0	1 (0.8)	0	0
New anti-cancer therapy started before first post-baseline assessment	0	2 (1.5)	0	0
SD too early (<6 weeks after Randomization date)	1 (0.7)	4 (3.1)	0	1 (2.0)
PD too late (>12 weeks after Randomization date)	1 (0.7)	0	0	0
Objective Response (CR+PR), n (%)	8 (5.8)	1 (0.8)	0	2 (4.0)
95% CI [1]	2.5, 11.0	0.0, 4.2	0.0, 15.4	0.5, 13.7
Disease Control (CR+PR+SD+Non-CR/Non-PD), n (%)	56 (40.3)	34 (26.0)	5 (22.7)	15 (30.0)
95% CI [1]	32.1, 48.9	18.7, 34.3	7.8, 45.4	17.9, 44.6

The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
[1] Clopper-Pearson method used.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Source Data: ADRSB Output File: ./B9991001/CHMP_IA/adrsb_borc_s001b_pdl_mo Date of Generation: 28AUG2020 (14:28) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

All randomized patients (including patients with CR following first-line chemotherapy) were included in the analysis of objective response (refer to study B9991001 SAP Section 6.2.2.3). For patients with no evidence of disease, the BOR can only be NE or PD, which is different from patients without measurable disease as the latter can also have BOR of CR or non-CR/non-PD. Subgroup analyses including only patients with measurable tumours at baseline were performed.

Among the 78 patients with measurable disease by BICR at baseline with PD-L1-positive tumours treated with avelumab plus BSC, 7.7% achieved CR (BICR), 10.3% PR and 24.4% SD and 48.7% displayed PD. For the 78 patients treated with BSC, 1.3% achieved CR, 1.3% PR and 29.5% SD and 56.4% displayed PD. Among the 77 patients with measurable disease by BICR at baseline with PD-L1-negative tumours treated with avelumab plus BSC, 1.3% achieved CR (BICR), 6.5% PR and 31.2% SD and 55.8% displayed PD. For the 62 patients treated with BSC, 0% achieved CR or PR and 22.6% SD and 64.5% displayed PD.

Time to Response and Duration of Response

Table 31. Summary of Time to Response Based on BICR Assessment (RECIST v1.1, 21 Oct. 2019))

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=34)	BSC (N=5)	Avelumab+BSC (N=26)	BSC (N=2)
Time to Response (TTR) (Months)				
Mean (SD)	3.83 (3.28)	3.29 (2.24)	3.72 (3.29)	2.81 (1.42)
Q1	1.9	1.8	1.9	1.8
Median	2.0	2.0	2.0	2.8
Q3	5.5	3.8	3.8	3.8
Range (min, max)	(1.7, 16.4)	(1.8, 7.0)	(1.7, 16.4)	(1.8, 3.8)

Table 32. Summary of Duration of Response Based on BICR Assessment (RECIST v1.1) – Patients with confirmed CR or PR (21 Oct. 2019)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=34)	BSC (N=5)	Avelumab+BSC (N=26)	BSC (N=2)
Subjects with event, n (%)	10 (29.4)	0	8 (30.8)	0
Type of event, n (%)				
Progressive disease	9 (26.5)	0	7 (26.9)	0
Death	1 (2.9)	0	1 (3.8)	0
Subjects censored, n (%)	24 (70.6)	5 (100.0)	18 (69.2)	2 (100.0)
Reason for censoring, n (%)				
Start of new anti-cancer therapy	2 (5.9)	1 (20.0)	2 (7.7)	0
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0	0	0
Withdrawal of consent	0	0	0	0
Lost to follow-up	0	0	0	0
No adequate post-baseline tumor assessment	0	0	0	0
Ongoing without an event	22 (64.7)	4 (80.0)	16 (61.5)	2 (100.0)

Table 33 Summary of Duration of Response Based on BICR Assessment (RECIST v1.1) – Patients with confirmed CR or PR, Subjects with PD-L1-negative (exploratory analysis) and PD-L1-Unknown tumours (not prespecified endpoint, 21 Oct. 2019)

	Subjects with PD-L1-Negative Tumors		Subjects with PD-L1-Unknown Tumors	
	Avelumab+BSC (N=8)	BSC (N=1)	Avelumab+BSC (N=0)	BSC (N=2)
Subjects with event, n (%)	2 (25.0)	0	0	0
Type of event, n (%)				
Progressive disease	2 (25.0)	0		
Death	0	0		
Subjects censored, n (%)	6 (75.0)	1 (100.0)	0	2 (100.0)
Reason for censoring, n (%)				
Start of new anti-cancer therapy	0	0	0	1 (50.0)
Event after ≥ 2 missing or inadequate post-baseline assessments	0	0	0	0
Withdrawal of consent	0	0	0	0
Lost to follow-up	0	0	0	0
No adequate post-baseline tumor assessment	0	0	0	0
Ongoing without an event	6 (75.0)	1 (100.0)	0	1 (50.0)
Kaplan-Meier estimates of Time to Event (months) Quartiles (95% CI) [2]				
Q1	8.3 (3.7, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Median	NE (3.7, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Q3	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)

Overall Response and objective responses are higher in patients with PD-L1-expression. Very few patients in the Avelumab+BSC arm (5.8%) with PD-L1-negative tumours had an objective response and no patients with PD-L1-unknown tumours. Due to the low number of responses an assessment of duration of the responses cannot be made.

Time to end of next line treatment

PFS2 was not recorded during study B99910001. Time to end of next line treatment was not a prespecified endpoint. No detrimental effect on end of next line treatment is detected when avelumab plus BSC is compared to BSC.

Figure 36. Kaplan-Meier Plot of Time to End-of-next-line-treatment - Full Analysis Set (21 Oct. 2019)

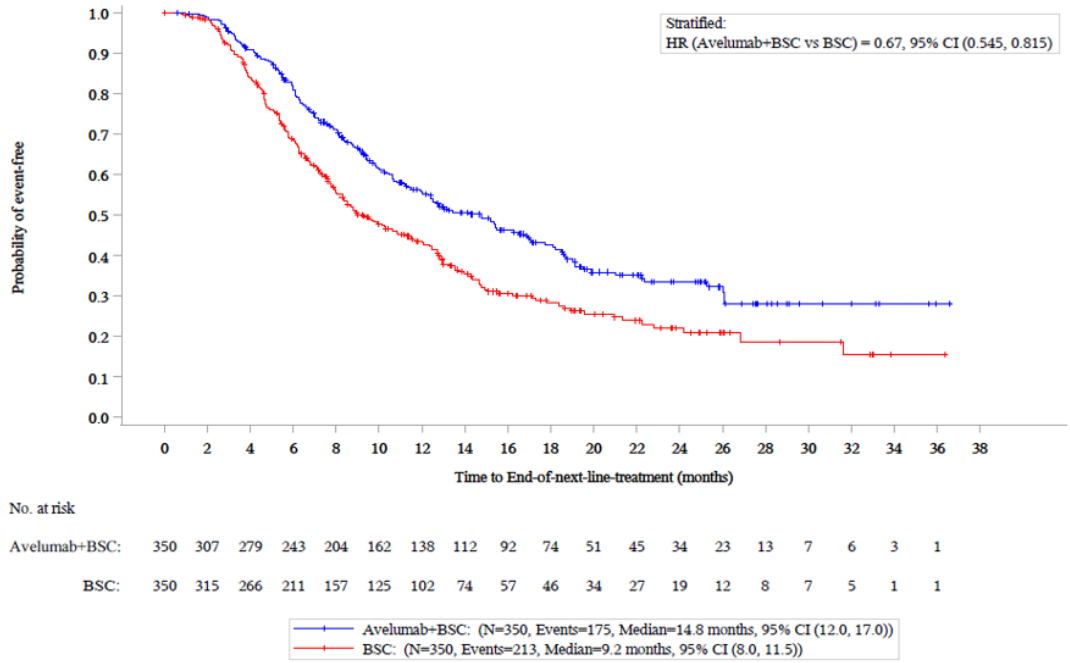


Figure 37. Kaplan-Meier Plot of Time to End-of-next-line-treatment - Subjects with PD-L1-Positive Tumours (21 Oct. 2019)

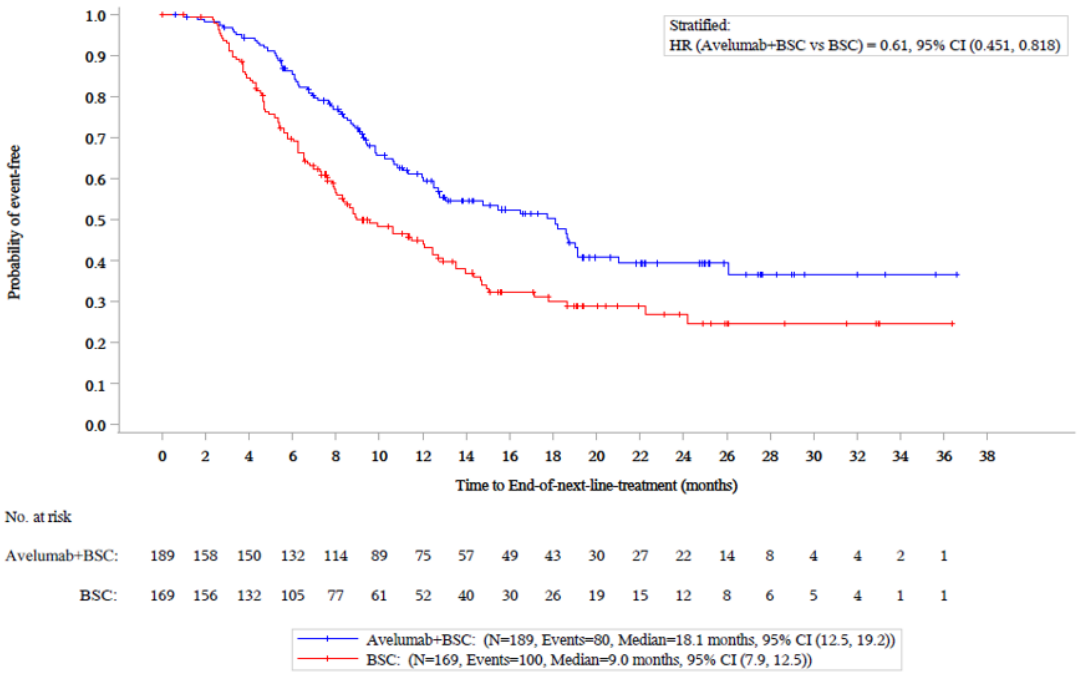


Figure 38. Kaplan-Meier Plot of Time to End-of-next-line-treatment - Subjects with PD-L1-Negative Tumours (21 Oct. 2019)

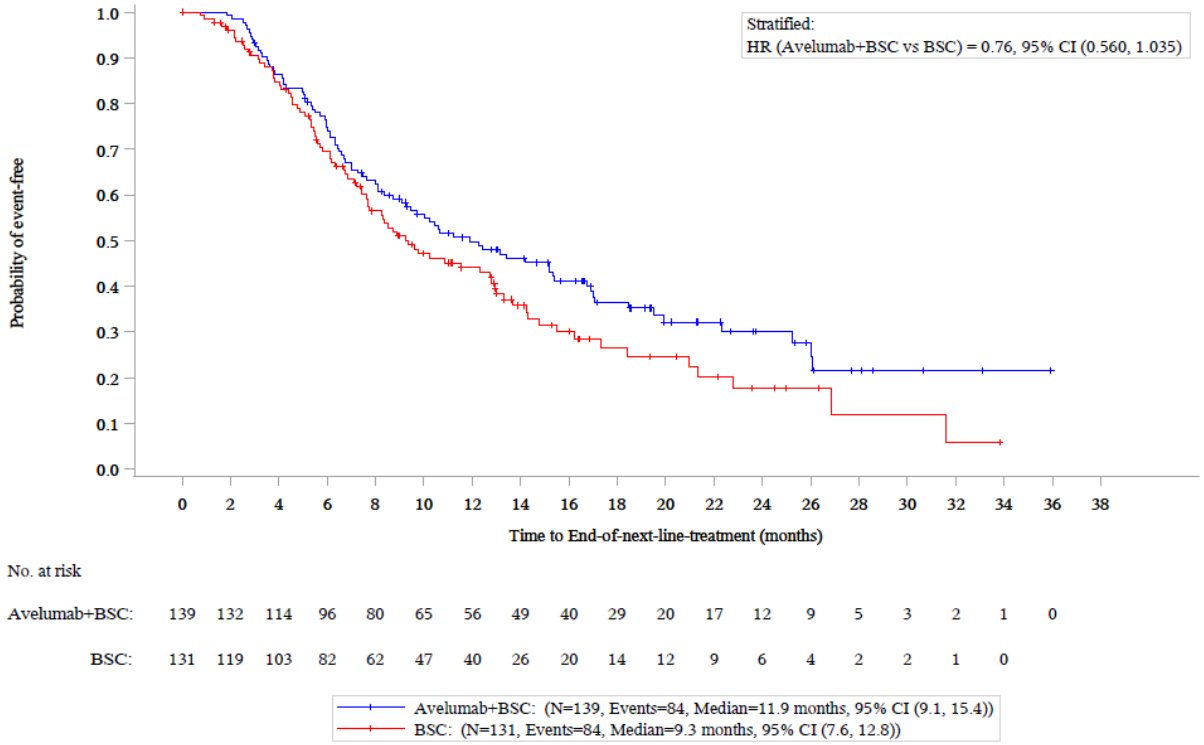
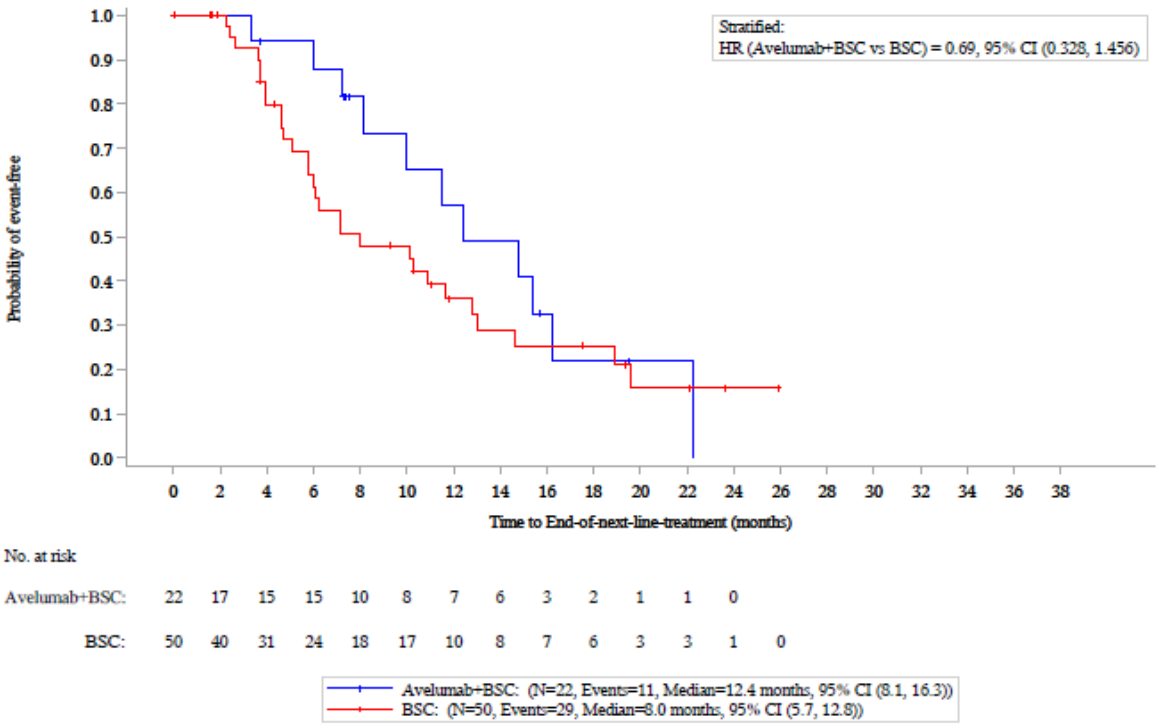


Figure 39. Kaplan-Meier Plot of Time to End-of-next-line-treatment - Subjects with PD-L1-Unknown Tumours (21 Oct. 2019)



Follow-up anti-cancer therapies

The majority of patients, regardless of PD-L1 tumour status, reported at least one type of follow-up anti-cancer therapy. However, follow-up anti-cancer drug therapies were more common among patients treated with BSC in patients with both PD-L1-positive and PD-L1-negative tumours. 6.3% of patients in the avelumab plus BSC arm were treated with a PD-1 or PD-L1 inhibitor whereas 43.7% of the patients in the BSC arm were treated with PD-1 or PD-L1 inhibitor.

Table 34. Summary of Follow-up Anti-Cancer Therapies - Full Analysis Set (Protocol B9991001).

	Avelumab+BSC (N=350)	BSC (N=350)
Subjects discontinued from study treatment^	265 (75.7)	324 (92.6)
Subjects ongoing with study treatment^	85 (24.3)	26 (7.4)
Subjects with at least one type of follow-up anti-cancer therapy		
Yes	167 (47.7)	228 (65.1)
No	47 (13.4)	37 (10.6)
Not reported*	136 (38.9)	85 (24.3)
Subjects with at least one follow-up anti-cancer drug therapy		
Yes	148 (42.3)	216 (61.7)
No	73 (20.9)	50 (14.3)
Not reported*	129 (36.9)	84 (24.0)
Subjects with at least one follow-up anti-cancer radiotherapy		
Yes	52 (14.9)	57 (16.3)
No	160 (45.7)	190 (54.3)
Not reported*	138 (39.4)	103 (29.4)
Subjects with at least one follow-up anti-cancer radiotherapy [1]		
Curative	2 (0.6)	3 (0.9)
Palliative	50 (14.3)	54 (15.4)
Subjects with at least one follow-up anti-cancer surgery		
Yes	13 (3.7)	14 (4.0)
No	197 (56.3)	227 (64.9)
Not reported*	140 (40.0)	109 (31.1)
Follow-up anti-cancer drug therapy regimens [2]		
0 regimen	73 (20.9)	50 (14.3)
1 regimen	102 (29.1)	150 (42.9)
2 regimens	33 (9.4)	52 (14.9)
3 regimens	11 (3.1)	11 (3.1)
≥ 4 regimens	2 (0.6)	3 (0.9)
Not reported*	129 (36.9)	84 (24.0)

Follow-up anti-cancer therapies as recorded in the Follow-up Cancer Therapy, Follow-up Radiation Therapy and Follow-up Surgery CRF pages.
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
^ Refer to Module 2.7.3 SCE In-text Table 2
* Includes subjects ongoing with study treatment

	Avelumab+BSC (N=350)	BSC (N=350)

[1] Subjects are counted once per category but may be counted in multiple categories.
[2] Includes the overall number of regimens in neoadjuvant, adjuvant, advanced/metastatic or locoregional disease/recurrence drug therapies

Table 35. Follow-up Anti-Cancer Drug Therapies by Category - All Subjects and Subjects with PD-L1-Positive Tumours in the Full Analysis Set (Protocol B9991001, 21 Oct. 2019)

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=350)	BSC (N=350)	Avelumab+BSC (N=189)	BSC (N=169)
Category	n (%)	n (%)	n (%)	n (%)
Subjects with any follow-up anti-cancer drug therapies	148 (42.3)	216 (61.7)	68 (36.0)	109 (64.5)
Any PD-1 or PD-L1 inhibitor	22 (6.3)	153 (43.7)	10 (5.3)	81 (47.9)
FGFR inhibitor	9 (2.6)	8 (2.3)	3 (1.6)	4 (2.4)
Any other drug therapy	140 (40.0)	119 (34.0)	67 (35.4)	57 (33.7)

Subjects are counted only once within a given category but may be counted in more than one category.
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCM Output File: ./B9991001/B9991001_CSR/adcm_s009b_pdl1c Date of Generation: 14JAN2020 (21:38) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.4.2.7.1.4 is for Pfizer internal use.

Table 36. Follow-up Anti-Cancer Drug Therapies by Category - Subjects with PD-L1-Negative Tumours and Subjects with PD-L1-Unknown Tumours in the Full Analysis Set (Protocol B9991001, 21 Oct. 2019)

	Subjects with PD-L1-Negative Tumours		Subjects with PD-L1-Unknown Tumours	
	Avelumab+BSC (N=139)	BSC (N=131)	Avelumab+BSC (N=22)	BSC (N=50)
Category	n (%)	n (%)	n (%)	n (%)
Subjects with any follow-up anti-cancer drug therapies	69 (49.6)	79 (60.3)	11 (50.0)	28 (56.0)
Any PD-1 or PD-L1 inhibitor	8 (5.8)	51 (38.9)	4 (18.2)	21 (42.0)
FGFR inhibitor	6 (4.3)	3 (2.3)	0	1 (2.0)
Any other drug therapy	62 (44.6)	48 (36.6)	11 (50.0)	14 (28.0)

Subjects are counted only once within a given category but may be counted in more than one category.
The denominator to calculate percentages is N, the number of subjects in the full analysis set within each treatment group.
Cutoff date: 21OCT2019

PRO

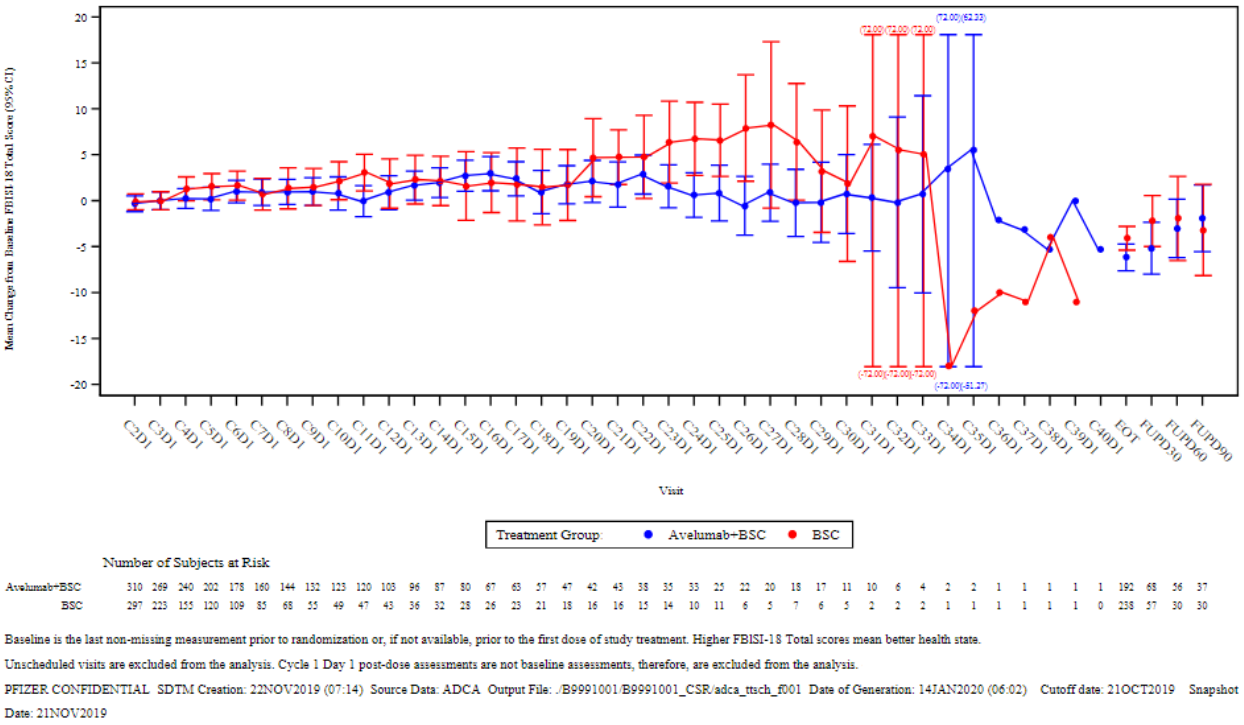
Over 90% of all randomized patients filled in the FB1SI-18 and this was similar in all groups. The proportion of patients completing the whole form was more variable and in general around 60% answered all questions during the treatment period and around 40% during the follow up phase in the FAS. It should be noted that not all items of FBlSI are required to be completed for scoring and one item was only applicable for male patients.

Time to deterioration (TTD) was defined as ≥3-point decrease from baseline FB1SI-DRS-P for 2 consecutive assessments (death and progression were not considered as a deterioration event). The HR for TTD in all randomized patients was 1.26 (95% CI: 0.901, 1.768). Median TTD was not reached in the avelumab plus BSC arm (95% CI: 13.9 months, not reached) and 13.8 months in the BSC alone arm (95% CI: 12.9 months, not reached). The HR for TTD in all randomized patients with PD-L1-positive tumours was 1.51 (95% CI: 0.946, 2.401). Median TTD was not reached in the avelumab plus BSC arm (95% CI: 9.3 months, not reached) and 28.5 months in the BSC alone arm (95% CI: 13.7 months, not reached).

The proportion of answered EQ-5D-5L forms were greater than 90% for the majority of the treatment periods and also the proportion of fully completed forms were high, generally greater than 90%. At the end of treatment, the proportion of completed forms where at least one question was answered was around 80% and the proportion of fully completed forms just under 80%. For the follow up period, the proportion of forms where at least one question was answered was between 50-70% and also the proportion of fully complete forms was between 50-70%.

The results of the FB1SI-18 and EQ-5D-5L forms were similar between avelumab + BSC and BSC alone for all randomized patients and for the patients with PD-L1 positive tumours.

Figure 40. Summary of FB1SI-18 Total Score Change from Baseline by Visit – FAS Study B9991001

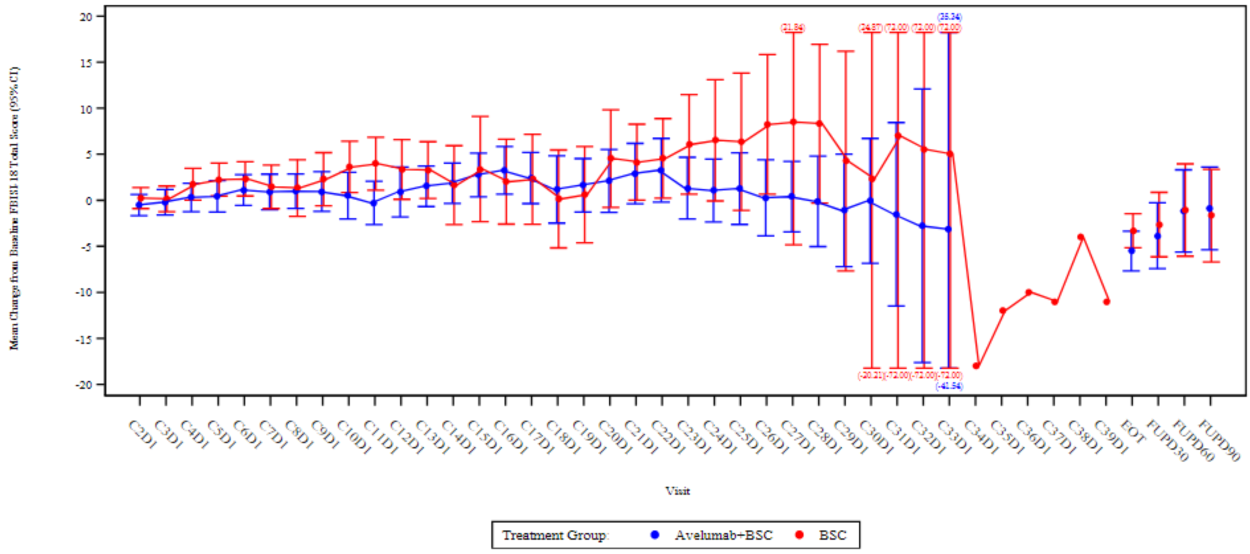


Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher FBISI-18 Total scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCA Output File: ./B9991001/B9991001_CSR/adca_ttsch_f001 Date of Generation: 14JAN2020 (06:02) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Figure 41. Summary of FB1SI-18 Total Score Change from Baseline by Visit – Subjects with PD-L1-positive Tumours FAS Study B9991001



Number of Subjects at Risk

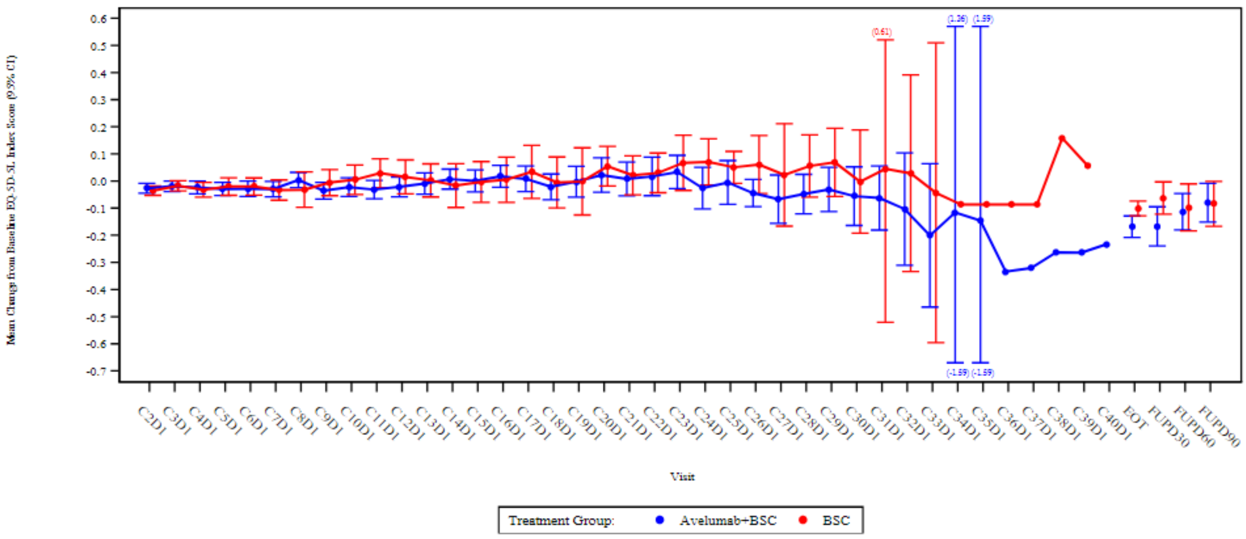
Avelumab+BSC	165	151	135	117	108	96	88	83	76	73	62	57	51	46	39	36	32	28	24	25	22	21	21	18	14	15	12	12	7	6	4	2	0	0	0	0	0	0	95	34	33	23
BSC	147	116	81	70	62	50	40	29	26	25	22	19	16	13	12	12	11	9	9	9	8	8	6	6	5	4	5	4	3	2	2	2	1	1	1	1	1	1	115	36	18	18

Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher FBISI-18 Total scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADCA Output File: ./B9991001/B9991001_CSR/adca_ttschp_f001 Date of Generation: 14JAN2020 (06:04) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Figure 42. Summary of EQ-5D-5L Index Score Change from Baseline by Visit – FAS Study B9991001



Number of Subjects at Risk

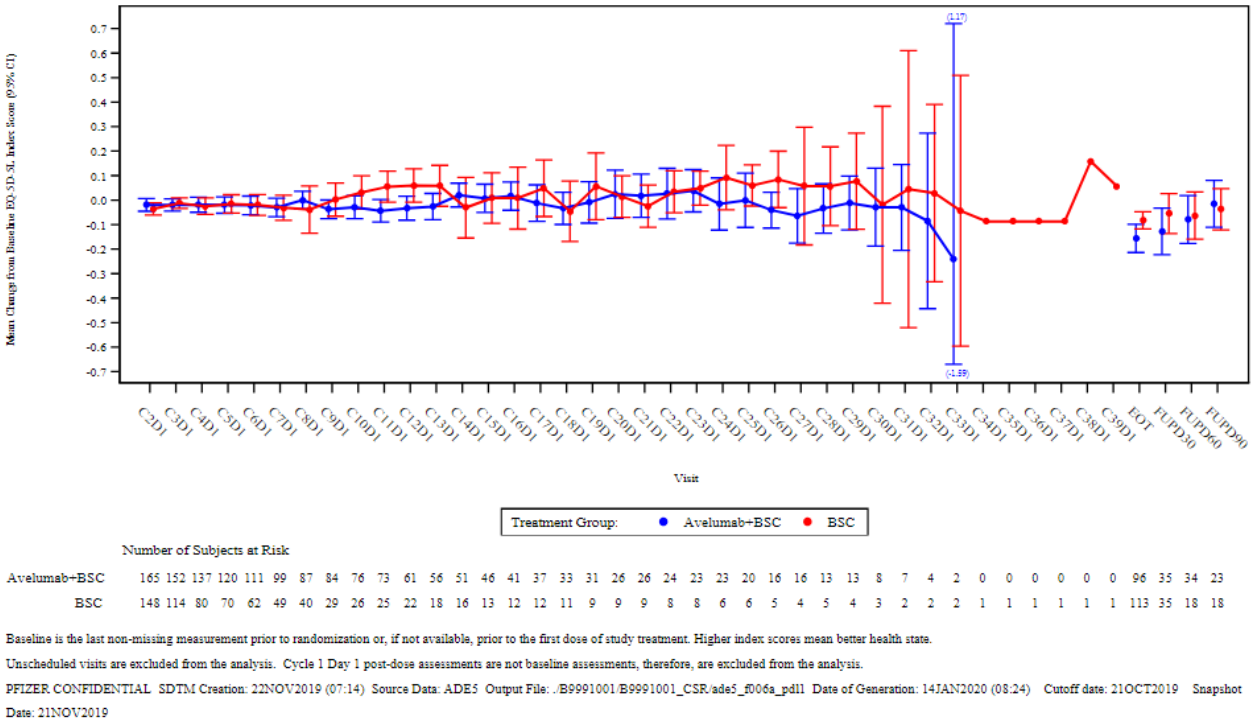
Avelumab+BSC	310	273	244	208	181	164	144	134	124	120	103	97	88	81	70	65	58	49	44	44	40	37	35	27	24	21	19	18	12	11	6	4	2	2	1	1	1	1	1	193	69	58	38
BSC	298	221	154	123	111	84	67	55	49	47	43	34	32	28	26	23	21	18	16	16	15	14	10	11	6	5	7	6	5	2	2	2	1	1	1	1	1	1	0	238	56	30	30

Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher index scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADE5 Output File: ./B9991001/B9991001_CSR/ade5_f006a Date of Generation: 14JAN2020 (08:22) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Figure 43. Summary of EQ-5D-5L Index Score Change from Baseline by Visit – Subjects with PD-L1-positive Tumours FAS Study B9991001



Baseline is the last non-missing measurement prior to randomization or, if not available, prior to the first dose of study treatment. Higher index scores mean better health state.

Unscheduled visits are excluded from the analysis. Cycle 1 Day 1 post-dose assessments are not baseline assessments, therefore, are excluded from the analysis.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADE5 Output File: ./B9991001/B9991001_CSR/ade5_f006a_pdl1 Date of Generation: 14JAN2020 (08:24) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Exploratory Endpoints

Data for exploratory endpoints were not available at the time of the interim analysis.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37. Summary of efficacy for Study B9991001

Title: A phase 3, multicenter, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy		
Study identifier	Study B9991001, (JAVELIN Bladder 100)	
Design	A multicentre randomized, open label study for avelumab+BSC compared to BSC	
	Duration of main phase:	FPI: May 2016 LPI: June 2019
Hypothesis	Superiority	
Treatments groups	Avelumab+BSC – All subjects	Maintenance avelumab 10 mg/kg Q2W, continued until confirmed disease progression as assessed by BICR or unacceptable toxicity, n=350

	BSC – All subjects		Per current treatment practices investigational site and per individual patient needs. BSC did not include any active anti-tumour therapy. Until disease progression or start of active anti-cancer treatment, n=350
	Avelumab+BSC – PD-L1-positive tumour		Maintenance avelumab 10 mg/kg Q2W, continued until confirmed disease progression as assessed by BICR or unacceptable toxicity, n=189
	BSC – PD-L1-positive tumour		Per current treatment practices investigational site and per individual patient needs. BSC did not include any active anti-tumour therapy. Until disease progression or start of active anti-cancer treatment, n=169
Endpoints and definitions	Co-Primary endpoint	OS in: 1. patients with PD-L1-positive tumours 2. all randomized patients	Time from the date of randomization to the date of death due to any cause.
	Secondary endpoint	Progression Free Survival Based on BICR Assessment per RECIST v1.1.	Time from the date of randomization to the date of the first documentation of progressive disease (PD) or death due to any cause, whichever occurs first.
	Secondary endpoint	Objective Response (OR), as assessed per RECIST v1.1 by BICR.	Complete response (CR), or partial response (PR), from the date of randomization, until the date of the first documentation of PD.
Database lock	*21 Oct. 2019 (efficacy, interim analysis), 19 Jan. 2020 (updated OS analysis)*		

Results and Analysis

Analysis description	**Updated OS (19 Jan 2020), PFS and OR Interim Analysis (21 Oct. 2020)**			
Analysis population and time point description	Intent to treat (FAS), Interim analysis			
Descriptive statistics and estimate variability	Treatment group	**Avelumab+BSC – All subjects**	**BSC – All subjects**	Hazard Ration/ p-value (1-sided)
	Number of subjects	350	350	700
	OS (Median, months, 1-sided p: 2-sided P)	22.1	14.6	0.70 p=0.0004 p=0.0008
	95% CI	(19.0, 26.1)	(12.8, 17.8)	(0.564, 0.862)
	PFS (Median, months)	3.7	2.0	0.62 p= <0.0001
	95% CI	(3.5, 5.5)	(1.9, 2.7)	(0.519, 0.751)
	OR (CR+PR, n (%))	34 (9.7)	5 (1.4)	NA

	95% CI	(6.8, 13.3)	(0.5, 3.3)	NA
	Treatment group	**Avelumab+BSC –PD-L1-positive tumours**	**BSC –PD-L1-positive tumours**	Hazard Ration/ p-value
	Number of subjects	189	169	358
	OS (Median, months, 1-sided p; 2-sided p)	NE	17.5	0.60 p=0.0010 p=0.0019
	95% CI	(20.6, NE)	(13.5, 31.6)	(0.439, 0.833)
	PFS (Median, months)	5.7	2.1	0.56 p= <0.0001
	95% CI	(3.7, 7.4)	(1.9, 3.5)	(0.431, 0.728)
	OR (CR+PR, n (%))	26 (13.8)	2 (1.2)	NA
	95% CI	(9.2, 19.5)	(0.1, 4.2)	NA
Notes				
Analysis description				

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The applicant provided data from a single phase 3 study, study B9991001 (JAVELIN Bladder 100), to support the proposed use of avelumab as maintenance treatment in patients with locally advanced or metastatic UC. The rationale for conducting an open trial is acknowledged. Eligibility criteria are considered acceptable. Measures taken to maintain objectivity by independent reviewers are noted. Data provided are from the interim analysis that was to be performed after 315 deaths, all patients had been randomized and at least 146 deaths among patients with PD-L1-positive tumours. The final analysis was planned to be performed after at least 425 of all randomized patients and at least 219 patients with PD-L1-positve tumours had died, and the last randomized patient has been followed for at least 12 months after randomization.

700 patients were randomized, and the randomization was stratified by best response to first-line chemotherapy (CR or PR vs SD), and metastatic disease site (visceral vs non-visceral) at the time of initiating first-line chemotherapy.

The primary objective of study B9991001 was to demonstrate the benefit of maintenance treatment with avelumab plus BSC versus BSC alone in prolonging OS in each coprimary aUC patient population: 1) all randomized patients and 2) patients determined to have PD-L1 positive tumours. To analyse the PD-L1 positive tumours separately is also appropriate. However, it is of importance that the efficacy in the entire population is evident also for patients without PD-L1 positive tumours in order to convincingly establish that the positive benefit-risk ratio is detected also in this patient population. Secondary and exploratory objectives are considered acceptable. In general, the assumptions in the sample size calculations seem overall reasonable.

12.0% of the patients in the avelumab plus BSC and 20.0% in the BSC group did not meet the inclusion/exclusion criteria. This is of concern and introduces uncertainty towards the integrity of the study. However, a sensitivity analysis has been performed considering actual strata. This is almost completely overlapping with the primary OS analysis with a slight moderation of the stratified analysis with no clinical relevance. The results were also similar when patients with the clinically most important protocol deviations were removed as a sensitivity analysis.

The amendments introduced in the study protocol are overall acceptable, and they are not considered to have compromised the integrity of the study or been driven by knowledge of study results.

Potential important protocol deviations occurred in 38.9% of the patients in the study. The protocol deviations were generally quite evenly distributed between the treatment arms. The high number of randomization and inclusion/exclusion deviations are concerning. However, a sensitivity analysis has been performed considering actual strata. This is almost completely overlapping with the primary OS analysis with a slight moderation of the stratified analysis with no clinical relevance. The results were also similar when patients with the clinically most important protocol deviations were removed as a sensitivity analysis.

Baseline demographics and disease characteristics were generally balanced across the treatment arms in all the randomized patients. 77.3% of the patients were male in total and the mean and median age was 67.5 and 69.0 years respectively. 60.6% of the patients had ECOG performance status of 0 at baseline. There are however more patients under 65 years of age in the avelumab plus BSC group. For patients with PD-L1-positive tumours, the age is more homogenous between the two groups, albeit a slight tendency towards a larger proportion of patients under 65 years of age appears also here in the avelumab +BSC arm. PD-L1 status was unknown in 14..0% patients in the BSC arm which is more than double the proportion of unknowns in the avelumab plus BSC treatment group. In both coprimary populations, approximately three-quarters of patients in each arm entered the study with a best response to first-line chemotherapy of CR or PR, and approximately one-quarter of patients entered with a best response of SD. The patients with CR and PR are evenly distributed between the treatment groups for the different PD-L1-statuses. It is noted that the proportion of patients with CR is lower for patients with PD-L1-negative tumours ((18.5%) compared to patients with PD-L1-positive tumours (31.6%).

The choice of not randomizing for PD-L1-status introduced larger uncertainty in the interpretation of the results and a larger risk for non-comparable patient populations between treatment options.

Efficacy data and additional analyses

For OS, results from two data cut-offs are available, including a requested later cut-off 90 days after the pre-planned interim analysis (19 January 2020), while the results from all other efficacy endpoints stem from the interim analysis (21 October 2019).

Efficacy data are provided from the interim analysis for PFS (both BICR and INV), overall response, objective response, disease control rate and subgroup analyses of PFS and OS. In addition, data from two PRO instrumentshave been presented.

The primary endpoint OS (21 Oct 2019) was improved in a statistically significant way in all patients (n=700) assigned to avelumab plus BSC compared with patients assigned to BSC (stratified HR 0.69; 95% CI 0.556, 0.863; 1-sided p-value 0.0005). The median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC arm. In patients with PD-L1-positive tumours (n=358), a statistically significant improvement in OS was also demonstrated for patients assigned to avelumab plus BSC compared with patients assigned to BSC

(stratified HR 0.56; 95% CI: 0.404, 0.787; 1-sided p -value 0.0003). The median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab plus BSC arm, and was 17.1 months (95% CI: 13.5, 23.7) in the BSC arm.

The updated OS-data (19 Jan 2020) with an additional 90 days of follow-up rendered a median OS for all patients assigned to avelumab plus BSC of 22.1 months (95% CI 19.0, 26.1) and for patients treated with BSC of 14.6 months (95% CI 12.8, 17.8) and HR 0.70 (95% CI 0.564, 0.862). For patients with PD-L1-positive tumours the updated median OS was NE (95% CI 20.6, NE) for patients treated with avelumab plus BSC and 17.5 months (95% CI 13.5, 31.6) for the BSC patients, HR 0.60 (95% CI 0.439, 0.833). The OS results from the later data cut-off date are very similar to the results presented from the planned data cut-off date.

In all randomized patients, those assigned to avelumab plus BSC had a prolonged PFS (by BICR assessment per RECIST v1.1), compared with patients assigned to BSC with stratified HR 0.62 (95% CI: 0.519, 0.751; nominal 1-sided p value <0.0001). The median PFS for avelumab plus BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC 2.0 months (95% CI: 1.9, 2.7) in all randomized patients. In patients with PD-L1-positive tumours, the median PFS for avelumab plus BSC was 5.7 months (95% CI: 3.7, 7.4) and for BSC 2.1 months (95% CI: 1.9, 3.5) with stratified HR 0.56 (95% CI 0.431, 0.728; 1-sided p-value <0.0001).

OS and PFS for patients with PD-L1-negative tumours were exploratory analysis and part of the subgroup analysis. OS and PFS for patients with PD-L1-unknown tumours (n=72) were not prespecified endpoints. In patients with PD-L1-negative tumours (n=270), the median OS (19 Jan 2020) was 18.9 months (95% CI 13.3, 22.1) for patients treated with avelumab plus BSC and for BSC 13.4 months (95% CI 10.4, 17.3), with a HR 0.83 (95% CI 0.603, 1.131). There were no signs of a detrimental effect on OS in patients with PD-L1-negative tumours treated with avelumab plus BSC compared to BSC. PFS by BICR assessment for patients with PD-L1-negative tumours was prolonged for patients treated with avelumab in combination with BSC (3.6 months (95% CI 1.9, 16.7)) compared to BSC (2.1 months (95% CI 1.9, 6.8), HR 0.63 (95% CI 0.474, 0.847)). Subgroup analysis of PFS for patients with PD-L1-negative tumours should be interpreted with caution weighing in the small sample size and the risk of chance findings. Generally, the different subgroups present with HR of ≤1 with wide confidence intervals suggesting no identified subgroup with a seemingly detrimental PFS.

ORR was higher in patients treated with avelumab plus BSC compared to patients assigned to BSC, for all randomized patients and for patients with PD-L1-positive tumours. The proportion of patients with PD-L1-negative tumours that achieved objective response was higher for the patients treated with avelumab in combination with BSC, but the absolute numbers are low with 8 patients (5.8%, 95% CI 2.5, 11.0) achieving objective response.

PD-1 or PD-L1 inhibitors were administered as subsequent anti-cancer drug treatments in a higher proportion of patients in the BSC alone arm compared with the avelumab plus BSC arm in all patients and in each PD-L1-strata. Few patients (6.3%) treated with avelumab plus BSC received PD-1 or PD-L1 inhibitor as subsequent anti-cancer therapy while a considerable proportion (43.7%) of patients from the BSC arm were treated with a PD-1 or PD-L1 inhibitor as subsequent anti-cancer therapy. The analysis of time to end-of-next-line treatment (as an approximation for PFS2) for all patients and in each PD-L1-strata do not imply a detrimental effect on time to end-of-next-line treatment. This supports the apparent lack of a detrimental effect of avelumab on OS for the patients with PD-L1-negative tumours.

Subgroup analysis of OS for all patients and for patients with PD-L1-positive tumours display no detrimental effect in any subgroup of reasonable size. Subgroup analysis of OS for patients with PD-

L1-negative tumours (data not shown) generally present with HR of ≤1, albeit with large confidence intervals due to small patient numbers and more heterogeneity compared to the PFS subgroup results. It is also notable that for the subgroups of PD-L1 negative patients where the HR for OS is ≥1, the HR for PFS is <1.

The efficacy data from patients with PD-L1-unknown tumours are challenging to interpret due to very low patient numbers. However, no evident detrimental effect on PFS or OS is seemingly detected in patients with PD-L1-unknown tumours.

A majority of the patients continued with anti-PD-L1 treatment after progression. The median number of infusions received after progression was 3.0 across all PD-L1-strata, the mean was 5.4 (SD 7.09) for patients with PD-L1-positive tumours and 6.4 (SD 10.41) for patients with PD-L1-negative tumours. The posology proposed state that treatment should continue until progression or unacceptable toxicity. We currently have no indication that the OS efficacy is driven by the post-progression treatment.

PRO

The results for the PRO NCCN/FACT Bladder Symptom Index (NFB1SI-18) and EQ-5D-5L) do not imply that addition of avelumab to BSC conferred a detrimental effect on the quality of life of patients. These results should however be interpreted with caution due to the open label study design and imputation of answers in the analyses for NFB1SI-18. The results from the EQ-5D-5L form do not suggest that the avelumab addition to BSC conferred a detrimental effect of the quality of life for the patients. However, due to the open-label study design the results are open to patient bias, conferring a degree of uncertainty.

2.4.3. Conclusions on the clinical efficacy

Based on the currently provided data, a benefit for the addition of avelumab as a maintenance treatment has been demonstrated in the overall population. Although this OS benefit is not solely driven by the PD-L1-positive tumour population, the benefit of the addition of avelumab to BSC for patients with PD-L1-negative tumours is less pronounced. Patients with PD-L1-negative tumours on a group level display a modest prolongation of PFS in combination with no display of detrimental effect on OS.

2.5. Clinical safety

Introduction

Safety data are presented for the use of avelumab plus BSC vs. BSC as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy (study B9991001). Safety data from study EMR100070-001 included two cohorts (secondary expansion n=44; efficacy expansion n=205) where patients with aUC had progressive disease and the majority having received 2 or more lines of prior therapy are also presented. Study B9991001 and study EMR100070-001 are not pooled as the MAH considers the populations to be different. Study EMR100070-001 enrolled heavily pre-treated patients whereas study B9991001 enrolled patients with aUC who had received only 1 line of chemotherapy without PD.

Safety database cut-off date was January 19, 2020 (12 weeks after primary efficacy cut-off date).

The safety database includes data from 689 patients, who received any amount of study treatment in study B9991001 (344 patients treated with avelumab plus BSC; 345 in the BSC arm). The Pooled Safety Data that consists of data from 1738 patients treated with avelumab 10 mg/kg Q2W as a single agent (1650 patients with various solid tumours from study EMR100070-001, including the 249 patients from the aUC cohorts, and 88 patients with mMCC from Part A of Study EMR100070-003 with a data cut-off of 09 June 2016) are presented for reference. Study EMR100070-003, the pivotal study for the mMCC indication, is an open-label, multicentre, single arm study in patients with mMCC.

The safety profile of avelumab has been described previously when used as monotherapy for mMCC. The general class safety profile for PD-L1-inhibitors is considered well known.

Table 38 . Summary of studies with Single-Agent Avelumab contributing to the safety evaluation

Protocol Number/ Study Design/ Sponsor	Primary Objective(s)/ Key Secondary Objectives (if applicable)/ Primary Endpoint(s)	Single or Multicenter/ Location Planned Countries	Status[a]/ Dates	No. of Patients Treated/ Doses Evaluated
B9991001 Phase 3, multicenter, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy Pfizer Inc.	Primary Objective: To demonstrate the benefit of maintenance treatment with avelumab plus BSC versus BSC in prolonging OS in 2 co-primary aUC patient populations: 1) patients determined to have PD-L1-positive tumours (including infiltrating immune cells) by a verified GMP PD-L1 IHC test, and 2) all randomized patients Primary Endpoint: OS	187 centers North America, Central/South America, Asia-Pacific including Japan, and Europe	Completed FPFD: May 2016 Data cut-off date efficacy: 21 Oct 2019 Data cut-off date safety: 19 Jan 2020	1:1 randomization of 700 patients to 2 treatment arms including 689 patients in the safety data set Avelumab plus BSC arm (344 patients) BSC alone arm (345 patients) Avelumab dose: 10 mg/kg IV Q2W
Study EMR100070-003 Phase 2, single arm, open-label, multicenter study to investigate the clinical activity and safety of avelumab in subjects with Merkel cell carcinoma Merck KGaA/EMD Serono	Part A - Primary Objective: To assess the clinical activity of avelumab in patients with mMCC whose disease progressed during or after receiving chemotherapy (Part A) or in systemic chemotherapy naïve patients with mMCC (Part B) Primary Endpoint: ORR for Part A; Durable response rate for Part B	Part A: 38 centers Part B: 46 centers US, Australia, Europe, and Asia	Completed Part A First patient informed consent: 03 Jul 2014 Part B First patient informed consent: 31 Mar 2016	As of 02 May 2019: Part A: 88 patients Part B: 116 patients (not included in the safety evaluations) Avelumab dose: 10 mg/kg IV Q2W

EMR100070-001 Phase 1, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pk, biological and clinical activity of avelumab and expansion to selected indications in subjects with metastatic or locally advanced solid tumours Merck KGaA/EMD Serono	Primary Objective: To assess the safety and tolerability of avelumab and to determine the MTD of avelumab; To assess the best overall response according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) in the efficacy expansion cohorts Primary Endpoints: Dose-escalation part: Occurrence of DLTs during the first 3 weeks of treatment Efficacy expansion cohorts: Confirmed best overall response, per RECIST v1.1, as adjudicated by an Independent Endpoint Review Committee	Patients with aUC were enrolled at 1 center for dose-escalation and 89 centers for treatment expansion) US, Europe, and Asian Countries	Completed Dose-escalation: First patient informed consent date: 31 Jan 2013 First aUC cohort patient informed consent date: 03 Sep 2014 Data cut-off date for aUC cohorts: 31 March 2017	As of 27 Apr 2018: 1758 patients (1650 included in the safety evaluations) Dose Escalation Phase: 61 patients • 1 mg/kg Q2W - 4 • 3 mg/kg Q2W - 13 • 10 mg/kg Q2W - 15 • 10 mg/kg weekly - 8 • 20 mg/kg Q2W - 21 Expansion Phase: 1697 patients • aUC secondary expansion cohort – 44 (2 active as of 27 Aug 2019) • aUC efficacy expansion cohort – 205 (2 active as of 27 Aug 2019) Dose selected for Expansion Phase: 10 mg/kg Q2W

a. "Completed" refers to a study for which the primary analysis has been conducted and a CSR finalized; patients enrolled in these studies may still be receiving treatment or continue to be followed for safety and survival data per protocol. "Ongoing" refers to a study for which the primary analysis has not been conducted.

Patient exposure

The median treatment duration in study B9991001 was 25.3 weeks (range: 2.0, 173.9) in the avelumab plus BSC arm and considerably shorter, 13.1 weeks (range: 0.1, 168.4) in the BSC alone arm (19 Jan 2020). The following results are presented with data from 21 October 2019 cut-off. Mean number of infusions with avelumab in study B9991001 was 18.4 (SD 16.26) with a wide interval for standard deviation. The median number of avelumab infusions was 11.0 (range 1.0, 80.0). 45.9% of the patients treated with avelumab experienced dose delays. Few patients had dose reductions which is to be expected with the study design not permitting dose modifications. 9.3% of the avelumab patients in study B9991001 had at least one infusion rate reduction of 50% or more. 6.4% had 4 or more infusion rate reductions. 4.7% had infusion interruptions.

Patients with PD-L1-positive tumours were exposed to avelumab for longer time compared to patients with PD-L1-negative tumours.

The duration of treatment is longer and cumulative dose is higher in study B99910001 compared to the reported safety set.

Table 39. Duration and extent of exposure to study drug

	B9991001 Avelumab+ BSC (N=344)	B9991001 BSC (N=345)	Pooled Safety Population (N=1738)	Overall (N=2082)
Duration of treatment (weeks)[1]				
N	344	345	1738	2082
Mean (SD)	38.7 (33.74)	23.2 (24.59)	19.9 (20.69)	23.0 (24.37)
Q1	13.2	8.4	6.0	6.1
Median	24.9	13.1	12.0	12.6
Q3	57.9	26.7	24.1	30.0
Range (min, max)	(2.0, 159.9)	(0.1, 155.6)	(2.0; 137.9)	(2.0; 159.9)
Person exposure-100 years [2]	2.55	1.53	6.63	9.18
Cumulative dose (mg/kg) [3]				
N	344	NA	1738	2082
Mean (SD)	182.6 (161.6)	NA	95.8 (99.37)	110.1 (116.56)
Q1	60.0	NA	30.0	30.1
Median	112.6	NA	60.0	60.1
Q3	266.7	NA	120.1	140.3
Range (min, max)	(1.6, 787.7)	NA	(3.0; 630.1)	(1.6; 787.7)
Dose intensity (mg/kg/cycle) [4]				
N	344	NA	1738	NA
Mean (SD)	16.9 (2.56)	NA	9.7 (0.84)	NA
Q1	16.0	NA	9.7	NA
Median	17.6	NA	10.0	NA
Q3	18.7	NA	10.0	NA
Range (min, max)	(1.6, 20.4)	NA	(3.0; 11.2)	NA
Relative dose intensity (%) [5]				
N	344	NA	1738	2082
Mean (SD)	84.6 (12.82)	NA	96.7 (8.44)	94.7 (10.33)
Q1	80.0	NA	96.6	92.3
Median	88.2	NA	100	99.9
Q3	93.5	NA	100.2	100.0
Range (min, max)	(8.0, 102.1)	NA	(30.0; 112.0)	(8.0; 112.0)

N is the number of subjects in the safety analysis set within each treatment group.

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab – first dose date of avelumab + 14)/7.

Duration of BSC treatment is defined as Duration (weeks) = (end date of BSC – start date of BSC + 1)/7

[2] Person exposure-100 years = Sum of duration of exposure (in days) to study drug for all patients / (100*365.25).

[3] Cumulative dose (mg/kg) = sum of all doses (mg/kg) of avelumab.

[4] Dose Intensity (mg/kg/cycle) = [Overall cumulative dose (mg/kg)] / [(intended duration of avelumab treatment (weeks)/cycle length]. Dose Intensity is calculated as mg/kg/4-week cycle for Study B9991001 and as mg/kg/2-week cycle for the Pooled Safety Population, therefore Dose Intensity for the Overall is not available.

[5] Relative Dose Intensity (%) = 100 × [Dose Intensity (mg/kg/cycle)] / [intended dose (mg/kg/cycle)]

The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of study drug.

Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21OCT2019 on study B9991001

Table 40. Exposure to avelumab – SAS Study B9991001

	Avelumab+BSC (N=344)
Duration of treatment (weeks)[1]	
n	344
Mean (SD)	38.7 (33.74)
Q1	13.2
Median	24.9
Q3	57.9
Range (min, max)	(2.0, 159.9)
Total number of infusions received	
n	344
Mean (SD)	18.4 (16.26)
Q1	6.0
Median	11.0
Q3	27.0
Range (min, max)	(1.0, 80.0)
Number of cycles [2]	
n	344
Mean (SD)	9.8 (8.39)
Q1	3.0
Median	6.0
Q3	14.0
Range (min, max)	(1.0, 40.0)
Subjects starting [2], n (%)	
1 cycle	344 (100.0)
2 cycles	325 (94.5)
3 cycles	296 (86.0)
4 cycles	256 (74.4)
5 cycles	218 (63.4)
6 cycles	193 (56.1)
7 cycles	171 (49.7)
8 cycles	158 (45.9)
≥9 cycles	148 (43.0)

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab – first dose date of avelumab + 14)/7
[2] Includes cycles with missed doses of avelumab
[3] Includes only cycles with at least one dose of avelumab > 0
The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADEX Output File: ./B9991001/B9991001_CSR/adex_s001a Date of Generation: 14JAN2020 (09:05) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Table 41. Dose modifications – SAS Study B9991001.

	Avelumab+BSC (N=344) n (%)
Duration of dose delays [1]	
No Delay	186 (54.1)
0 days	81 (23.5)
1 - 3 days	105 (30.5)
Dose delays	158 (45.9)
4 - 6 days	28 (8.1)
≥7 days	130 (37.8)

Table 41. Dose modifications – SAS Study B9991001.

	Avelumab+BSC (N=344) n (%)
Subjects with at least one dose reduction [2]	11 (3.2)
1 reduction	10 (2.9)
2 reductions	1 (0.3)
3 reductions	0
≥4 reductions	0
Subjects with at least one infusion rate reduction of 50% or more [3]	32 (9.3)
1 infusion rate reduction	7 (2.0)
2 infusion rate reductions	1 (0.3)
3 infusion rate reductions	2 (0.6)
≥4 infusion rate reductions	22 (6.4)
Subjects with at least one infusion interruption [4]	16 (4.7)
1 infusion interruption	14 (4.1)
2 infusion interruptions	2 (0.6)
3 infusion interruptions	0
≥4 infusion interruptions	0

[1] Dose delay is the difference between the actual time between two consecutive non-zero doses and the planned time between the same two consecutive non-zero doses. A delay of 1-3 days is not counted as a delay.
[2] Dose reduction is defined as actual non-zero dose < 90% of the planned dose.
[3] Infusion rate reduction is defined as decrease in the infusion rate by 50% or more compared to the first infusion rate.
[4] An infusion interruption is defined as an infusion that is stopped and re-started on the same day.
The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
Cut-off date: 21OCT2019

Table 42. Exposure to Study Drugs - All Subjects and Subjects with PD-L1-Positive Tumours in the Safety Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=344)	BSC (N=345)	Avelumab+BSC (N=187)	BSC (N=167)
Duration of treatment (weeks)[1]				
N	344	345	187	167
Mean (SD)	41.5 (37.13)	24.1 (26.89)	45.2 (38.04)	26.0 (28.28)
Q1	13.2	8.4	14.0	8.9
Median	25.3	13.1	35.1	16.0
Q3	62.0	26.7	64.0	29.1
Range (min, max)	(2.0, 173.9)	(0.1, 168.4)	(2.0, 144.0)	(0.3, 168.4)

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab – first dose date of avelumab + 14)/7
Duration of BSC treatment is defined as Duration (weeks) = (end date of BSC – start date of BSC + 1)/7.
The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of the study drug.
Cutoff date: 19JAN2020

Table 43. Exposure to Study Drugs - Subjects with PD-L1-Negative Tumours and Subjects with PD-L1-Unknown Tumours in the Safety Analysis Set (Protocol B9991001)

	Subjects with PD-L1-Negative Tumours		Subjects with PD-L1-Unknown Tumours	
	Avelumab+BSC (N=137)	BSC (N=131)	Avelumab+BSC (N=20)	BSC (N=47)
Duration of treatment (weeks)[1]				
N	137	131	20	47
Mean (SD)	35.1 (32.99)	19.9 (19.79)	34.4 (31.11)	25.6 (30.13)
Q1	12.4	8.3	9.5	8.1
Median	21.1	13.1	24.1	9.4
Q3	50.3	24.0	45.2	37.1
Range (min, max)	(2.0, 159.9)	(0.1, 118.7)	(4.0, 105.9)	(0.1, 121.1)

[1] Duration of avelumab treatment is defined as Duration (weeks) = (last dose date of avelumab – first dose date of avelumab + 14)/7
Duration of BSC treatment is defined as Duration (weeks) = (end date of BSC – start date of BSC + 1)/7.
The descriptive summary statistics are calculated based on n, the number of subjects who have received at least one dose of the study drug.
Cutoff date: 21OCT2019

Adverse events

Summary of Adverse events

Nearly all patients reported AEs, as expected, with avelumab treatment. The proportion of patients that reported AE of grade 3 or higher was lower in study B9991001 compared to the pooled safety set, 47.4% compared to 58.0% respectively.

The frequency of each AE of grade ≥3 is mostly relatively low in study B9991001 and the pooled safety set. The most common AEs of grade ≥3 for patients in study B9991001 are urinary tract infection and anaemia. Generally, the frequency is lower with the exception of urinary tract infection and haematuria when comparing study B9991001 to the pooled safety set. The general frequency of AEs of any grade differs slightly from the pooled safety set in study B9991001 but does not raise serious concerns and the deviations go both ways.

Exposure adjusted data does not indicate that treatment of the new suggested indication would confer a more serious AE profile. The incident rate per 100 patient months (IR) are similar or appear lower for study B9991001 compared to the pooled safety population for the overview of safety parameters (Table 46), most common AE (Table 51) with a few exceptions where the IR frequency is higher.

Table 44. Summary of adverse events – SAS Study B9991001.

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=344)	BSC (N=345)	Avelumab+BSC (N=187)	BSC (N=167)
Number (%) of Subjects	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with TEAEs	337 (98.0)	268 (77.7)	186 (99.5)	133 (79.6)
Subjects with grade ≥ 3 TEAEs	163 (47.4)	87 (25.2)	94 (50.3)	40 (24.0)
Subjects with treatment-related TEAEs	266 (77.3)	4 (1.2)	150 (80.2)	2 (1.2)
Subjects with grade ≥ 3 treatment-related TEAEs	57 (16.6)	0	36 (19.3)	0
Subjects with serious TEAEs	96 (27.9)	69 (20.0)	51 (27.3)	34 (20.4)
Subjects with serious treatment-related TEAEs	31 (9.0)	0	20 (10.7)	0
Subjects with TEAEs leading to dose reduction of Avelumab	1 (0.3)	0	0	0
Subjects with TEAEs leading to interruption of Avelumab	140 (40.7)	0	81 (43.3)	0
Subjects with TEAEs leading to discontinuation of study drug	41 (11.9)	0	28 (15.0)	0
Subjects with treatment-related TEAEs leading to discontinuation of study drug	33 (9.6)	0	25 (13.4)	0
Subjects with TEAEs leading to death	4 (1.2)	24 (7.0)	2 (1.1)	13 (7.8)
Subjects with treatment-related TEAEs leading to death	1 (0.3)	0	1 (0.5)	0
Subjects with immune-related adverse events (irAEs)	101 (29.4)	5 (1.4)	63 (33.7)	2 (1.2)
Subjects with infusion-related reactions (IRRs)	74 (21.5)	0	40 (21.4)	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 SCS/adae s012 pdl1c Date of Generation: 16JAN2020 (14:51) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.1.1.1 is for Pfizer internal use.

Table 45. Summary of AE – Pooled safety set and avelumab treated in Study B9991001.

Table 12.13.9 : Overview of Treatment Emergent Adverse Events

	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n(%)
Subjects with TEAEs	1697 (97.6)	337 (98.0)	2034 (97.7)
Subjects with grade >= 3 TEAEs	1008 (58.0)	163 (47.4)	1171 (56.2)
Subjects with treatment-related TEAEs	1164 (67.0)	266 (77.3)	1430 (68.7)
Subjects with grade >= 3 treatment-related TEAEs	177 (10.2)	57 (16.6)	234 (11.2)
Subjects with serious TEAEs	777 (44.7)	96 (27.9)	873 (41.9)
Subjects with serious treatment-related TEAEs	108 (6.2)	31 (9.0)	139 (6.7)
Subjects with TEAEs leading to dose reduction of Avelumab	NA	1 (0.3)	1 (0.0)
Subjects with TEAEs leading to interruption of Avelumab	363 (20.9)	140 (40.7)	503 (24.2)
Subjects with TEAEs leading to discontinuation of study drug	244 (14.0)	41 (11.9)	285 (13.7)
Subjects with treatment-related TEAEs leading to discontinuation of study drug	107 (6.2)	33 (9.6)	140 (6.7)
Subjects with TEAEs leading to death	228 (13.1)	4 (1.2)	232 (11.1)
Subjects with treatment-related TEAEs leading to death	4 (0.2)	1 (0.3)	5 (0.2)
Subjects with immune-related adverse events (irAEs)	247 (14.2)	101 (29.4)	348 (16.7)
Subjects with infusion-related reactions (IRRs)	439 (25.3)	74 (21.5)	513 (24.6)

NA = Information not available in Safety set.
N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
Events are coded in the latest MedDRA version available at the time of cut-off.
Grading categories determined using NCI-CTCAE version 4.0 in pooled safety population and version 4.03 in B9991001.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 46 Exposure-Adjusted Analysis of Summary of Adverse Event - Pooled Safety Population and Avelumab-Treated Patients in Study B9991001

	Pooled Safety Population (N=1738) PM (IR)	B9991001 Avelumab + BSC (N=344) PM (IR)	Overall (N=2082) PM (IR)
Subjects with TEAEs	844.6 (200.9)	350.8 (96.1)	1195.4 (170.2)
Subjects with grade ≥3 TEAEs	5973.6 (16.9)	2224.5 (7.3)	8198.0 (14.3)
Subjects with treatment-related TEAEs	3042.9 (38.3)	1030.6 (25.8)	4073.5 (35.1)
Subjects with grade ≥3 treatment-related TEAEs	8190.8 (2.2)	2912.4 (2.0)	11103.2 (2.1)
Subjects with serious TEAEs	7007.3 (11.1)	2685.4 (3.6)	9692.7 (9.0)
Subjects with serious treatment-related TEAEs	8340.3 (1.3)	3055.2 (1.0)	11395.5 (1.2)
Subjects with TEAEs leading to interruption of Avelumab	7261.7 (5.0)	2304.1 (6.1)	9565.8 (5.3)
Subjects with TEAEs leading to discontinuation of study drug	8363.7 (2.9)	3140.6 (1.3)	11504.3 (2.5)
Subjects with treatment-related TEAEs leading to discontinuation of study drug	8437.4 (1.3)	3144.5 (1.0)	11581.9 (1.2)
Subjects with TEAEs leading to death	8469.7 (2.7)	3174.2 (0.1)	11644.0 (2.0)
Subjects with treatment-related TEAEs leading to death	8514.5 (0.0)	3174.2 (0.0)	11688.7 (0.0)
Subjects with immune-related adverse events (irAEs)	7436.6 (3.3)	2435.7 (4.1)	9872.3 (3.5)
Subjects with infusion-related reactions (IRRs)	6446.4 (6.8)	2600.1 (2.8)	9046.5 (5.7)

irAEs = Immune-related adverse events.
IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure
The exposure-adjusted incidence rate is defined as the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial occurrence of AE.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 47 Exposure-adjusted analysis of Summary of Adverse Events –All Subjects and Subjects with PD-L1-Positive Tumours in the Safety Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=344)	BSC (N=345)	Avelumab+BSC (N=187)	BSC (N=167)
Number (IR) of Subjects	**PM (IR)**	**PM (IR)**	**PM (IR)**	**PM (IR)**
Subjects with TEAEs	350.8 (96.1)	737.0 (36.4)	166.2 (111.9)	373.4 (35.6)
Subjects with grade ≥ 3 TEAEs	2224.5 (7.3)	1827.6 (4.8)	1201.6 (7.8)	953.7 (4.2)
Subjects with treatment-related TEAEs	1030.6 (25.8)	2014.0 (0.2)	549.1 (27.3)	1048.1 (0.2)
Subjects with grade ≥ 3 treatment-related TEAEs	2912.4 (2.0)	2033.1 (0.0)	1660.4 (2.2)	1056.3 (0.0)
Subjects with serious TEAEs	2685.4 (3.6)	1853.2 (3.7)	1535.8 (3.3)	960.4 (3.5)
Subjects with serious treatment-related TEAEs	3055.2 (1.0)	2033.1 (0.0)	1761.1 (1.1)	1056.3 (0.0)
Subjects with TEAEs leading to dose reduction of Avelumab	3171.2 (<0.1)	2033.1 (0.0)	1851.1 (0.0)	1056.3 (0.0)
Subjects with TEAEs leading to interruption of Avelumab	2304.1 (6.1)	2033.1 (0.0)	1223.5 (6.6)	1056.3 (0.0)
Subjects with TEAEs leading to discontinuation of study drug	3140.6 (1.3)	2033.1 (0.0)	1825.2 (1.5)	1056.3 (0.0)
Subjects with treatment-related TEAEs leading to discontinuation of study drug	3144.5 (1.0)	2033.1 (0.0)	1826.4 (1.4)	1056.3 (0.0)
Subjects with TEAEs leading to death	3174.2 (0.1)	2033.1 (1.2)	1851.1 (0.1)	1056.3 (1.2)
Subjects with treatment-related TEAEs leading to death	3174.2 (<0.1)	2033.1 (0.0)	1851.1 (<0.1)	1056.3 (0.0)
Subjects with immune-related adverse events (irAEs)	2435.7 (4.1)	2011.7 (0.2)	1349.9 (4.7)	1047.6 (0.2)
Subjects with infusion-related reactions (IRRs)	2600.1 (2.8)	2033.1 (0.0)	1542.5 (2.6)	1056.3 (0.0)

IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure
The exposure-adjusted incidence rate is defined as the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial
occurrence of AE.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
Cutoff date: 21OCT2019

There were no major differences with regard to safety based on PD-L1-status.

Summary of most common adverse events

Table 48. Summary of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period – SAS Study B9991001

	All Subjects				Subjects with PD-L1-Positive Tumours			
	Avelumab + BSC (N=344)		BSC (N=345)		Avelumab + BSC (N=187)		BSC (N=167)	
Preferred Term	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Subjects with events	337 (98.0)	163 (47.4)	268 (77.7)	87 (25.2)	186 (99.5)	94 (50.3)	133 (79.6)	40 (24.0)
Fatigue	61 (17.7)	6 (1.7)	24 (7.0)	2 (0.6)	36 (19.3)	2 (1.1)	14 (8.4)	1 (0.6)
Pruritus	59 (17.2)	1 (0.3)	6 (1.7)	0	37 (19.8)	1 (0.5)	2 (1.2)	0
Urinary tract infection	59 (17.2)	15 (4.4)	36 (10.4)	9 (2.6)	38 (20.3)	11 (5.9)	16 (9.6)	3 (1.8)
Diarrhoea	57 (16.6)	2 (0.6)	17 (4.9)	1 (0.3)	32 (17.1)	2 (1.1)	8 (4.8)	0
Arthralgia	56 (16.3)	2 (0.6)	19 (5.5)	0	32 (17.1)	1 (0.5)	5 (3.0)	0
Asthenia	56 (16.3)	0	19 (5.5)	4 (1.2)	30 (16.0)	0	11 (6.6)	3 (1.8)
Constipation	56 (16.3)	2 (0.6)	31 (9.0)	0	35 (18.7)	1 (0.5)	17 (10.2)	0
Back pain	55 (16.0)	4 (1.2)	34 (9.9)	8 (2.3)	33 (17.6)	1 (0.5)	14 (8.4)	3 (1.8)
Nausea	54 (15.7)	1 (0.3)	22 (6.4)	2 (0.6)	31 (16.6)	0	7 (4.2)	0
Pyrexia	51 (14.8)	1 (0.3)	12 (3.5)	0	23 (12.3)	0	6 (3.6)	0
Decreased appetite	47 (13.7)	1 (0.3)	23 (6.7)	2 (0.6)	23 (12.3)	1 (0.5)	10 (6.0)	0
Cough	44 (12.8)	1 (0.3)	16 (4.6)	0	28 (15.0)	0	7 (4.2)	0
Vomiting	43 (12.5)	4 (1.2)	12 (3.5)	2 (0.6)	22 (11.8)	2 (1.1)	3 (1.8)	0
Hypothyroidism	40 (11.6)	1 (0.3)	2 (0.6)	0	21 (11.2)	0	1 (0.6)	0
Rash	40 (11.6)	1 (0.3)	4 (1.2)	0	22 (11.8)	0	2 (1.2)	0
Anaemia	39 (11.3)	13 (3.8)	23 (6.7)	10 (2.9)	17 (9.1)	8 (4.3)	10 (6.0)	5 (3.0)
Haematuria	36 (10.5)	6 (1.7)	37 (10.7)	5 (1.4)	17 (9.1)	2 (1.1)	16 (9.6)	2 (1.2)
Infusion related reaction	35 (10.2)	3 (0.9)	0	0	16 (8.6)	2 (1.1)	0	0
Abdominal pain	31 (9.0)	2 (0.6)	25 (7.2)	7 (2.0)	14 (7.5)	1 (0.5)	17 (10.2)	7 (4.2)
Myalgia	29 (8.4)	0	10 (2.9)	0	20 (10.7)	0	5 (3.0)	0
Lipase increased	17 (4.9)	14 (4.1)	1 (0.3)	1 (0.3)	12 (6.4)	10 (5.3)	0	0

Table 48. Summary of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period – SAS Study B9991001

	All Subjects				Subjects with PD-L1-Positive Tumours			
	Avelumab + BSC (N=344)		BSC (N=345)		Avelumab + BSC (N=187)		BSC (N=167)	
Preferred Term	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)	All Grades n (%)	Grade ≥ 3 n (%)
Disease progression	3 (0.9)	3 (0.9)	16 (4.6)	16 (4.6)	1 (0.5)	1 (0.5)	12 (7.2)	12 (7.2)

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.
Sorted in descending order of the frequency of PTs by All Grades in Avelumab+BSC arm.
MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.
Cut-off date: 21OCT2019 Snapshot Date: 21NOV2019.

Table 49 Exposure-adjusted analysis of Most Common TEAEs (Any Grade in ≥ 10% Subjects or Grade ≥ 3 in ≥ 5% Subjects in Any Treatment Group), by PT and Maximum CTCAE Grade During the On-Treatment Period - All Subjects and Subjects with PD-L1-Positive Tumours in the Safety Analysis Set (Protocol B9991001)

	All Subjects				Subjects with PD-L1-Positive Tumors			
	Avelumab + BSC (N=344)		BSC (N=345)		Avelumab + BSC (N=187)		BSC (N=167)	
Preferred Term	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)
			1.					
Subjects with events	350.8 (96.1)	2224.5 (7.3)	737.0 (36.4)	1827.6 (4.8)	166.2 (111.9)	1201.6 (7.8)	373.4 (35.6)	953.7 (4.2)
Fatigue	2747.6 (2.2)	3165.9 (0.2)	1966.2 (1.2)	2031.6 (<0.1)	1559.0 (2.3)	1849.3 (0.1)	1011.6 (1.4)	1055.4 (<0.1)
Pruritus	2673.8 (2.2)	3172.6 (<0.1)	2005.9 (0.3)	2033.1 (0.0)	1541.0 (2.4)	1849.5 (<0.1)	1040.4 (0.2)	1056.3 (0.0)
Urinary tract infection	2731.1 (2.2)	3062.9 (0.5)	1867.4 (1.9)	2010.0 (0.4)	1572.2 (2.4)	1769.0 (0.6)	978.3 (1.6)	1044.9 (0.3)
Diarrhoea	2753.6 (2.1)	3163.1 (<0.1)	1955.6 (0.9)	2028.2 (<0.1)	1579.1 (2.0)	1840.0 (0.1)	1018.6 (0.8)	1056.3 (0.0)
Arthralgia	2785.0 (2.0)	3168.8 (<0.1)	1922.9 (1.0)	2033.1 (0.0)	1583.4 (2.0)	1850.4 (<0.1)	1024.7 (0.5)	1056.3 (0.0)
Asthenia	2780.9 (2.0)	3174.2 (0.0)	1966.9 (1.0)	2031.4 (0.2)	1625.7 (1.8)	1851.1 (0.0)	1012.2 (1.1)	1054.9 (0.3)
Constipation	2848.3 (2.0)	3171.1 (<0.1)	1928.2 (1.6)	2033.1 (0.0)	1585.7 (2.2)	1850.2 (<0.1)	997.6 (1.7)	1056.3 (0.0)
Back pain	2886.5 (1.9)	3162.8 (0.1)	1895.5 (1.8)	2011.8 (0.4)	1655.8 (2.0)	1842.2 (<0.1)	1015.0 (1.4)	1038.9 (0.3)

Preferred Term	All Subjects				Subjects with PD-L1-Positive Tumors			
	Avelumab + BSC (N=344)		BSC (N=345)		Avelumab + BSC (N=187)		BSC (N=167)	
	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)	All Grades PM (IR)	Grade ≥ 3 PM (IR)
			1.					
Nausea	2841.9 (1.9)	3171.9 (<0.1)	1943.9 (1.1)	2032.0 (<0.1)	1614.4 (1.9)	1851.1 (0.0)	1031.8 (0.7)	1056.3 (0.0)
Pyrexia	2838.4 (1.8)	3173.4 (<0.1)	2001.2 (0.6)	2033.1 (0.0)	1717.2 (1.3)	1851.1 (0.0)	1046.3 (0.6)	1056.3 (0.0)
Decreased appetite	2932.7 (1.6)	3173.3 (<0.1)	1980.2 (1.2)	2032.0 (<0.1)	1690.4 (1.4)	1850.2 (<0.1)	1046.3 (1.0)	1056.3 (0.0)
Cough	2828.4 (1.6)	3173.7 (<0.1)	1972.8 (0.8)	2033.1 (0.0)	1601.3 (1.7)	1851.1 (0.0)	1033.3 (0.7)	1056.3 (0.0)
Vomiting	2954.3 (1.5)	3148.2 (0.1)	1982.1 (0.6)	2032.0 (<0.1)	1716.8 (1.3)	1828.0 (0.1)	1041.5 (0.3)	1056.3 (0.0)
Hypothyroidism	2855.3 (1.4)	3173.6 (<0.1)	2012.5 (<0.1)	2033.1 (0.0)	1618.8 (1.3)	1851.1 (0.0)	1048.8 (<0.1)	1056.3 (0.0)
Rash	2819.2 (1.4)	3168.7 (<0.1)	2005.5 (0.2)	2033.1 (0.0)	1625.8 (1.4)	1851.1 (0.0)	1045.3 (0.2)	1056.3 (0.0)
Anaemia	3044.1 (1.3)	3154.4 (0.4)	1967.7 (1.2)	2023.8 (0.5)	1779.2 (1.0)	1838.2 (0.4)	1034.9 (1.0)	1053.4 (0.5)
Haematuria	3016.3 (1.2)	3152.7 (0.2)	1892.6 (2.0)	2026.3 (0.2)	1757.9 (1.0)	1844.0 (0.1)	985.2 (1.6)	1053.8 (0.2)
Infusion related reaction	2951.0 (1.2)	3171.3 (<0.1)	2033.1 (0.0)	2033.1 (0.0)	1712.0 (0.9)	1849.2 (0.1)	1056.3 (0.0)	1056.3 (0.0)
Abdominal pain	3087.7 (1.0)	3172.9 (<0.1)	1987.4 (1.3)	2026.3 (0.3)	1801.4 (0.8)	1850.2 (<0.1)	1028.8 (1.7)	1049.5 (0.7)
Myalgia	2880.8 (1.0)	3174.2 (0.0)	1995.0 (0.5)	2033.1 (0.0)	1627.3 (1.2)	1851.1 (0.0)	1047.4 (0.5)	1056.3 (0.0)
Lipase increased	3069.1 (0.6)	3102.6 (0.5)	2029.7 (<0.1)	2029.7 (<0.1)	1776.1 (0.7)	1803.7 (0.6)	1056.3 (0.0)	1056.3 (0.0)
Disease progression	3174.2 (<0.1)	3174.2 (<0.1)	2033.1 (0.8)	2033.1 (0.8)	1851.1 (<0.1)	1851.1 (<0.1)	1056.3 (1.1)	1056.3 (1.1)

2. IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure

The exposure-adjusted incidence rate is defined as the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial occurrence of AE.

Subjects reporting more than one adverse event (AE) within a preferred term are counted only once in that preferred term.

Sorted in descending order of the frequency of PTs by All Grades in Avelumab+BSC arm.

MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.

PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (08:14) Source Data: ADAE Output

File: ./B9991001/CHMP_IA/adae_s999b_expadj Date of Generation: 21SEP2020 (11:13) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019

Table 23-3 is for Pfizer internal use.

Table 50. Summary of most common TEAE (Any grade in ≥ 10% Subjects or grade ≥3 in ≥5% subjects in any treatment group – Pooled safety population and avelumab treated patients in Study B9991001

Preferred Term	Pooled Safety Population (N=1738) All grades n (%)	Pooled Safety Population (N=1738) Grade >= 3 n (%)	B9991001 Avelumab+BSC (N=344) All grades n (%)	B9991001 Avelumab+BSC (N=344) Grade >=3 n (%)	Overall (N=2082) All grades n (%)	Overall (N=2082) Grade >=3 n (%)
Number of subjects with at least one event	1697 (97.6)	1008 (58.0)	337 (98.0)	163 (47.4)	2034 (97.7)	1171 (56.2)
Fatigue	563 (32.4)	51 (2.9)	61 (17.7)	6 (1.7)	624 (30.0)	57 (2.7)
Pruritus	128 (7.4)	2 (0.1)	59 (17.2)	1 (0.3)	187 (9.0)	3 (0.1)
Urinary tract infection	167 (9.6)	19 (1.1)	59 (17.2)	15 (4.4)	226 (10.9)	34 (1.6)
Diarrhoea	329 (18.9)	22 (1.3)	57 (16.6)	2 (0.6)	386 (18.5)	24 (1.2)
Arthralgia	180 (10.4)	18 (1.0)	56 (16.3)	2 (0.6)	236 (11.3)	20 (1.0)
Asthenia	151 (8.7)	29 (1.7)	56 (16.3)	0	207 (9.9)	29 (1.4)
Constipation	320 (18.4)	17 (1.0)	56 (16.3)	2 (0.6)	376 (18.1)	19 (0.9)
Back pain	205 (11.8)	24 (1.4)	55 (16.0)	4 (1.2)	260 (12.5)	28 (1.3)
Nausea	437 (25.1)	27 (1.6)	54 (15.7)	1 (0.3)	491 (23.6)	28 (1.3)
Pyrexia	237 (13.6)	5 (0.3)	51 (14.8)	1 (0.3)	288 (13.8)	6 (0.3)
Decreased appetite	320 (18.4)	19 (1.1)	47 (13.7)	1 (0.3)	367 (17.6)	20 (1.0)
Cough	240 (13.8)	2 (0.1)	44 (12.8)	1 (0.3)	284 (13.6)	3 (0.1)
Vomiting	281 (16.2)	31 (1.8)	43 (12.5)	4 (1.2)	324 (15.6)	35 (1.7)
Hypothyroidism	111 (6.4)	4 (0.2)	40 (11.6)	1 (0.3)	151 (7.3)	5 (0.2)
Rash	124 (7.1)	3 (0.2)	40 (11.6)	1 (0.3)	164 (7.9)	4 (0.2)
Anaemia	259 (14.9)	104 (6.0)	39 (11.3)	13 (3.8)	298 (14.3)	117 (5.6)
Haematuria	41 (2.4)	8 (0.5)	36 (10.5)	6 (1.7)	77 (3.7)	14 (0.7)
Infusion related reaction	297 (17.1)	10 (0.6)	35 (10.2)	3 (0.9)	332 (15.9)	13 (0.6)
Abdominal pain	250 (14.4)	52 (3.0)	31 (9.0)	2 (0.6)	281 (13.5)	54 (2.6)
Dyspnoea	229 (13.2)	68 (3.9)	23 (6.7)	5 (1.5)	252 (12.1)	73 (3.5)
Oedema peripheral	206 (11.9)	8 (0.5)	22 (6.4)	1 (0.3)	228 (11.0)	9 (0.4)
Weight decreased	288 (16.6)	12 (0.7)	13 (3.8)	1 (0.3)	301 (14.5)	13 (0.6)
Disease progression	179 (10.3)	172 (9.9)	3 (0.9)	3 (0.9)	182 (8.7)	175 (8.4)

Most common: Any Grade in >=10% subjects or Grade>=3 in >=5% subjects in any treatment group
N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
A patient with multiple occurrences of an AE is counted only once.
Events are coded in the latest MedDRA version available at the time of cut-off.
Grading categories determined using NCI-CTCAE version 4.0 in pooled safety population and version 4.03 in B9991001.
Sorted in descending order of the frequency of PTs by All Grades in B9991001 Avelumab + BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 51. Exposure-Adjusted Analysis of Most Common TEAE by PT

	Pooled Safety Population (N=1738)		B9991001 Avelumab+BSC (N=344)		Overall (N=2082)	
Preferred Term	**All Grades PM (IR)**	**Grade ≥3 PM (IR)**	**All Grades PM (IR)**	**Grade ≥3 PM (IR)**	**All Grades PM (IR)**	**Grade ≥3 PM (IR)**
Subjects with at least one event	844.6 (200.9)	5973.6 (16.9)	350.8 (96.1)	2224.5 (7.3)	1195.4 (170.2)	8198.0 (14.3)
Fatigue	6270.9 (9.0)	8431.5 (0.6)	2747.6 (2.2)	3165.9 (0.2)	9018.5 (6.9)	11597.4 (0.5)
Pruritus	7897.6 (1.6)	8509.2 (0.0)	2673.8 (2.2)	3172.6 (0.0)	10571.3 (1.8)	11681.8 (0.0)
Urinary tract infection	7849.6 (2.1)	8464.2 (0.2)	2731.1 (2.2)	3062.9 (0.5)	10580.7 (2.1)	11527.1 (0.3)
Diarrhoea	6988.1 (4.7)	8456.2 (0.3)	2753.6 (2.1)	3163.1 (0.1)	9741.7 (4.0)	11619.3 (0.2)
Arthralgia	7682.2 (2.3)	8487.8 (0.2)	2785.0 (2.0)	3168.8 (0.1)	10467.2 (2.3)	11656.5 (0.2)
Asthenia	8097.6 (1.9)	8492.6 (0.3)	2780.9 (2.0)	3174.2 (0.0)	10878.5 (1.9)	11666.9 (0.2)
Constipation	7555.6 (4.2)	8490.5 (0.2)	2848.3 (2.0)	3171.1 (0.1)	10403.9 (3.6)	11661.5 (0.2)
Back pain	7799.0 (2.6)	8482.0 (0.3)	2886.5 (1.9)	3162.8 (0.1)	10685.5 (2.4)	11644.8 (0.2)
Nausea	6930.0 (6.3)	8484.5 (0.3)	2841.9 (1.9)	3171.9 (0.0)	9771.9 (5.0)	11656.4 (0.2)
Pyrexia	7586.8 (3.1)	8511.2 (0.1)	2838.4 (1.8)	3173.4 (0.0)	10425.2 (2.8)	11684.7 (0.1)
Decreased appetite	7500.1 (4.3)	8499.9 (0.2)	2932.7 (1.6)	3173.3 (0.0)	10432.8 (3.5)	11673.2 (0.2)
Cough	7529.5 (3.2)	8503.4 (0.0)	2828.4 (1.6)	3173.7 (0.0)	10357.8 (2.7)	11677.0 (0.0)
Vomiting	7669.7 (3.7)	8469.0 (0.4)	2954.3 (1.5)	3148.2 (0.1)	10623.9 (3.0)	11617.2 (0.3)
Hypothyroidism	7992.9 (1.4)	8510.1 (0.0)	2855.3 (1.4)	3173.6 (0.0)	10848.3 (1.4)	11683.6 (0.0)
Rash	7918.9 (1.6)	8505.6 (0.0)	2819.2 (1.4)	3168.7 (0.0)	10738.1 (1.5)	11674.2 (0.0)
Anaemia	7831.9 (3.3)	8334.7 (1.2)	3044.1 (1.3)	3154.4 (0.4)	10876.0 (2.7)	11489.0 (1.0)
Haematuria	8338.6 (0.5)	8502.9 (0.1)	3016.3 (1.2)	3152.7 (0.2)	11354.8 (0.7)	11655.6 (0.1)
Infusion related reaction	7184.0 (4.1)	8503.9 (0.1)	2951.0 (1.2)	3171.3 (0.1)	10135.0 (3.3)	11675.2 (0.1)
Abdominal pain	7844.9 (3.2)	8456.2 (0.6)	3087.7 (1.0)	3172.9 (0.1)	10932.6 (2.6)	11629.2 (0.5)
Dyspnoea	7869.0 (2.9)	8402.8 (0.8)	3071.0 (0.7)	3169.0 (0.2)	10940.0 (2.3)	11571.7 (0.6)
Oedema peripheral	7795.5 (2.6)	8507.5 (0.1)	3021.1 (0.7)	3173.7 (0.0)	10816.6 (2.1)	11681.1 (0.1)
Weight decreased	7679.5 (3.8)	8501.1 (0.1)	3065.2 (0.4)	3168.2 (0.0)	10744.8 (2.8)	11669.3 (0.1)
Disease progression	8447.2 (2.1)	8456.5 (2.0)	3174.2 (0.1)	3174.2 (0.1)	11621.5 (1.6)	11630.8 (1.5)

Table 51. Exposure-Adjusted Analysis of Most Common TEAE by PT

	Pooled Safety Population (N=1738)		B9991001 Avelumab+BSC (N=344)		Overall (N=2082)	
Preferred Term	All Grades PM (IR)	Grade ≥3 PM (IR)	All Grades PM (IR)	Grade ≥3 PM (IR)	All Grades PM (IR)	Grade ≥3 PM (IR)

Most common: Any Grade in ≥10% subjects or Grade ≥3 in ≥5% subjects in any treatment group
IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure
The exposure-adjusted incidence rate is defined as the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial occurrence of AE.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001

Serious adverse event/deaths/other significant events

Summary of deaths

Table 52. Summary of deaths – SAS Study B9991001.

	All Subjects		Subjects with PD-L1-Positive Tumors	
	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)	Avelumab+BSC (N=187) n (%)	BSC (N=167) n (%)
Deaths	144 (41.9)	176 (51.0)	61 (32.6)	81 (48.5)
Cause of death				
Disease progression	133 (38.7)	157 (45.5)	57 (30.5)	77 (46.1)
Study treatment toxicity	2 (0.6)	0	1 (0.5)	0
Adverse event not related to study treatment	2 (0.6)	10 (2.9)	1 (0.5)	3 (1.8)
Other	2 (0.6)	3 (0.9)	1 (0.5)	1 (0.6)
Unknown	6 (1.7)	6 (1.7)	1 (0.5)	0
Deaths within 30 days after last dose of study treatment	5 (1.5)	33 (9.6)	3 (1.6)	18 (10.8)
Cause of death				
Disease progression	4 (1.2)	27 (7.8)	2 (1.1)	17 (10.2)
Study treatment toxicity	1 (0.3)	0	1 (0.5)	0
Adverse event not related to study treatment	0	6 (1.7)	0	1 (0.6)
Other	0	0	0	0
Unknown	0	0	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
A subject can have more than one cause of death.
Last dose of study treatment in BSC arm refers to the date of completion or discontinuation as collected on the End of treatment disposition CRF.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADSL Output File: ./B9991001/B9991001 SCS/adae s500a pdl1c Date of Generation: 17JAN2020 (14:32) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.2.1.1.1 is for Pfizer internal use.

Table 53 Exposure-adjusted analysis of Deaths – All Subjects and Subjects with PD-L1-Positive Tumours in the Safety Analysis Set (Protocol B9991001)

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=344) PM (IR)	BSC (N=345) PM (IR)	Avelumab+BSC (N=187) PM (IR)	BSC (N=167) PM (IR)
Deaths	5051.7 (2.9)	4378.9 (4.0)	2860.4 (2.1)	2224.6 (3.6)
Cause of death				
Disease progression	5051.7 (2.6)	4378.9 (3.6)	2860.4 (2.0)	2224.6 (3.5)
Study treatment toxicity	5051.7 (<0.1)	4378.9 (0.0)	2860.4 (<0.1)	2224.6 (0.0)
Adverse event not related to study treatment	5051.7 (<0.1)	4378.9 (0.2)	2860.4 (<0.1)	2224.6 (0.1)
Other	5051.7 (<0.1)	4378.9 (<0.1)	2860.4 (<0.1)	2224.6 (<0.1)
Unknown	5051.7 (0.1)	4378.9 (0.1)	2860.4 (<0.1)	2224.6 (0.0)
Deaths within 30 days after last dose of study treatment	3189.3 (0.2)	2132.2 (1.5)	1855.5 (0.2)	1105.2 (1.6)
Cause of death				
Disease progression	3189.3 (0.1)	2132.2 (1.3)	1855.5 (0.1)	1105.2 (1.5)
Study treatment toxicity	3189.3 (<0.1)	2132.2 (0.0)	1855.5 (<0.1)	1105.2 (0.0)
Adverse event not related to study treatment	3189.3 (0.0)	2132.2 (0.3)	1855.5 (0.0)	1105.2 (<0.1)
Other	3189.3 (0.0)	2132.2 (0.0)	1855.5 (0.0)	1105.2 (0.0)
Unknown	3189.3 (0.0)	2132.2 (0.0)	1855.5 (0.0)	1105.2 (0.0)

IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure
The exposure-adjusted incidence rate is defined as the number of patients with a particular cause of death divided by the total exposure time among patients in the
respective treatment group at risk of death.
A subject can have more than one cause of death.
Last dose of study treatment in BSC arm refers to the date of completion or discontinuation as collected on the End of treatment disposition CRF.
Cutoff date: 21OCT2019

Table 54 Summary of Deaths – Study B9991001 and Pooled safety population

	Avelumab+BSC (N=344) n (%)	BSC (N=345) n (%)	Pooled Safety Population (N=1738) n (%)	Overall (N=2082) n (%)
Deaths	144 (41.9)	176 (51.0)	911 (52.4)	1055 (50.7)
Cause of death				
Disease progression	133 (38.7)	157 (45.5)	744 (42.8)	877 (42.1)
Study treatment toxicity	2 (0.6)	0	4 (0.2)	6 (0.3)
AE not related to study treatment	2 (0.6)	10 (2.9)	59 (3.4)	61 (2.9)
Other	2 (0.6)	3 (0.9)	17 (1.0)	19 (0.9)
Unknown	6 (1.7)	6 (1.7)	83 (4.8)	89 (4.3)
Missing	0	0	4 (0.2)	4 (0.2)
Deaths within 30 days after last dose of study treatment	5 (1.5)	33 (9.6)	228 (13.1)	233 (11.2)
Cause of death				
Disease progression	4 (1.2)	27 (7.8)	174 (10.0)	178 (8.5)
Study treatment toxicity	1 (0.3)	0	4 (0.2)	5 (0.2)
AE not related to study treatment	0	6 (1.7)	41 (2.4)	41 (2.0)
Other	0	0	4 (0.2)	4 (0.2)
Unknown	0	0	5 (0.3)	5 (0.2)
Missing	0	0	0	0

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
A subject can have more than one cause of death.
Last dose of study treatment in BSC arm refers to the date of completion or discontinuation as collected on the End of treatment disposition CRF

Table 55 Exposure-Adjusted Analysis of Deaths

	Pooled Safety Population (N=1738) PM (IR)	B9991001 Avelumab + BSC (N=344) PM (IR)	Overall (N=2082) PM (IR)
Deaths	15394.8 (5.9)	5051.7 (2.9)	20446.5 (5.2)
Cause of death			
Disease Progression	15394.8 (4.8)	5051.7 (2.6)	20446.5 (4.3)
Study Treatment Toxicity	15394.8 (0.0)	5051.7 (0.0)	20446.5 (0.0)
AE Not Related to Study Treatment	15394.8 (0.4)	5051.7 (0.0)	20446.5 (0.3)
Other	15394.8 (0.1)	5051.7 (0.0)	20446.5 (0.1)
Unknown	15394.8 (0.5)	5051.7 (0.1)	20446.5 (0.4)
Missing	15394.8 (0.0)	5051.7 (0.0)	20446.5 (0.0)
Deaths within 30 days after last dose of study treatment	8598.7 (2.7)	3189.3 (0.2)	11788.0 (2.0)
Cause of death			
Disease Progression	8598.7 (2.0)	3189.3 (0.1)	11788.0 (1.5)
Study Treatment Toxicity	8598.7 (0.0)	3189.3 (0.0)	11788.0 (0.0)
AE Not Related to Study Treatment	8598.7 (0.5)	3189.3 (0.0)	11788.0 (0.3)
Other	8598.7 (0.0)	3189.3 (0.0)	11788.0 (0.0)
Unknown	8598.7 (0.1)	3189.3 (0.0)	11788.0 (0.0)
Missing	8598.7 (0.0)	3189.3 (0.0)	11788.0 (0.0)

IR: Incident Rate per 100 patient months, PM: Patient Months of Exposure
The exposure-adjusted incidence rate is defined as the number of patients with a particular AE divided by the total exposure time among patients in the respective treatment group at risk of an initial occurrence of AE.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001

Table 56. Summary of TEAEs During the On-Treatment Period Leading to Death by SOC and PT – SAS Study B9991001

	All Subjects		Subjects with PD-L1-Positive Tumours	
	Avelumab+BSC (N=344)	BSC (N=345)	Avelumab+BSC (N=187)	BSC (N=167)
System Organ Class and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with events	4 (1.2)	24 (7.0)	2 (1.1)	13 (7.8)
General disorders and administration site conditions	3 (0.9)	16 (4.6)	1 (0.5)	12 (7.2)
Disease progression	3 (0.9)	16 (4.6)	1 (0.5)	12 (7.2)
Infections and infestations	1 (0.3)	2 (0.6)	1 (0.5)	0
Sepsis	1 (0.3)	0	1 (0.5)	0
Biliary sepsis	0	1 (0.3)	0	0
Urosepsis	0	1 (0.3)	0	0
Cardiac disorders	0	1 (0.3)	0	1 (0.6)
Cardiogenic shock	0	1 (0.3)	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	4 (1.2)	0	0
Bladder cancer	0	1 (0.3)	0	0
Malignant neoplasm progression	0	1 (0.3)	0	0
Metastatic carcinoma of the bladder	0	1 (0.3)	0	0
Neoplasm progression	0	1 (0.3)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.3)	0	0
Chronic obstructive pulmonary disease	0	1 (0.3)	0	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 within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same system organ class (SOC) are counted only once within each SOC.
Sorted in descending order of the frequency of SOC and PTs in Avelumab + BSC arm in all subjects.
MedDRA v22.1 coding dictionary applied.
Cut-off date: 21OCT2019 Snapshot Date: 21NOV2019

Summary of serious adverse events

Table 57. Summary of most common serious AE (≥2 subjects in any treatment group) by PT during the on-treatment period – SAS Study B9991001.

	Avelumab + BSC (N=344)	BSC (N=345)
Preferred Term	**(n %)**	**(n %)**
Subjects with events	96 (27.9)	69 (20.0)
Urinary tract infection	16 (4.7)	7 (2.0)
Acute kidney injury	6 (1.7)	6 (1.7)
Haematuria	5 (1.5)	2 (0.6)
Infusion related reaction	4 (1.2)	0
Pain	4 (1.2)	1 (0.3)
Sepsis	4 (1.2)	1 (0.3)
Atrial fibrillation	3 (0.9)	1 (0.3)
Back pain	3 (0.9)	1 (0.3)
Disease progression	3 (0.9)	16 (4.6)
Hydronephrosis	3 (0.9)	1 (0.3)
Ileus	3 (0.9)	1 (0.3)
Pyelonephritis	3 (0.9)	3 (0.9)
Vomiting	3 (0.9)	0
Blood creatine phosphokinase increased	2 (0.6)	0
Colitis	2 (0.6)	0
Constipation	2 (0.6)	0
Dyspnoea	2 (0.6)	1 (0.3)
Kidney infection	2 (0.6)	0
Myocardial infarction	2 (0.6)	0
Pyrexia	2 (0.6)	1 (0.3)
Vascular device infection	2 (0.6)	0
Abdominal pain	1 (0.3)	3 (0.9)
Anaemia	1 (0.3)	2 (0.6)
Basal cell carcinoma	1 (0.3)	2 (0.6)
Urosepsis	1 (0.3)	2 (0.6)
Syncope	0	2 (0.6)
Tumour pain	0	2 (0.6)
Urinary tract obstruction	0	2 (0.6)

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.
Sorted in descending order of the frequency of PTs in the Avelumab+BSC arm.
MedDRA (v22.1) coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001/B9991001 CSR/adae s999 ser Date of Generation: 14JAN2020 (04:41) Cutoff date: 21OCT2019 Snapshot Date: 21NOV2019
Table 14.3.1.2.2.15 is for Pfizer internal use.

Table 58. Serious AE reported per organ class - Pooled safety population and avelumab treated patients in Study B9991001.

System Organ Class Preferred Term	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n (%)
Number of subjects with at least one event	777 (44.7)	96 (27.9)	873 (41.9)
Infections and infestations	162 (9.3)	28 (8.1)	190 (9.1)
Renal and urinary disorders	44 (2.5)	18 (5.2)	62 (3.0)
Gastrointestinal disorders	178 (10.2)	15 (4.4)	193 (9.3)
General disorders and administration site conditions	248 (14.3)	12 (3.5)	260 (12.5)
Injury, poisoning and procedural complications	51 (2.9)	11 (3.2)	62 (3.0)
Cardiac disorders	43 (2.5)	8 (2.3)	51 (2.4)
Musculoskeletal and connective tissue disorders	47 (2.7)	7 (2.0)	54 (2.6)
Respiratory, thoracic and mediastinal disorders	184 (10.6)	7 (2.0)	191 (9.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	53 (3.0)	4 (1.2)	57 (2.7)
Hepatobiliary disorders	22 (1.3)	3 (0.9)	25 (1.2)
Investigations	26 (1.5)	3 (0.9)	29 (1.4)
Nervous system disorders	55 (3.2)	3 (0.9)	58 (2.8)
Vascular disorders	42 (2.4)	3 (0.9)	45 (2.2)
Endocrine disorders	17 (1.0)	2 (0.6)	19 (0.9)
Blood and lymphatic system disorders	35 (2.0)	1 (0.3)	36 (1.7)
Metabolism and nutrition disorders	63 (3.6)	2 (0.6)	65 (3.1)
Ear and labyrinth disorders	1 (0.1)	1 (0.3)	2 (0.1)
Product issues	2 (0.1)	1 (0.3)	3 (0.1)
Psychiatric disorders	17 (1.0)	1 (0.3)	18 (0.9)
Reproductive system and breast disorders	4 (0.2)	1 (0.3)	5 (0.2)
Eye disorders	7 (0.4)	0	7 (0.3)
Immune system disorders	4 (0.2)	0	4 (0.2)
Skin and subcutaneous tissue disorders	4 (0.2)	0	4 (0.2)

N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
A patient with multiple occurrences of an AE under one treatment is counted only once.
Events are coded in the latest MedDRA version available at the time of cut-off.
Sorted in descending order of the frequency of SOC and PTs in B9991001 Avelumab + BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Adverse events leading to discontinuation of study drug or dose interruptions

Table 59. Adverse events leading to discontinuation of study drug - Pooled safety population and avelumab treated patients in Study B9991001

System Organ Class Preferred Term	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n (%)
Number of subjects with at least one event	244 (14.0)	41 (11.9)	285 (13.7)
Investigations	36 (2.1)	10 (2.9)	46 (2.2)
Lipase increased	3 (0.2)	3 (0.9)	6 (0.3)
Troponin T increased	0	3 (0.9)	3 (0.1)
Alanine aminotransferase increased	5 (0.3)	2 (0.6)	7 (0.3)
Amylase increased	1 (0.1)	2 (0.6)	3 (0.1)
Aspartate aminotransferase increased	7 (0.4)	1 (0.3)	8 (0.4)
Blood alkaline phosphatase increased	3 (0.2)	1 (0.3)	4 (0.2)
Gamma-glutamyltransferase increased	9 (0.5)	1 (0.3)	10 (0.5)
Neutrophil count decreased	1 (0.1)	1 (0.3)	2 (0.1)
Platelet count decreased	0	1 (0.3)	1 (0.0)
Blood bilirubin increased	2 (0.1)	0	2 (0.1)
Blood creatine phosphokinase increased	4 (0.2)	0	4 (0.2)
General physical condition abnormal	1 (0.1)	0	1 (0.0)
Haemoglobin decreased	1 (0.1)	0	1 (0.0)
Hepatic enzyme increased	1 (0.1)	0	1 (0.0)
Transaminases increased	3 (0.2)	0	3 (0.1)
Weight decreased	1 (0.1)	0	1 (0.0)
Gastrointestinal disorders	31 (1.8)	6 (1.7)	37 (1.8)
Colitis	3 (0.2)	2 (0.6)	5 (0.2)
Autoimmune pancreatitis	0	1 (0.3)	1 (0.0)
Gastric ulcer	0	1 (0.3)	1 (0.0)
Pancreatitis	0	1 (0.3)	1 (0.0)
Vomiting	1 (0.1)	1 (0.3)	2 (0.1)
Abdominal pain	2 (0.1)	0	2 (0.1)
Ascites	1 (0.1)	0	1 (0.0)
Diarrhoea	5 (0.3)	0	5 (0.2)
Dysphagia	3 (0.2)	0	3 (0.1)
Enterocolitis	1 (0.1)	0	1 (0.0)
Gastrointestinal haemorrhage	1 (0.1)	0	1 (0.0)
Ileus	2 (0.1)	0	2 (0.1)
Intestinal obstruction	3 (0.2)	0	3 (0.1)
Intestinal perforation	1 (0.1)	0	1 (0.0)
Nausea	1 (0.1)	0	1 (0.0)
Obstruction gastric	2 (0.1)	0	2 (0.1)
Rectal haemorrhage	1 (0.1)	0	1 (0.0)
Small intestinal obstruction	2 (0.1)	0	2 (0.1)
Small intestinal perforation	1 (0.1)	0	1 (0.0)
Stomatitis	1 (0.1)	0	1 (0.0)
Subileus	1 (0.1)	0	1 (0.0)
General disorders and administration site conditions	56 (3.2)	4 (1.2)	60 (2.9)
Disease progression	38 (2.2)	2 (0.6)	40 (1.9)
Fatigue	9 (0.5)	1 (0.3)	10 (0.5)
Malaise	0	1 (0.3)	1 (0.0)
Asthenia	1 (0.1)	0	1 (0.0)
General physical health deterioration	6 (0.3)	0	6 (0.3)
Influenza like illness	1 (0.1)	0	1 (0.0)
Localised oedema	1 (0.1)	0	1 (0.0)
Oedema peripheral	1 (0.1)	0	1 (0.0)
Injury, poisoning and procedural complications	33 (1.9)	4 (1.2)	37 (1.8)
Infusion related reaction	32 (1.8)	4 (1.2)	36 (1.7)
Radiation pneumonitis	1 (0.1)	0	1 (0.0)

Musculoskeletal and connective tissue disorders	10 (0.6)	3 (0.9)	13 (0.6)
Muscular weakness	1 (0.1)	1 (0.3)	2 (0.1)
Myositis	3 (0.2)	1 (0.3)	4 (0.2)
Rheumatoid arthritis	1 (0.1)	1 (0.3)	2 (0.1)
Arthralgia	3 (0.2)	0	3 (0.1)
Arthritis	1 (0.1)	0	1 (0.0)
Musculoskeletal chest pain	1 (0.1)	0	1 (0.0)
Pathological fracture	1 (0.1)	0	1 (0.0)
Renal and urinary disorders	7 (0.4)	3 (0.9)	10 (0.5)
Nephritis	0	1 (0.3)	1 (0.0)
Tubulointerstitial nephritis	0	1 (0.3)	1 (0.0)
Ureteric obstruction	0	1 (0.3)	1 (0.0)
Acute kidney injury	5 (0.3)	0	5 (0.2)
Nephrotic syndrome	1 (0.1)	0	1 (0.0)
Renal failure	1 (0.1)	0	1 (0.0)
Respiratory, thoracic and mediastinal disorders	22 (1.3)	3 (0.9)	25 (1.2)
Interstitial lung disease	0	2 (0.6)	2 (0.1)
Pneumonitis	3 (0.2)	1 (0.3)	4 (0.2)
Acute respiratory failure	3 (0.2)	0	3 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	0	1 (0.0)
Dyspnoea	5 (0.3)	0	5 (0.2)
Dyspnoea exertional	1 (0.1)	0	1 (0.0)
Epistaxis	1 (0.1)	0	1 (0.0)
Hypoxia	2 (0.1)	0	2 (0.1)
Pleural effusion	3 (0.2)	0	3 (0.1)
Respiratory distress	2 (0.1)	0	2 (0.1)
Respiratory failure	3 (0.2)	0	3 (0.1)
Cardiac disorders	6 (0.3)	2 (0.6)	8 (0.4)
Acute myocardial infarction	0	1 (0.3)	1 (0.0)
Myocardial infarction	1 (0.1)	1 (0.3)	2 (0.1)
Atrial fibrillation	1 (0.1)	0	1 (0.0)
Cardiac tamponade	2 (0.1)	0	2 (0.1)
Cardio-respiratory arrest	1 (0.1)	0	1 (0.0)
Pericardial effusion	1 (0.1)	0	1 (0.0)
Endocrine disorders	4 (0.2)	2 (0.6)	6 (0.3)
Autoimmune thyroiditis	0	1 (0.3)	1 (0.0)
Hyperthyroidism	1 (0.1)	1 (0.3)	2 (0.1)
Adrenal insufficiency	2 (0.1)	0	2 (0.1)
Hypothyroidism	1 (0.1)	0	1 (0.0)
Hepatobiliary disorders	6 (0.3)	2 (0.6)	8 (0.4)
Autoimmune hepatitis	2 (0.1)	1 (0.3)	3 (0.1)
Hepatotoxicity	0	1 (0.3)	1 (0.0)
Cholestasis	1 (0.1)	0	1 (0.0)
Hepatitis	1 (0.1)	0	1 (0.0)
Hepatocellular injury	1 (0.1)	0	1 (0.0)
Hyperbilirubinaemia	1 (0.1)	0	1 (0.0)
Infections and infestations	15 (0.9)	2 (0.6)	17 (0.8)
Sepsis	2 (0.1)	2 (0.6)	4 (0.2)
Aspergillus infection	1 (0.1)	0	1 (0.0)
Cellulitis	1 (0.1)	0	1 (0.0)
Gastroenteritis viral	1 (0.1)	0	1 (0.0)
Lung infection	2 (0.1)	0	2 (0.1)
Pelvic abscess	1 (0.1)	0	1 (0.0)
Pneumonia	3 (0.2)	0	3 (0.1)
Pulmonary sepsis	1 (0.1)	0	1 (0.0)
Pyelonephritis	1 (0.1)	0	1 (0.0)
Streptococcal bacteraemia	1 (0.1)	0	1 (0.0)
Urosepsis	1 (0.1)	0	1 (0.0)
Blood and lymphatic system disorders	5 (0.3)	1 (0.3)	6 (0.3)
Anaemia	2 (0.1)	1 (0.3)	3 (0.1)
Autoimmune neutropenia	1 (0.1)	0	1 (0.0)
Neutropenia	1 (0.1)	0	1 (0.0)
Thrombocytopenia	1 (0.1)	0	1 (0.0)
Metabolism and nutrition disorders	7 (0.4)	1 (0.3)	8 (0.4)
Hypokalaemia	0	1 (0.3)	1 (0.0)
Decreased appetite	1 (0.1)	0	1 (0.0)
Dehydration	1 (0.1)	0	1 (0.0)
Diabetes mellitus	1 (0.1)	0	1 (0.0)
Failure to thrive	1 (0.1)	0	1 (0.0)
Hyperglycaemia	1 (0.1)	0	1 (0.0)
Hyperkalaemia	1 (0.1)	0	1 (0.0)
Hyponatraemia	1 (0.1)	0	1 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	10 (0.6)	1 (0.3)	11 (0.5)
Oesophageal squamous cell carcinoma	0	1 (0.3)	1 (0.0)
Hepatic cancer	1 (0.1)	0	1 (0.0)
Leukaemia	1 (0.1)	0	1 (0.0)
Malignant pleural effusion	1 (0.1)	0	1 (0.0)
Metastases to meninges	1 (0.1)	0	1 (0.0)
Myelodysplastic syndrome	2 (0.1)	0	2 (0.1)
Neoplasm progression	1 (0.1)	0	1 (0.0)
Prostate cancer	1 (0.1)	0	1 (0.0)
Tumour compression	1 (0.1)	0	1 (0.0)
Tumour pain	1 (0.1)	0	1 (0.0)
Nervous system disorders	10 (0.6)	1 (0.3)	11 (0.5)
Toxic neuropathy	0	1 (0.3)	1 (0.0)
Ataxia	1 (0.1)	0	1 (0.0)
Brain injury	1 (0.1)	0	1 (0.0)
Brain oedema	1 (0.1)	0	1 (0.0)
Cerebral infarction	1 (0.1)	0	1 (0.0)
Cerebrovascular accident	1 (0.1)	0	1 (0.0)
Guillain-Barre syndrome	1 (0.1)	0	1 (0.0)
Peripheral motor neuropathy	1 (0.1)	0	1 (0.0)
Posterior reversible encephalopathy syndrome	1 (0.1)	0	1 (0.0)
Seizure	1 (0.1)	0	1 (0.0)
Syncope	1 (0.1)	0	1 (0.0)

Skin and subcutaneous tissue disorders	4 (0.2)	1 (0.3)	5 (0.2)
Pruritus	0	1 (0.3)	1 (0.0)
Rash maculo-papular	1 (0.1)	1 (0.3)	2 (0.1)
Erythema	1 (0.1)	0	1 (0.0)
Pemphigoid	1 (0.1)	0	1 (0.0)
Rash	1 (0.1)	0	1 (0.0)
Immune system disorders	3 (0.2)	0	3 (0.1)
Anaphylactic reaction	1 (0.1)	0	1 (0.0)
Sarcoidosis	1 (0.1)	0	1 (0.0)
Type I hypersensitivity	1 (0.1)	0	1 (0.0)
Psychiatric disorders	2 (0.1)	0	2 (0.1)
Confusional state	1 (0.1)	0	1 (0.0)
Mental status changes	1 (0.1)	0	1 (0.0)
Vascular disorders	2 (0.1)	0	2 (0.1)
Embolism	2 (0.1)	0	2 (0.1)

N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
A patient with multiple occurrences of an AE under one treatment is counted only once.
Events are coded in the latest MedDRA version available at the time of cut-off.
Sorted in descending order of the frequency of SOC and PTs in B9991001 Avelumab + BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Immune related adverse events

Table 60. Summary of irAEs: Overall – SAS Study B9991001

	Avelumab+BSC (N=344)	**BSC (N=345)**
	n (%)	**n (%)**
Subjects with irAEs (maximum severity)		
Any Grade	101 (29.4)	5 (1.4)
Grade ≥ 3	24 (7.0)	1 (0.3)
Subjects with irAEs leading to discontinuation	19 (5.5)	0
Subjects with serious irAEs	16 (4.7)	1 (0.3)

The denominator to calculate percentages is N, the number of subjects in the safety analysis set within each treatment group.
MedDRA v22.1 coding dictionary applied.
Cut-off date: 21OCT2019

Table 61. Overview of irAEs - Pooled safety set and avelumab treated patients in Study B9991001.

	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n(%)
Subjects with irAEs (maximum severity)	247 (14.2)	101 (29.4)	348 (16.7)
Any Grade			
Grade >= 3	39 (2.2)	24 (7.0)	63 (3.0)
Subjects with irAEs leading to discontinuation	34 (2.0)	19 (5.5)	53 (2.5)
Subjects with serious irAEs	43 (2.5)	16 (4.7)	59 (2.8)

Events are coded in the latest MedDRA version available at the time of cut-off.
irAEs with an onset after the on-treatment period are also considered in the avelumab + BSC arm of study B9991001, whereas treatment-emergent irAEs are shown for the Pooled Safety population.
Grading categories determined using NCI-CTCAE version 4.0 in pooled safety population and version 4.03 in B9991001.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 62. Summary of irAEs by Cluster, PT and Maximum CTCAE Grade – SAS Study B9991001

	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cluster and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with events	101 (29.4)	24 (7.0)	5 (1.4)	1 (0.3)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	42 (12.2)	1 (0.3)	2 (0.6)	0
Hypothyroidism	35 (10.2)	1 (0.3)	1 (0.3)	0
Hyperthyroidism	16 (4.7)	0	1 (0.3)	0
Autoimmune thyroiditis	2 (0.6)	0	0	0
Autoimmune hypothyroidism	1 (0.3)	0	0	0
Blood thyroid stimulating hormone increased	1 (0.3)	0	0	0
Thyroiditis	1 (0.3)	0	0	0
Thyroxine free decreased	1 (0.3)	0	0	0
IMMUNE-RELATED RASH	35 (10.2)	5 (1.5)	1 (0.3)	0
Rash	17 (4.9)	1 (0.3)	0	0
Rash maculo-papular	8 (2.3)	1 (0.3)	0	0
Pruritus	7 (2.0)	0	1 (0.3)	0
Erythema	2 (0.6)	1 (0.3)	0	0
Purpura	2 (0.6)	0	0	0
Rash erythematous	2 (0.6)	0	0	0
Drug eruption	1 (0.3)	1 (0.3)	0	0
Erythema multiforme	1 (0.3)	1 (0.3)	0	0
Lichen planus	1 (0.3)	0	0	0
Rash popular	1 (0.3)	0	0	0
Rash pruritic	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: OTHER	9 (2.6)	2 (0.6)	0	0
Psoriasis	3 (0.9)	0	0	0
Vitiligo	2 (0.6)	0	0	0
Arthritis	1 (0.3)	0	0	0
Dermatitis psoriasiform	1 (0.3)	0	0	0
Oligoarthritis	1 (0.3)	1 (0.3)	0	0
Polyarthritis	1 (0.3)	0	0	0
Rheumatoid arthritis	1 (0.3)	1 (0.3)	0	0
IMMUNE-RELATED PNEUMONITIS	7 (2.0)	1 (0.3)	0	0
Pneumonitis	5 (1.5)	1 (0.3)	0	0
Interstitial lung disease	2 (0.6)	0	0	0
IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION	6 (1.7)	1 (0.3)	0	0
Nephritis	3 (0.9)	0	0	0
Renal failure	3 (0.9)	1 (0.3)	0	0
Tubulointerstitial nephritis	1 (0.3)	0	0	0
IMMUNE-RELATED COLITIS	5 (1.5)	3 (0.9)	0	0
Colitis	3 (0.9)	2 (0.6)	0	0
Diarrhoea	2 (0.6)	0	0	0
Enteritis	1 (0.3)	1 (0.3)	0	0
Proctitis	1 (0.3)	0	0	0
IMMUNE-RELATED HEPATITIS	5 (1.5)	5 (1.5)	0	0
Alanine aminotransferase increased	3 (0.9)	3 (0.9)	0	0
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	0	0
Autoimmune hepatitis	1 (0.3)	1 (0.3)	0	0
Hepatotoxicity	1 (0.3)	1 (0.3)	0	0
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	3 (0.9)	0	0	0
Adrenal insufficiency	3 (0.9)	0	0	0

Table 62. Summary of irAEs by Cluster, PT and Maximum CTCAE Grade – SAS Study B9991001

	Avelumab+BSC (N=344)		BSC (N=345)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cluster and Preferred Term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS	3 (0.9)	3 (0.9)	1 (0.3)	1 (0.3)
Hyperglycaemia	3 (0.9)	3 (0.9)	0	0
Diabetes mellitus	0	0	1 (0.3)	1 (0.3)
IMMUNE-RELATED PANCREATITIS	2 (0.6)	1 (0.3)	0	0
Autoimmune pancreatitis	1 (0.3)	1 (0.3)	0	0
Pancreatitis	1 (0.3)	0	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: MYOSITIS	2 (0.6)	2 (0.6)	0	0
Myositis	2 (0.6)	2 (0.6)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: GUILLAIN-BARRE SYNDROME	1 (0.3)	1 (0.3)	0	0
Miller Fisher syndrome	1 (0.3)	1 (0.3)	0	0
OTHER IMMUNE-RELATED ADVERSE EVENTS: UVEITIS	1 (0.3)	0	1 (0.3)	0
Uveitis	1 (0.3)	0	1 (0.3)	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.
Subjects reporting multiple preferred terms within the same cluster are counted only once within each cluster.
For subjects reporting more than one AE within a cluster or preferred term, the AE with maximum grade are included in the table.
Sorted in descending order of the frequency of clusters and PTs within cluster for all grades in the Avelumab+BSC arm.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
Cut-off date: 21OCT2019

Table 63. Summary of irAE by irAE category - Pooled safety set and avelumab treated patients in Study B9991001.

	Pooled Safety Population (N=1738)		B9991001 Avelumab+BSC (N=344)		Overall (N=2082)	
irAE category Preferred Term	All grades n (%)	Grade >= 3 n (%)	All grades n (%)	Grade >=3 n (%)	All grades n (%)	Grade >=3 n (%)
Any irAEs	247 (14.2)	39 (2.2)	101 (29.4)	24 (7.0)	348 (16.7)	63 (3.0)
Immune related endocrinopathies: Thyroid disorders	98 (5.6)	3 (0.2)	42 (12.2)	1 (0.3)	140 (6.7)	4 (0.2)
Hypothyroidism	88 (5.1)	3 (0.2)	35 (10.2)	1 (0.3)	123 (5.9)	4 (0.2)
Hyperthyroidism	7 (0.4)	0	16 (4.7)	0	23 (1.1)	0
Autoimmune thyroiditis	2 (0.1)	0	2 (0.6)	0	4 (0.2)	0
Autoimmune hypothyroidism	2 (0.1)	0	1 (0.3)	0	3 (0.1)	0
Blood thyroid stimulating hormone increased	0	0	1 (0.3)	0	1 (0.0)	0
Thyroiditis	2 (0.1)	0	1 (0.3)	0	3 (0.1)	0
Thyroxine free decreased	0	0	1 (0.3)	0	1 (0.0)	0
Immune related rash	90 (5.2)	1 (0.1)	35 (10.2)	5 (1.5)	125 (6.0)	6 (0.3)
Rash	40 (2.3)	1 (0.1)	17 (4.9)	1 (0.3)	57 (2.7)	2 (0.1)
Rash maculo-papular	20 (1.2)	0	8 (2.3)	1 (0.3)	28 (1.3)	1 (0.0)
Pruritus	26 (1.5)	0	7 (2.0)	0	33 (1.6)	0
Erythema	5 (0.3)	0	2 (0.6)	1 (0.3)	7 (0.3)	1 (0.0)
Purpura	0	0	2 (0.6)	0	2 (0.1)	0
Rash erythematous	4 (0.2)	0	2 (0.6)	0	6 (0.3)	0
Drug eruption	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Erythema multiforme	1 (0.1)	0	1 (0.3)	1 (0.3)	2 (0.1)	1 (0.0)
Lichen planus	0	0	1 (0.3)	0	1 (0.0)	0
Rash papular	2 (0.1)	0	1 (0.3)	0	3 (0.1)	0
Rash pruritic	7 (0.4)	0	1 (0.3)	0	8 (0.4)	0
Dermatitis exfoliative	1 (0.1)	0	0	0	1 (0.0)	0
Pemphigoid	1 (0.1)	0	0	0	1 (0.0)	0
Pruritus generalised	1 (0.1)	0	0	0	1 (0.0)	0
Rash generalised	5 (0.3)	0	0	0	5 (0.2)	0
Rash macular	3 (0.2)	0	0	0	3 (0.1)	0
Other immune related adverse events: Other	8 (0.5)	2 (0.1)	9 (2.6)	2 (0.6)	17 (0.8)	4 (0.2)
Psoriasis	5 (0.3)	1 (0.1)	3 (0.9)	0	8 (0.4)	1 (0.0)
Vitiligo	0	0	2 (0.6)	0	2 (0.1)	0
Arthritis	0	0	1 (0.3)	0	1 (0.0)	0
Dermatitis psoriasiform	0	0	1 (0.3)	0	1 (0.0)	0
Oligoarthritis	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Polyarthritis	0	0	1 (0.3)	0	1 (0.0)	0
Rheumatoid arthritis	2 (0.1)	0	1 (0.3)	1 (0.3)	3 (0.1)	1 (0.0)
Systemic inflammatory response syndrome	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Immune related pneumonitis	21 (1.2)	7 (0.4)	7 (2.0)	1 (0.3)	28 (1.3)	8 (0.4)
Pneumonitis	21 (1.2)	7 (0.4)	5 (1.5)	1 (0.3)	26 (1.2)	8 (0.4)
Interstitial lung disease	0	0	2 (0.6)	0	2 (0.1)	0
Immune related nephritis and renal dysfunction	1 (0.1)	0	6 (1.7)	1 (0.3)	7 (0.3)	1 (0.0)
Nephritis	0	0	3 (0.9)	0	3 (0.1)	0
Renal failure	0	0	3 (0.9)	1 (0.3)	3 (0.1)	1 (0.0)
Tubulointerstitial nephritis	1 (0.1)	0	1 (0.3)	0	2 (0.1)	0

Immune related colitis	26 (1.5)	7 (0.4)	5 (1.5)	3 (0.9)	31 (1.5)	10 (0.5)
Colitis	5 (0.3)	4 (0.2)	3 (0.9)	2 (0.6)	8 (0.4)	6 (0.3)
Diarrhoea	21 (1.2)	4 (0.2)	2 (0.6)	0	23 (1.1)	4 (0.2)
Enteritis	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Proctitis	0	0	1 (0.3)	0	1 (0.0)	0
Autoimmune colitis	1 (0.1)	0	0	0	1 (0.0)	0
Enterocolitis	1 (0.1)	0	0	0	1 (0.0)	0
Immune related hepatitis	16 (0.9)	13 (0.7)	5 (1.5)	5 (1.5)	21 (1.0)	18 (0.9)
Alanine aminotransferase increased	9 (0.5)	4 (0.2)	3 (0.9)	3 (0.9)	12 (0.6)	7 (0.3)
Aspartate aminotransferase increased	10 (0.6)	3 (0.2)	2 (0.6)	2 (0.6)	12 (0.6)	5 (0.2)
Autoimmune hepatitis	5 (0.3)	4 (0.2)	1 (0.3)	1 (0.3)	6 (0.3)	5 (0.2)
Hepatotoxicity	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Acute hepatic failure	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Hepatic failure	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Hepatitis	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Transaminases increased	2 (0.1)	2 (0.1)	0	0	2 (0.1)	2 (0.1)
Immune related endocrinopathies: Adrenal insufficiency	8 (0.5)	1 (0.1)	3 (0.9)	0	11 (0.5)	1 (0.0)
Adrenal insufficiency	8 (0.5)	1 (0.1)	3 (0.9)	0	11 (0.5)	1 (0.0)
Adrenocortical insufficiency acute	1 (0.1)	0	0	0	1 (0.0)	0
Immune related endocrinopathies: Type 1 Diabetes Mellitus	2 (0.1)	2 (0.1)	3 (0.9)	3 (0.9)	5 (0.2)	5 (0.2)
Hyperglycaemia	1 (0.1)	1 (0.1)	3 (0.9)	3 (0.9)	4 (0.2)	4 (0.2)
Diabetes mellitus	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Immune related pancreatitis	0	0	2 (0.6)	1 (0.3)	2 (0.1)	1 (0.0)
Autoimmune pancreatitis	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Pancreatitis	0	0	1 (0.3)	0	1 (0.0)	0
Other immune related adverse events: Myositis	9 (0.5)	5 (0.3)	2 (0.6)	2 (0.6)	11 (0.5)	7 (0.3)
Myositis	5 (0.3)	2 (0.1)	2 (0.6)	2 (0.6)	7 (0.3)	4 (0.2)
Blood creatine phosphokinase increased	5 (0.3)	3 (0.2)	0	0	5 (0.2)	3 (0.1)
Other immune related adverse events: Guillain-Barre Syndrome	1 (0.1)	1 (0.1)	1 (0.3)	1 (0.3)	2 (0.1)	2 (0.1)
Miller Fisher syndrome	0	0	1 (0.3)	1 (0.3)	1 (0.0)	1 (0.0)
Guillain-Barre syndrome	1 (0.1)	1 (0.1)	0	0	1 (0.0)	1 (0.0)
Other immune related adverse events: Uveitis	1 (0.1)	0	1 (0.3)	0	2 (0.1)	0
Uveitis	1 (0.1)	0	1 (0.3)	0	2 (0.1)	0
Immune related endocrinopathies: Hypogonadism	0	0	0	0	0	0
Immune related endocrinopathies: Pituitary dysfunction	1 (0.1)	0	0	0	1 (0.0)	0
Hypopituitarism	1 (0.1)	0	0	0	1 (0.0)	0
Immune related myocarditis	0	0	0	0	0	0
Other immune related adverse events: Encephalitis	0	0	0	0	0	0
Other immune related adverse events: GVHD	0	0	0	0	0	0
Other immune related adverse events: Myasthenic syndrome	0	0	0	0	0	0

irAEs = Immune-related adverse events. N: the number of subjects who have received at least one dose of avelumab. The denominator to calculate percentages is N. Events are coded in the latest MedDRA version available at the time of cut-off. irAEs with an onset after the on-treatment period are also considered in the avelumab + BSC arm of study B9991001, whereas treatment-emergent irAEs are shown for the Pooled Safety population.
A patient with multiple occurrences of an AE under one treatment is counted only once.
Grading categories determined using NCI-CTCAE version 4.0 in pooled safety population and version 4.03 in B9991001.
Sorted in descending order of the frequency of irAE category and PTs within irAE category for all grades in the B9991001 Avelumab+BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 64. Serious irAE by irAE category - Pooled safety set and avelumab treated patients in Study B9991001

irAE category Preferred Term	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n(%)
Any irAEs	43 (2.5)	16 (4.7)	59 (2.8)
Immune related colitis	8 (0.5)	3 (0.9)	11 (0.5)
Colitis	4 (0.2)	2 (0.6)	6 (0.3)
Enteritis	0	1 (0.3)	1 (0.0)
Diarrhoea	4 (0.2)	0	4 (0.2)
Immune related nephritis and renal dysfunction	1 (0.1)	3 (0.9)	4 (0.2)
Nephritis	0	1 (0.3)	1 (0.0)
Renal failure	0	1 (0.3)	1 (0.0)
Tubulointerstitial nephritis	1 (0.1)	1 (0.3)	2 (0.1)
Immune related endocrinopathies: Thyroid disorders	6 (0.3)	2 (0.6)	8 (0.4)
Hyperthyroidism	1 (0.1)	1 (0.3)	2 (0.1)
Hypothyroidism	4 (0.2)	1 (0.3)	5 (0.2)
Thyroiditis	1 (0.1)	0	1 (0.0)
Immune related hepatitis	7 (0.4)	2 (0.6)	9 (0.4)
Autoimmune hepatitis	3 (0.2)	1 (0.3)	4 (0.2)
Hepatotoxicity	0	1 (0.3)	1 (0.0)
Acute hepatic failure	1 (0.1)	0	1 (0.0)
Aspartate aminotransferase increased	1 (0.1)	0	1 (0.0)
Hepatic failure	1 (0.1)	0	1 (0.0)
Hepatitis	1 (0.1)	0	1 (0.0)
Transaminases increased	2 (0.1)	0	2 (0.1)
Immune related pneumonitis	10 (0.6)	2 (0.6)	12 (0.6)
Interstitial lung disease	0	1 (0.3)	1 (0.0)
Pneumonitis	10 (0.6)	1 (0.3)	11 (0.5)
Immune related pancreatitis	0	1 (0.3)	1 (0.0)
Autoimmune pancreatitis	0	1 (0.3)	1 (0.0)
Immune related rash	1 (0.1)	1 (0.3)	2 (0.1)
Drug eruption	0	1 (0.3)	1 (0.0)
Rash generalised	1 (0.1)	0	1 (0.0)
Other immune related adverse events: Guillain-Barre Syndrome	1 (0.1)	1 (0.3)	2 (0.1)
Miller Fisher syndrome	0	1 (0.3)	1 (0.0)
Guillain-Barre syndrome	1 (0.1)	0	1 (0.0)
Other immune related adverse events: Myositis	4 (0.2)	1 (0.3)	5 (0.2)
Myositis	2 (0.1)	1 (0.3)	3 (0.1)
Blood creatine phosphokinase increased	2 (0.1)	0	2 (0.1)
Immune related endocrinopathies: Adrenal insufficiency	3 (0.2)	0	3 (0.1)
Adrenal insufficiency	2 (0.1)	0	2 (0.1)
Adrenocortical insufficiency acute	1 (0.1)	0	1 (0.0)
Immune related endocrinopathies: Hypogonadism	0	0	0
Immune related endocrinopathies: Pituitary dysfunction	0	0	0
Immune related endocrinopathies: Type 1 Diabetes Mellitus	2 (0.1)	0	2 (0.1)
Diabetes mellitus	1 (0.1)	0	1 (0.0)
Hyperglycaemia	1 (0.1)	0	1 (0.0)
Immune related myocarditis	0	0	0
Other immune related adverse events: Encephalitis	0	0	0
Other immune related adverse events: GVHD	0	0	0
Other immune related adverse events: Myasthenic syndrome	0	0	0
Other immune related adverse events: Other	2 (0.1)	0	2 (0.1)
Psoriasis	1 (0.1)	0	1 (0.0)
Systemic inflammatory response syndrome	1 (0.1)	0	1 (0.0)
Other immune related adverse events: Uveitis	0	0	0

irAEs = Immune-related adverse events.
N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
irAEs with an onset after the on-treatment period are also considered in the avelumab + BSC arm of study B9991001, whereas treatment-emergent irAEs are shown for the Pooled Safety population.
A patient with multiple occurrences of an AE under one treatment is counted only once.
Events are coded in the latest MedDRA version available at the time of cut-off. Sorted in descending order of the frequency of irAE category and PTs within irAE category in the B9991001 Avelumab+BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

In the BSC arm of Study B9991001 only one subject presented with a serious irAE event, diabetes mellitus.

Table 65. irAE leading to permanent treatment discontinuation by irAE category - Pooled safety set and avelumab treated patients in Study B9991001

irAE category Preferred Term	Pooled Safety Population (N=1738) n (%)	B9991001 Avelumab + BSC (N=344) n (%)	Overall (N=2082) n(%)
Any irAEs	34 (2.0)	19 (5.5)	53 (2.5)
Immune related hepatitis	9 (0.5)	4 (1.2)	13 (0.6)
Alanine aminotransferase increased	3 (0.2)	2 (0.6)	5 (0.2)
Aspartate aminotransferase increased	1 (0.1)	1 (0.3)	2 (0.1)
Autoimmune hepatitis	2 (0.1)	1 (0.3)	3 (0.1)
Hepatotoxicity	0	1 (0.3)	1 (0.0)
Hepatitis	1 (0.1)	0	1 (0.0)
Transaminases increased	2 (0.1)	0	2 (0.1)
Immune related nephritis and renal dysfunction	0	3 (0.9)	3 (0.1)
Nephritis	0	1 (0.3)	1 (0.0)
Renal failure	0	1 (0.3)	1 (0.0)
Tubulointerstitial nephritis	0	1 (0.3)	1 (0.0)
Immune related pneumonitis	3 (0.2)	3 (0.9)	6 (0.3)
Interstitial lung disease	0	2 (0.6)	2 (0.1)
Pneumonitis	3 (0.2)	1 (0.3)	4 (0.2)
Immune related colitis	8 (0.5)	2 (0.6)	10 (0.5)
Colitis	3 (0.2)	2 (0.6)	5 (0.2)
Diarrhoea	5 (0.3)	0	5 (0.2)
Enterocolitis	1 (0.1)	0	1 (0.0)
Immune related endocrinopathies: Thyroid disorders	1 (0.1)	2 (0.6)	3 (0.1)
Autoimmune thyroiditis	0	1 (0.3)	1 (0.0)
Hyperthyroidism	0	1 (0.3)	1 (0.0)
Hypothyroidism	1 (0.1)	0	1 (0.0)
Immune related pancreatitis	0	2 (0.6)	2 (0.1)
Autoimmune pancreatitis	0	1 (0.3)	1 (0.0)
Pancreatitis	0	1 (0.3)	1 (0.0)
Immune related rash	3 (0.2)	1 (0.3)	4 (0.2)
Pruritus	0	1 (0.3)	1 (0.0)
Rash maculo-papular	1 (0.1)	1 (0.3)	2 (0.1)
Pemphigoid	1 (0.1)	0	1 (0.0)
Rash	1 (0.1)	0	1 (0.0)
Other immune related adverse events: Myositis	5 (0.3)	1 (0.3)	6 (0.3)
Myositis	3 (0.2)	1 (0.3)	4 (0.2)
Blood creatine phosphokinase increased	2 (0.1)	0	2 (0.1)
Other immune related adverse events: Other	1 (0.1)	1 (0.3)	2 (0.1)
Rheumatoid arthritis	1 (0.1)	1 (0.3)	2 (0.1)
Immune related endocrinopathies: Adrenal insufficiency	1 (0.1)	0	1 (0.0)

Adrenal insufficiency	1 (0.1)	0	1 (0.0)
Immune related endocrinopathies: Hypogonadism	0	0	0
Immune related endocrinopathies: Pituitary dysfunction	0	0	0
Immune related endocrinopathies: Type 1 Diabetes Mellitus	2 (0.1)	0	2 (0.1)
Diabetes mellitus	1 (0.1)	0	1 (0.0)
Hyperglycaemia	1 (0.1)	0	1 (0.0)
Immune related myocarditis	0	0	0
Other immune related adverse events: Encephalitis	0	0	0
Other immune related adverse events: GVHD	0	0	0
Other immune related adverse events: Guillain-Barre Syndrome	1 (0.1)	0	1 (0.0)
Guillain-Barre syndrome	1 (0.1)	0	1 (0.0)
Other immune related adverse events: Myasthenic syndrome	0	0	0
Other immune related adverse events: Uveitis	0	0	0

irAEs = Immune-related adverse events.
N: the number of subjects who have received at least one dose of avelumab.
The denominator to calculate percentages is N.
irAEs with an onset after the on-treatment period are also considered in the avelumab + BSC arm of study B9991001, whereas treatment-emergent irAEs are shown for the Pooled Safety population.
A patient with multiple occurrences of an AE under one treatment is counted only once.
Events are coded in the latest MedDRA version available at the time of cut-off. Sorted in descending order of the frequency of irAE category and PTs within irAE category in the B9991001 Avelumab+BSC arm.
Cut-off dates: 09Jun2016 on pooled safety population (EMR100070-001 and EMR100070-003 Part A), 21Oct2019 on study B9991001.

Table 66. Summary of irAEs Leading to Interruption of Avelumab by Cluster and PT – SAS Study B9991001

Cluster and Preferred Term	Avelumab+BSC (N=344)
	n (%)
Subjects with events	28 (8.1)
IMMUNE-RELATED ENDOCRINOPATHIES: THYROID DISORDERS	8 (2.3)
Hyperthyroidism	5 (1.5)
Hypothyroidism	3 (0.9)
IMMUNE-RELATED RASH	6 (1.7)
Rash	2 (0.6)
Erythema	1 (0.3)
Erythema multiforme	1 (0.3)
Purpura	1 (0.3)
Rash erythematous	1 (0.3)
Rash maculo-papular	1 (0.3)
IMMUNE-RELATED COLITIS	3 (0.9)
Colitis	2 (0.6)
Enteritis	1 (0.3)
Proctitis	1 (0.3)
IMMUNE-RELATED NEPHRITIS AND RENAL DYSFUNCTION	3 (0.9)
Renal failure	2 (0.6)
Nephritis	1 (0.3)
IMMUNE-RELATED PNEUMONITIS	3 (0.9)
Pneumonitis	2 (0.6)
Interstitial lung disease	1 (0.3)
IMMUNE-RELATED ENDOCRINOPATHIES: ADRENAL INSUFFICIENCY	2 (0.6)
Adrenal insufficiency	2 (0.6)
IMMUNE-RELATED HEPATITIS	2 (0.6)
Alanine aminotransferase increased	2 (0.6)
Aspartate aminotransferase increased	2 (0.6)
IMMUNE-RELATED ENDOCRINOPATHIES: TYPE 1 DIABETES MELLITUS	1 (0.3)
Hyperglycaemia	1 (0.3)

Table 66. Summary of irAEs Leading to Interruption of Avelumab by Cluster and PT – SAS Study B9991001

Cluster and Preferred Term	Avelumab+BSC (N=344)
	n (%)
OTHER IMMUNE-RELATED ADVERSE EVENTS: MYOSITIS	1 (0.3)
Myositis	1 (0.3)
OTHER IMMUNE-RELATED ADVERSE EVENTS: OTHER	1 (0.3)
Arthritis	1 (0.3)

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 within a preferred term are counted only once in that preferred term.
Subjects reporting multiple preferred terms within the same cluster are counted only once within each cluster.
Sorted in descending order of the frequency of Cluster and PTs in Avelumab + BSC arm.
MedDRA v22.1 coding dictionary applied.
Cut-off date: 21OCT2019 Snapshot Date: 21NOV2019

Immune-Related Adverse Events by Cluster

Immune-related pneumonitis

Immune-related pneumonitis occurred in 7 (2.0%) of patients receiving avelumab including 1 (0.3%) patient with grade 3 immune-related pneumonitis. Immune-related pneumonitis led to permanent discontinuation of avelumab in 0.9% of patients. Among the 7 patients with immune-related pneumonitis, the median time to onset was 3.6 months (range: 1.5 months to 13.8 months) and the median duration was 2.3 months (range: 1 month to 4.9 months). All 7 patients were treated with systemic corticosteroids; 4 (57.1%) of the 7 patients received high-dose corticosteroids for a median of 2.8 weeks (range: 1 week to 1.6 months). No patients received additional immunosuppressants. Resolution of immune-related pneumonitis occurred in 6 (85.7%) of the 7 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): immune-related pneumonitis occurred in 1.2% of patients receiving avelumab including 1 patient with grade 5 (0.1%), 1 with grade 4 (0.1%), and 5 with grade 3 (0.3%) pneumonitis.

Immune-related hepatitis

Immune-related hepatitis occurred in 1.5% of patients receiving avelumab including 5 (1.5%) patients with grade 3 immune-related hepatitis. Immune-related hepatitis led to permanent discontinuation of avelumab in 1.2% of patients. Among the 5 patients with immunerelated hepatitis, the median time to onset was 4.2 months (range: 2.8 months to 8.9 months), and the median duration was 2.2 months (range: 1.3 weeks to 3.0 months). All 5 patients were treated with high dose systemic corticosteroids for a median of 3.3 weeks (range: 1.9 weeks to 4.1 months). Resolution of immunerelated hepatitis occurred in 3 (60%) of the 5 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (Pooled Safety Dataset): Immune-related hepatitis occurred in 0.9% of patients receiving avelumab including 2 patients (0.1%) with Grade 5 and 11 patients (0.6 %) with Grade 3 immune-mediated hepatitis.

Immune-related colitis

Immune-related colitis occurred in 1.5% of patients receiving avelumab including 3 (0.9%) patients with grade 3 immune-related colitis. Immune-related colitis led to permanent discontinuation of

avelumab in 0.6% of patients. Among the 5 patients with immune-related-colitis, the median time to onset was 4.0 months (range: 2.1 weeks to 5.8 months) and the median duration was 3.7 weeks (range: 2 weeks to 5.4+ months). All 5 patients were treated with systemic corticosteroids; 4 (80%) of the 5 patients received high-dose corticosteroids for a median of 2 weeks (range: 1.0 day to 1.1 months). One patient was treated with a non-steroidal immunosuppressant. Resolution of immune-related colitis occurred in 4 (80%) of the 5 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (Pooled Safety Dataset): Immune-related colitis occurred in 1.5% of patients receiving avelumab including 7 patients (0.4%) with Grade 3 colitis.

Immune-related adrenal insufficiency

Immune-related adrenal insufficiency occurred in 0.9% of patients receiving avelumab. Immune-related adrenal insufficiency led to permanent discontinuation of avelumab in 0 patients. Among the 3 patients with immune-related adrenal insufficiency, the median time to onset was 3.7 months (range: 2 weeks to 6.5 months), and the median duration was 2.1 weeks (range: 2 weeks to 2.2 months). All 3 patients were treated with systemic corticosteroids; 1 (33.3%) of the 3 patients received high-dose corticosteroids for 2.3 weeks. Resolution of immune-related adrenal insufficiency occurred in 3 (100.0%) of the 3 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): immune-related adrenal insufficiency occurred in 0.5% of patients receiving avelumab including 1 patient (0.1%) with grade 3 adrenal insufficiency.

Immune-related: thyroid disorders

Immune-related thyroid disorders occurred in 12.2% of patients receiving avelumab including 1 (0.3%) patient with grade 3 immune-related thyroid disorders. Immune-related thyroid disorders led to permanent discontinuation of avelumab in 0.6% of patients. Hypothyroidism occurred in 37 (10.8%) patients; hyperthyroidism in 16 (4.7%) patients; and thyroiditis in 3 (0.9%) patients treated with avelumab. Among the 42 patients with immune-related thyroid disorders, the median time to onset was 1.9 months (range: 2.1 weeks to 9.4 months), and the median duration was not estimable (range: 3.0 days to 27.6+ months).

A total of 38 (90.5%) patients with immune-related thyroid disorders required thyroid hormonal replacement therapy, with 37 (88.1%) maintaining thyroid hormonal replacement therapy as of the data cut-off date. Five (11.9%) patients with immune-related thyroid disorders required antithyroid preparations.

Seven (16.7%) patients were treated with systemic corticosteroids; 6 (14.3%) of 42 patients received high-dose corticosteroids for a median of 1.9 weeks (range: 1.0 days to 2.2 months). Resolution off immune-related thyroid disorders occurred in 7 (16.7%) of the 42 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (Pooled Safety Dataset): Immune-related thyroid disorders occurred in 6% of patients receiving avelumab including 3 patients (0.2%) with Grade 3 immune-mediated thyroid disorders.

Immune-related type 1 diabetes mellitus

Immune-related type 1 diabetes mellitus occurred in 0.9% of patients receiving avelumab including 3 (0.9%) patients with grade 3 immune-related type 1 diabetes mellitus. Immune-related type 1 diabetes mellitus led to permanent discontinuation of avelumab in 0 patients. Among the 3 patients with immune-related type 1 diabetes mellitus, the median time to onset was 2.0 months (range: 0.7 days to 9.2 months) and the median duration was 4.1 weeks (range: 2 weeks to 4.8+ months).

Three (100.0%) patients with immune-related type 1 diabetes mellitus were treated with insulin. Resolution of immune-related type 1 diabetes mellitus occurred in 2 (66.7%) of the 3 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): immune-related type 1 diabetes mellitus without an alternative etiology occurred in 0.1% of patients including 2 cases (0.1%) of grade 3 hyperglycaemia that led to permanent discontinuation of avelumab.

Immune-related nephritis and renal dysfunction

Immune-related nephritis and renal dysfunction occurred in 1.7% of patients receiving avelumab including 1 (0.3%) patient with grade 3 immune-related nephritis and renal dysfunction. Immune-related nephritis and renal dysfunction led to permanent discontinuation of avelumab in 0.9% of patients. Among the 6 patients with immune-related nephritis and renal dysfunction, the median time to onset was 3.0 months (range: 1.6 months to 21.9 months), and the median duration was 3.1 weeks (range: 1.3 weeks to 6.1 months). All 6 patients were treated with systemic corticosteroids; 5 (83.3%) of the 6 patients received high-dose corticosteroids for a median of 2.4 weeks (range: 6.0 days to 2.8 months). Resolution of immune-related nephritis and renal dysfunction occurred in 4 (66.7%) of the 6 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): immune-related nephritis and renal dysfunction occurred in 0.1% of patients receiving avelumab.

Immune-related rash

Immune-related rash occurred in 10.2% of patients receiving avelumab including 5 (1.5%) patients with grade 3 immune-related rash. The grade 3 events were rash, erythema, drug eruption, rash maculo-papular, and erythema multiforme (1 patient each). None of these grade 3 events led to treatment discontinuation. The event of drug eruption was serious, occurred after the end of the on-treatment period, and at the start of another anticancer treatment. However, the event was adjudicated as an irAE based on clinical presentation and a conservative assessment. Immune-related rash led to permanent discontinuation of avelumab in 0.3% of patients. Among the 35 patients with immune-related rash, the median time to onset was 2.6 months (range: 0.7 days to 18.3 months), and the median duration was 2.5 months (range: 3.0 days to 21.5+ months).

Twenty two (62.9%) patients were treated with topical corticosteroids, for a median of 3.8 months (range: 1.0 day to 19.9 months). One (2.9%) patient received topical immunosuppressive drugs only (pimecrolimus). Eight (22.9%) patients were treated with systemic corticosteroids. Four (11.4%) of the 8 patients treated with systemic corticosteroids, received high-dose corticosteroids for a median of 1.9 weeks (range: 1.1 weeks to 3.8 months). Resolution of immune-related rash occurred in 22 (62.9%) of the 35 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): there is no specific section for immune-mediated rash in the current product information. However, the frequencies of immune-related rash events are presented in the table of adverse reactions:

  Common (≥1/100 to <1/10 patients): rash, pruritus, and rash maculo-papular

  Uncommon (≥1/1,000 to <1/100 patients): rash pruritic, erythema, rash generalised, psoriasis, rash erythematous, rash macular, rash papular, dermatitis exfoliative, erythema multiforme, pemphigoid, pruritus generalised.

Immune-related myositis

Immune-related myositis occurred in 0.6% of patients receiving avelumab including 2 (0.6%) patients with grade 3 immune-related myositis. Immune-related myositis led to permanent discontinuation of avelumab in 0.3% of patients. Among the 2 patients with immune-related myositis, the median time to onset was 2.3 months (range: 2.1 weeks to 4.2 months), and the median duration was 2.0 months (range: 2.3 weeks to 3.4 months). Both patients were treated with high dose systemic corticosteroids for a median of 2 weeks (range: 6.0 days to 3.1 weeks). Resolution of immune-related myositis occurred in 2 (100.0%) of the 2 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): there is no section specific to immune-related myositis in the current product information. However, immune-related myositis was reported in less than 1% of patients in studies of avelumab as a single agent in patients with solid tumours.

Immune-related pancreatitis

Immune-related pancreatitis occurred in 0.6% of patients receiving avelumab including 1 (0.3%) patient with grade 3 immune-related pancreatitis. Immune-related pancreatitis led to permanent discontinuation of avelumab in 0.6% of patients. Among the 2 patients with immune-related pancreatitis, the median time to onset was 1.5 months (range: 1.4 months to 1.6 months), and the median duration was not estimable (range: 1 week to 2.6+ months). Both patients were treated with systemic corticosteroids; 1 (50%) of the 2 patients received high-dose corticosteroids for 2 days. Resolution of immune-related pancreatitis occurred in 1 (50.0%) of the 2 patients at the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): immune-related pancreatitis occurred in less than 1% of patients receiving avelumab as a single agent.

Immune-related other: uveitis

Immune-related uveitis occurred in 1 (0.3%) patient receiving avelumab, with an onset at 9.1 months and a duration of 2.0 months. Immune related uveitis resolved by the time of data cut-off.

Prior experience:

- Current avelumab product information (pooled safety dataset): there is no section specific to immune-mediated uveitis in the current product information. However, immune-related uveitis was reported in less than 1% of patients in studies of avelumab as a single agent in patients with solid tumours.

Immune-related other: Guillain-Barre syndrome

Grade 3 immune-related Guillain-Barre syndrome (PT = Miller-Fisher Syndrome) occurred in 1 (0.3%) patient receiving avelumab with an onset at 2.6 months. Immune related Guillain-Barre syndrome did not resolve by the time of data cut-off. The patient was treated with high-dose systemic corticosteroids for 15.8 months.

Prior experience:

- Current avelumab product information (pooled safety dataset): there is no section specific to immune-related Guillain-Barre syndrome. However, immune-related Guillain-Barre syndrome was reported in less than 1% of patients in studies of avelumab as a single agent in patients with solid tumours.

Immune-related other: other

Immune-related other adverse events occurred in 2.6% of patients receiving avelumab, including 1 (0.3%) patient with grade 3 rheumatoid arthritis, and 1 (0.3) patient with grade 3 oligoarthritis. Grade 3 rheumatoid arthritis led to permanent discontinuation of avelumab.

The patient with grade 3 rheumatoid arthritis had been diagnosed with this disease before study entry and experienced a disease flare during the study. Avelumab was withdrawn and the patient was treated with dexamethasone, hydroxychloroquine, prednisone, methotrexate and sulfasalazine. The patient was recovering at the time of data cut-off.

The patient with grade 3 oligoarthritis was also suffering with psoriasis and received several short cycles of systemic corticosteroids over a period of approximately 2 months to manage the event. Avelumab was continued. The events resolved.

Prior experience:

- Current avelumab product information (pooled safety dataset): there is no section in the current product information for events categorized here as "other". The exception is psoriasis which is listed as an uncommon (≥1/1,000 to <1/100 patients) immune-related AE.

Safety in special populations

Table 67 Selected Safety Data by Age Group in the Avelumab + BSC Arm of Study B9991001

MedDRA Terms	<65 years (N=129) n (%)	65-<75 years (N=130) n (%)	75-<85 years (N=80) n (%)	≥ 85 years (N=5) n (%)
Total AEs	127 (98.4)	128 (98.5)	77 (96.3)	5 (100.0)
Patients with SAEs - Total	29 (22.5)	38 (29.2)	25 (31.3)	4 (80.0)
Serious AEs – Total	44	61	40	8
- Fatal	3 (6.8)	1 (1.6)	2 (5.0)	0
- Hospitalization/prolong existing hospitalization	43 (97.7)	54 (88.5)	37 (92.5)	8 (100.0)
- Life-threatening	1 (2.3)	1 (1.6)	0	0
- Disability/incapacity	1 (2.3)	0	0	0
- Other (medically significant)	3 (6.8)	5 (8.2)	3 (7.5)	0
AE leading to drop-out[1]	13 (10.1)	15 (11.5)	11 (13.8)	2 (40.0)
Psychiatric disorders	18 (14.0)	10 (7.7)	8 (10.0)	2 (40.0)
Nervous system disorders	35 (27.1)	26 (20.0)	21 (26.3)	3 (60.0)
Accidents and injuries	11 (8.5)	15 (11.5)	13 (16.3)	1 (20.0)

MedDRA Terms	<65 years (N=129) n (%)	65-<75 years (N=130) n (%)	75-<85 years (N=80) n (%)	≥ 85 years (N=5) n (%)
Cardiac disorders	6 (4.7)	12 (9.2)	3 (3.8)	1 (20.0)
Vascular disorders	9 (7.0)	13 (10.0)	13 (16.3)	1 (20.0)
Cerebrovascular disorders	1 (0.8)	2 (1.5)	1 (1.3)	0
Infections and infestations	68 (52.7)	61 (46.9)	43 (53.8)	5 (100.0)
Anticholinergic syndrome	35 (27.1)	31 (23.8)	25 (31.3)	2 (40.0)
Quality of life decreased[2]	NA	NA	NA	NA
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[3]	12 (9.3)	13 (10.0)	13 (16.3)	1 (20.0)
irAEs	33 (25.6)	35 (26.9)	31 (38.8)	2 (40.0)
IRRs	23 (17.8)	24 (18.5)	27 (33.8)	0

1. AEs leading to drop-out are TEAEs leading to permanent treatment discontinuation, 2. No analysis of QoL by age was done for Study B9991001 3. The "Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures" includes the PTs of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and the HLGT of Fractures. The following AE categories have been analyzed by MedDRA SMQs (broad and narrow): Accidents and Injuries (SMQ: Accidents and Injuries), Cerebrovascular disorders (SMQ: Central nervous system vascular disorders), and Anticholinergic syndrome (SMQ: Anticholinergic syndrome). The "Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures" includes the PTs of Orthostatic hypotension, Fall, Loss of consciousness, Syncope, Dizziness, Ataxia, and the HLGT of Fractures

Immunogenicity

Blood samples for evaluation of avelumab immunogenicity were collected from patients on Arm A within 2 hours before the start of the avelumab infusion on Day 1 and Day 15 of Cycles 1 through 3 and then on Day 1 of Cycle 5, 7, 9, 11, and 13.

Treatment-induced ADA incidence was 62 of 325 patients (19.1%) treated with avelumab with 43 (13.2%) having persistent ADA response and 19 (5.8%) having transient response in study B9991001. Of the patients who were ADA positive at baseline (n=4, 1.2% patients), none had treatment-boosted ADA (Table 68).

Table 68. Summary of Subject ADA Categories - Immunogenicity Analysis Set Study B9991001

	Avelumab+BSC (N=344) n (%)
Subjects with at least one valid ADA result at any time point (N0)	344 (100.0)
Subjects with valid baseline ADA result (N1)	329 (95.6)
Subjects with valid baseline ADA results and at least one valid post-baseline ADA result (N2)	329 (95.6)
Subjects with at least one valid post-baseline ADA result and without positive baseline ADA result (N3)	325 (94.5)
ADA never-positive (n/N0)	278 (80.8)
ADA ever-positive (n/N0)	66 (19.2)
Baseline ADA positive (n/N1)	4 (1.2)
Treatment-boosted ADA (n/N2)	0
Treatment-induced ADA (n/N3)	62 (19.1)
Transient ADA response (n/N3)	19 (5.8)
Persistent ADA response (n/N3)	43 (13.2)

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: 29DEC2019 (22:00) Source Data: ADIS Output File: ./B9991001_restricted/B9991001/adis_s001 Date of Generation: 14JAN2020 (09:20) Cutoff Date: 30JUN2019 Snapshot Date: 24DEC2019

Of the 62 patients with treatment-induced ADA, the median time to ADA positive value was 10.2 weeks (range: 2.1, 35.7). The median duration seropositivity was 2.4 weeks (95% CI 0.1, 7.7).

No effect of ADA status on avelumab PK was detected (see Pharmacokinetics section above).

Adverse events by treatment-induced ADA vs ADA never-positive or baseline ADA positive status are summarized in Table 69. The percentage of patients reporting TEAEs was similar for treatment-induced ADA-positive patients (98.4%) and ADA never-positive or baseline ADA-positive patients (97.9%). The proportions of patient with reported Grade ≥ 3 TEAEs (51.6% versus 46.5%), serious TEAEs (35.5% versus 26.2%), TEAEs leading to discontinuation of avelumab (17.7% versus 10.6%), and IRRs (27.4% versus 20.2%) were numerically higher in the treatment-induced ADA positive patients than in the ADA never-positive or baseline ADA positive patients, respectively; however, the comparison was limited by the overall low incidence of immunogenicity.

Table 69. Summary of Adverse Events, by Treatment-Induced ADA versus ADA Never-Positive or Baseline ADA Positive - Immunogenicity Analysis Set Study B9991001

	Avelumab+BSC		
	Treatment-induced ADA (N=62)	ADA never-positive or baseline ADA positive (N=282)	Total (N=344)
Number (%) of Subjects	n (%)	n (%)	n (%)
Subjects with TEAEs	61 (98.4)	276 (97.9)	337 (98.0)
Subjects with Grade ≥3 TEAEs	32 (51.6)	131 (46.5)	163 (47.4)
Subjects with Serious TEAEs	22 (35.5)	74 (26.2)	96 (27.9)
Subjects with TEAEs Leading to Dose Reduction of Avelumab	0	1 (0.4)	1 (0.3)
Subjects with TEAEs Leading to Discontinuation of Avelumab	11 (17.7)	30 (10.6)	41 (11.9)
Subjects with Infusion-Related Reactions (IRRs)	17 (27.4)	57 (20.2)	74 (21.5)

The denominator to calculate percentages is N, the number of subjects in the immunogenicity analysis set within each ADA category.
MedDRA v22.1 coding dictionary and CTCAE version 4.03 applied.
PFIZER CONFIDENTIAL SDTM Creation: 22NOV2019 (07:14) Source Data: ADAE Output File: ./B9991001_restricted/B9991001/adae_ada_s020_1 Date of Generation: 14JAN2020 (10:00) Cutoff Date: 30JUN2019 Snapshot Date: 24DEC2019

A previously assessed ADA assay (aRCC indication) was used in the current analysis. The incidence of treatment induced ADAs in the UC population was 19.1%, which is slightly higher than in the aRCC population (14.6%) where the same ADA assay was used. It is, however, agreed that ADA formation does not seem to be influential for avelumab PK or safety in the UC population.

2.5.1. Discussion on clinical safety

The safety data to support the claimed extension of indication for bavencio as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy, are based on data from the interim analysis of the phase 3 study B9991001. The safety database for study B9991001 consisted of 689 patients receiving any study treatment with avelumab plus BSC (n=344) or BSC (n=345). Safety database cut-off date was January 19, 2020 (12 weeks after CSR data cut-off date).

The pooled safety data set for avelumab monotherapy consisted of patients from EMR100070-001 and study EMR100070-003, in total 1738 patients.

The median treatment duration in study B9991001 was 25.3 weeks (range: 2.0, 173.9) in the avelumab plus BSC arm and considerably shorter, 13.1 weeks (range: 0.1, 168.4) in the BSC alone arm (19 Jan 2020). Patients with PD-L1-positive tumours are exposed to avelumab for longer time compared to patients with PD-L1-negative tumours. Mean and median exposure to avelumab is about double in study B9991001 compared to the pooled safety set.

Adverse events were observed in nearly all patients treated with avelumab. Compared with only BSC, the incidence for AEs was higher in patients treated with avelumab. The difference is more pronounced for ARs of grade 3 or higher. AEs reported from study B9991001, which were considerably more common in the avelumab plus BSC arm, were irAEs and IRRs, which could be expected. In relation to

the pooled safety set, IRRs were similar as observed in study B9991001, but irAEs were more common in Study B9991001.

The most commonly reported AE for patients in study B9991001 treated with avelumab plus BSC was fatigue, 17.7%. This was more common in the pooled safety set with 32.4%. The most frequent AEs were generally more common in study B9991001 for patients treated with avelumab plus BSC compared to only BSC. There are no major differences between patients with PD-L1-positive tumours and the entire population in study B9991001.

Overall, the majority of deaths was caused by disease progression in both the pooled safety set and study B9991001. The proportion was lower in patients with PD-L1-positive tumours compared to all other groups. Deaths caused by study treatment toxicity was higher in patients in study B9991001 treated with avelumab plus BSC (0.6%) compared to the pooled safety population (0.2%). However, the absolute number of deaths assessed by the investigator to be due to study treatment is low and the reported cases display several confounding factors that do not support a clear relationship to study treatment.

The frequency of deaths attributed to AEs not related to study treatment is lower (0.6%) in the avelumab plus BSC care arm compared to the pooled safety set (3.4%). The frequency of death related to unknown causes was the same in both treatment arms (1.7%) of study B9991001 and lower compared to the pooled safety population (4.8%). In the avelumab + BSC arm of study B9991001, all patients in the "Unknown" subgroup were diagnosed with disease progression, 3 out of 6 patients received some new anti-cancer therapy after avelumab, and in all patients the death occurred ≥3 months after the last dose of avelumab.

In conclusion, the frequency of deaths not attributed to disease progression in study B9991001 do not raise any serious new safety concerns for avelumab monotherapy treatment for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.

Serious AEs were less frequent or similar in study B9991001 compared to the pooled safety set overall and for all organ system except for "renal and urinary disorders" where the proportion of affected was doubled. For intra study comparison of serious AEs in study B9991001, serious adverse events are more common among patients treated with avelumab plus BSC, 27.9% compared to the BSC arm, 20.0%. The similar incidence of serious acute kidney injury in both arms (1.7%) in study B9991001 suggest that this, in part, can be attributed to the patient population. However, the incidence of serious acute kidney injury is similar also in the pooled safety set (1.6%). Overall, the profile of serious AEs in study B9991001 does not raise any concern.

The proportion of patients that interrupted the treatment with avelumab was almost double for patients in study B9991001 compared to the pooled safety set, 40.7% compared to 20.9 %. The exposure adjusted analysis shows a slight increase for patients with AEs leading to interruption of avelumab treatment. Incidence rate per 100 patient months for study B9991001 was 6.1 compared to the pooled safety population 5.0. This is not as pronounced as the non-adjusted analysis. The proportion of patients that discontinued treatment was quite similar between the groups, 11.9% for the study B9991001 and 14.0% for the pooled safety set. Exposure adjusted analysis show a lower treatment (about half) discontinuation of avelumab in study B9991001 compared to the Pooled Safety Set (1.3 vs. 2.9). In conclusion, the dose interruptions and proportion of patients discontinuing avelumab treatment raises no new safety concerns.

The most common irAEs categories in study B9991001 of any grade and with an incidence over 1% for patients treated with avelumab plus BSC were: immune-related endocrinopathies: thyroid disorders (12.2%), immune-related rash (10.2%), other immune-related adverse events: other (2.6%),

immune-related pneumonitis (2.0%), immune-related nephritis and renal dysfunction (1.7%), immune-related colitis (1.5%) and immune-related hepatitis (1.5%). The most common irAE categories of grade 3 and above and with an incidence over 1% in study B9991001 for patients treated with avelumab plus BSC was: immune-related rash (1.5%) and immune-related hepatis (1.5%). For the pooled safety population, the most common irAE categories of any grade and with an incidence over 1% were: immune-related endocrinopathies: thyroid disorders (5.6%), immune-related rash (5.2%), immune-related pneumonitis (1.2%) and immune-related colitis (1.5%). There was no irAE category of grade 3 and above with an incidence over 1% in the pooled safety set.

IrAEs weremore common in study B9991001 for patients treated with avelumab plus BSC, 29.4% compared to 14.2% in the pooled safety set. There was also a higher frequency of irAEs of grade 3 and above (7.0% vs. 2.2%), irAEs leading to discontinuation (5.5% vs. 2.0%) and serious irAEs (4.7 % vs. 2.5%). Generally, the irAE categories of all grades and 3 and higher were more common in study B9991001 compared to the pooled safety population or of similar frequency.1.4% of the patients in the BSC arm in study B9991001 reported irAEs, and 0.3% were of grade 3 and higher. The median time to onset of irAEs is highly variable. The resolution of irAEs differed between irAEs from 16.7% for immune related thyroid disorders to 100% for immune related adrenal insufficiency at the time of data cut-off. The exposure adjusted IR per 100 patient months of irAEs is higher in study B9991001 compared to the pooled population, 4.1 compared to 3.3However, this increase raises no major concern in relation to the benefit risk assessment.

Overall, presented data do not imply that the safety profile would be markedly different in patients with PD-L1-positive and PD-L1-negative tumours.

The incidence of treatment induced ADAs in the UC population was 19.1%, which is slightly higher than in the aRCC population (14.6%) where the same ADA assay was used. The graphical analysis based on the population PK analysis does not indicate that ADA formation is influential for PK. Furthermore, the exposure-safety analysis did not indicate that ADA formation is a factor for the probability of adverse events. Thus, it is agreed that ADA formation does not seem to be influential for avelumab PK or safety in the UC population.

2.5.2. Conclusions on clinical safety

Overall, the safety profile of avelumab in the pivotal study B9991001 is similar, regardless of PD-L1-status, to the previously reported safety profile of avelumab monotherapy. No new safety concerns were raised, and the safety profile is considered manageable.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 5.0 is acceptable.

The CHMP endorsed the Risk Management Plan version 5.0 with the following content: The safety profile of Bavencio monotherapy in the new indication is comparable to the already established safety profile of avelumab monotherapy in other solid tumours.

Therefore, no changes to the safety concerns, Pharmacovigilance plan or Risk minimisations measures are needed.

Existing pharmacovigilance plan and risk minimisations measures remain sufficient to address the risk of the product in all approved indications.

Safety concerns

Summary of safety concerns	
Important identified risks	Immune-related pneumonitis Immune-related hepatitis Immune-related colitis Immune-related pancreatitis Immune-related myocarditis Immune-related endocrinopathies (thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus, pituitary disorders) Other immune-related events (myositis, Guillain-Barré syndrome, uveitis, myasthenia gravis/myasthenic syndrome) Immune-related nephritis and renal dysfunction Severe infusion-related reactions (grade ≥ 3)
Important potential risks	Other immune-related events (encephalitis) Severe cutaneous reactions Immunogenicity Embryofetal toxicity
Missing information	Safety in patients with autoimmune disease Safety in patients with HIV, Hepatitis B or C infections Safety in patients with organ transplants Long-term treatment Safety and efficacy in immune compromised patients

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None				
Non-interventional cohort registry study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070-0031) Planned	5-year open cohort study (based on primary data collection) of patients with MCC in Germany to 1) describe patient characteristics (including co-morbidities and concomitant medications), 2) estimate background rates of relevant comorbidities, 3) describe treatment patterns, 4) characterize disease outcomes (overall, per treatment and in immune compromised patients treated with avelumab), 5) describe safety events of interest (e.g., immune-related adverse drug reactions) overall and in immune compromised patients treated with avelumab Exploratory objectives: Compare safety and effectiveness profile of avelumab in immune compromised patients with immune competent patients	Safety in immune compromised patients in addition to gathering of other real-world data	Interim reports	Interim reports (first interim annual progress update report on 03/2020 and following reports yearly)
			Final report	31/12/2024

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Immune-related pneumonitis	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of pneumonitis in SmPC section 4.2* *Warning to monitor for immune-related pneumonitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related pneumonitis in patients exposed to avelumab in the ongoing clinical trials*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Description of immune-related pneumonitis observed in clinical trials in SmPC section 4.8 *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their lungs in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Additional pharmacovigilance activities: *None*
Immune-related hepatitis	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of hepatitis in SmPC section 4.2* *Warning to monitor for immune-related hepatitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related hepatitis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their liver in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related hepatitis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immune-related colitis	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of colitis in SmPC section 4.2* *Warning to monitor for immune-related colitis and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of Immune-related colitis observed in clinical trials in SmPC section 4.8*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related colitis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their intestines in PL section 2 *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	
Immune-related pancreatitis	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab due to immune-related pancreatitis in SmPC section 4.2* *Warning to monitor for immune-related pancreatitis and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their pancreas in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related pancreatitis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immune-related myocarditis	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab due to immune-related myocarditis in SmPC section 4.2* *Warning to monitor for immune-related myocarditis and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems due to inflammation of their heart in PL section 2* *PL section 4* *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related myocarditis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: *Patient Educational Material*	
Immune-related endocrinopathies (thyroid disorders)	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for changes in thyroid function and signs and symptoms of thyroid disorders and treatment advice in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related endocrinopathies including thyroid disorders observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related endocrinopathies (thyroid disorders) in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immune-related endocrinopathies (adrenal insufficiency)	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for signs and symptoms of adrenal insufficiency and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of Immune-related endocrinopathies including adrenal insufficiency observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related endocrinopathies (adrenal insufficiency) in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: *Patient Educational Material*	
Immune-related endocrinopathies (type 1 diabetes mellitus)	Routine risk minimization measures: *Guidance for withholding avelumab based on the severity of endocrinopathies in SmPC section 4.2* *Warning to monitor for hyperglycaemia or other signs and symptoms of diabetes and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of immune-related endocrinopathies including type 1 diabetes mellitus observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have type 1 diabetes mellitus including acid in the blood produced from diabetes in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related endocrinopathies (type 1 diabetes mellitus) in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immune-related endocrinopathies (pituitary disorders)	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (hypopituitarism) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their hormone producing glands in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related endocrinopathies (pituitary disorders) in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
Other immune-related events (myositis)	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (myositis) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have inflammation of their muscles in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related myositis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Other immune-related events (Guillain-Barré syndrome)	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (Guillain-Barré syndrome) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have an autoimmune disease in PL section 2* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of other immune-related events (Guillain-Barré syndrome) in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Other immune-related events (uveitis)	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to monitor for other immune-related adverse reactions (uveitis) and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of other immune-related events (uveitis) in patients exposed to avelumab in the ongoing clinical trials*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Warning for the patient to talk to their doctor before receiving avelumab if they have an autoimmune disease in PL section 2 *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Additional pharmacovigilance activities: *None*
Other immune-related events (myasthenia gravis/myasthenic syndrome)	Routine risk minimisation measures: *Guidance for withholding or discontinuing avelumab based on the severity of other immune-related adverse reactions in SmPC section 4.2* *Warning to adequately evaluate other immune-related adverse reactions (*myasthenia gravis/myasthenic syndrome) *and treatment advice based on severity in SmPC section 4.4.* *SmPC section 4.8* *Myasthenia gravis/myasthenic syndrome listed as an adverse reaction in SmPC section 4.8* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of other immune-related myasthenia gravis/ myasthenic syndrome in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immune-related nephritis and renal dysfunction	Routine risk minimization measures: *Guidance for withholding or discontinuing avelumab based on the severity of nephritis and renal dysfunction in SmPC section 4.2* *Warning to monitor for immune-related nephritis and renal dysfunction and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Description of the case of immune-related nephritis observed in clinical trials in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have problems with their kidneys in PL section 2* *PL section 4* *Legal status (prescription only medicine)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of immune-related nephritis and renal dysfunction in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: *Patient Educational Material*	
Severe infusion-related reactions (grade ≥ 3)	Routine risk minimization measures: *Guidance to pre-medicate with an antihistamine and paracetamol prior to the first 4 infusions of avelumab in SmPC section 4.2* *Guidance for withholding or discontinuing avelumab based on the severity of infusion-related reactions in SmPC section 4.2* *Description of infusion-related reactions observed in clinical trials in SmPC section 4.4* *Warning to monitor for infusion-related reactions and treatment advice based on severity in SmPC section 4.4* *SmPC section 4.8* *Information that anti-drug antibodies (ADA) positive patients may be at increased risk of infusion-related reactions in SmPC section 4.8* *Warning for the patient to talk to their doctor before receiving avelumab if they have infusion-related reactions in PL section 2* *Information for the patient that they will receive paracetamol and an antihistamine before at least the first 4 treatments of avelumab in PL section 3* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *Patient Educational Material*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of severe infusion-related reactions in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Other immune-related events (encephalitis)	Routine risk minimization measures: *Warning to monitor for immune-related adverse reactions and treatment advice based on etiology in SmPC section 4.4* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL section 4*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of other immune-related event encephalitis in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Legal status (prescription only medicine) Additional risk minimization measures: None	*None*
Severe cutaneous reactions	Routine risk minimization measures: *Warning to monitor for immune-related adverse reactions and treatment advice based on etiology in SmPC section 4.4* *SmPC section 4.8* *Information that avelumab works on the immune system and may cause inflammation which may be serious and life-threatening requiring avelumab withdrawal or treatment in PL section 4* *PL section 4* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of severe cutaneous reactions in patients exposed to avelumab in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Immunogenicity	Routine risk minimization measures: *Information that treatment-emergent ADA were observed in clinical trials and that there may be an increased risk for infusion-related reactions in ADA positive patients but the impact of ADA on pharmacokinetics, efficacy and safety is uncertain and the impact of neutralizing antibodies (nAb) is unknown in SmPC section 4.8* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of subjects developing ADAs in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Embryofetal toxicity	Routine risk minimization measures: *Guidance for women of childbearing to avoid becoming pregnant and to use effective contraception during treatment and for at least 1 month after the last dose in SmPC section 4.6* *Guidance that avelumab is not recommended for use during pregnancy unless the woman requires treatment in SmPC section 4.6*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Information that there are no or limited data in pregnant women in SmPC section 4.6 *Information that blockade of PD-L1 signalling has been shown to disrupt tolerance to the fetus and result in increased fetal loss in murine models of pregnancy in SmPC section 5.3* *Guidance for the patient to seek advice before taking avelumab if they are pregnant, think they may be pregnant or are planning to have a baby in PL section 2* *Warning for the patient not to use avelumab if they are pregnant unless their doctor specifically recommends it in PL section 2* *Guidance for a woman to use effective contraceptives while they are being treated and for at least 1 month after their last dose in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	
Safety in patients with autoimmune disease	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease were excluded from clinical trials in SmPC section 4.4* *Information that patients with active or a history of autoimmune disease were excluded from Study EMR100070-003 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Safety in patients with HIV, Hepatitis B or C infections	Routine risk minimization measures: *Information that patients with conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical trials in SmPC section 4.4 and section 5.1*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities:

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have human immunodeficiency virus (HIV) infection or acquired immune deficiency syndrome (AIDS) in PL section 2 *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have ever had chronic viral infection of the liver, including hepatitis B (HBV) or hepatitis C (HCV) in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	*None*
Safety in patients with organ transplants	Routine risk minimization measures: *Information that patients with an organ transplant were excluded from clinical trials in SmPC section 4.4* *Information that patients with an organ transplant were excluded from Study EMR100070-003 in SmPC section 5.1* *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have had an organ transplant in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *None*
Long-term treatment	Routine risk minimization measures: *Legal status (prescription only medicine)* Additional risk minimization measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Further monitoring and characterization of long-term avelumab treatment in the ongoing clinical trials* Additional pharmacovigilance activities: *None*
Safety and efficacy in immune compromised patients	Routine risk minimization measures: *Information that patients with active or a history of autoimmune disease, organ transplant, conditions requiring therapeutic immune suppression or active infection with HIV, or hepatitis B or C were excluded from clinical*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Review of data from an Early Access Program with mMCC patients*

Safety concern	Risk minimization measures	Pharmacovigilance activities
	trials in SmPC section 4.4 and section 5.1 *Guidance for the patient to check with their doctor or nurse before receiving avelumab if they have an autoimmune disease in PL section 2* *Legal status (prescription only medicine)* Additional risk minimization measures: None	Additional pharmacovigilance activities: *Non-interventional cohort study to assess characteristics and management of patients with Merkel cell carcinoma in Germany (Study MS100070_0031)*

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the Package Leaflet has been submitted by the MAH. However, the changes to the Package Leaflet are minimal and do not require user consultation with target patient groups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bavencio (avelumab) is included in the additional monitoring list as it is a new active substance and it is biological product that is authorised after 1 January 2011.

Therefore, the Summary of Product Characteristics and the Package Leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Final Indication:

Bavencio is indicated as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.

The aim of the maintenance therapy with avelumab is to extend the durability of the initial benefit of platinum-based chemotherapy.

3.1.2. Available therapies and unmet medical need

Platinum-based regimens are the standard-of-care first-line treatment for patients with aUC and result in median OS ranging from 9-14 months (De Santis et al, 2012; Calabro et al, 2009). Despite initial high response rates, durations of progression free survival (PFS) and overall survival (OS) are limited because of emergent chemotherapy resistance. Further, severe side effects limit long-term use of current chemotherapy agents. Following successful first-line treatment, patients are typically managed with best supportive care (BSC) until disease progression. Most patients will experience disease progression within 9 months after the initiation of treatment (von der Maase et al, 2005).

Recently approved PD-L1 inhibitors are new systemic therapies for metastatic UC, both for first-line treatment in cisplatin-ineligible patients for patients with tumours expressing ≥ 5% PD-L1 and for patients experiencing disease progression after platinum-based chemotherapy regardless of PD-L1-status.

Galsky et al evaluated PD-1 inhibitor pembrolizumab as a maintenance treatment versus placebo in a Phase 2 study in patients with metastatic UC following first-line treatment. PFS according to irRECIST was significantly longer in patients randomized to pembrolizumab versus placebo (log-rank p=0.038; Galsky et al, 2019).

3.1.3. Main clinical studies

The pivotal trial for this application is study B9991001 ("JAVELIN Bladder 100"), a Phase 3, multicentre, multinational, randomized, open-label, parallel-arm study of avelumab (MSB0010718C) plus BSC versus BSC alone as a maintenance treatment in patients with locally advanced or metastatic urothelial carcinoma whose disease did not progress after completion of first-line platinum-containing chemotherapy.

Primary objective was to demonstrate the benefit of avelumab plus BSC versus BSC alone in prolonging OS for patients with PD-L1 positive tumours and in all randomized patients.

3.2. Favourable effects

The primary objective of OS is appropriate as it also would weigh in the answer to the question of whether it is preferable to use the treatment option PD-L1 following response to first-line chemotherapy treatment or save the option for use in later treatment lines. The proportion of patients receiving second line treatment with a PD-L1-inhibitor was considerably higher for patients receiving BSC as maintenance treatment, 43.7%, than for patients receiving avelumab plus BSC, 6.3%.

For OS, results from two data cut-offs are available, including a requested later cut-off 90 days after the pre-planned interim analysis (19 January 2020), while the results from all other efficacy endpoints stem from the interim analysis (21 October 2019).

The primary endpoint OS (21 October 2019) was statistically significant in all patients (n=700) assigned to avelumab plus BSC compared with patients assigned to BSC (stratified hazard ratio (HR) 0.69; 95% confidence interval (CI) 0.556, 0.863; 1-sided p-value 0.0005). The median OS was 21.4 months (95% CI: 18.9, 26.1) in the avelumab plus BSC arm, and 14.3 months (95% CI: 12.9, 17.9) in the BSC arm. In patients with PD-L1-positive tumours (n=358) a statistically significant OS was also demonstrated for patients assigned to avelumab plus BSC compared with patients assigned to BSC (stratified HR 0.56; 95% CI: 0.404, 0.787; 1-sided p -value 0.0003). The median OS was not reached (95% CI: 20.3 months, not reached) in the avelumab plus BSC arm, and was 17.1 months (95% CI: 13.5, 23.7) in the BSC arm.

The updated OS-data (19 January 2020) with an additional 90 days of follow-up rendered a median OS for all patients assigned to avelumab plus BSC of 22.1 months (95% CI 19.0, 26.1) and for patients treated with BSC of 14.6 months (95% CI 12.8, 17.8) and HR 0.70 (95% CI 0.564, 0.862; 2 sided p-value 0.0008). For patients with PD-L1-positive tumours the updated median OS was not evaluable (NE) (95% CI 20.6, NE) for patients treated with avelumab plus BSC and 17.5 months (95% CI 13.5, 31.6) for the BSC patients, HR 0.60 (95% CI 0.439, 0.833; 2-sided p-value 0.0019). The OS results from the later data cut-off date are very similar to the results presented from the planned data cut-off date.

In all randomized patients, patients assigned to avelumab plus BSC had a statistically significant PFS (by BICR assessment per RECIST v1.1), compared with patients assigned to BSC with stratified HR 0.62 (95% CI: 0.519, 0.751; nominal 2-sided p value <0.0001). The median PFS for avelumab plus BSC was 3.7 months (95% CI: 3.5, 5.5) and for BSC 2.0 months (95% CI: 1.9, 2.7) in all randomized patients. In patients with PD-L1-positive tumours, the median PFS for avelumab plus BSC was 5.7 months (95% CI: 3.7, 7.4) and for BSC 2.1 months (95% CI: 1.9, 3.5) with stratified HR 0.56 (95% CI 0.431, 0.728; 2-sided p-value <0.0001).

OS and PFS for patients with PD-L1-negative tumours was an exploratory analysis and part of the subgroup analysis. OS and PFS for patients with PD-L1-unknown tumours (n=72) was not a prespecified endpoint. In patients with PD-L1-negative tumours (n=270), the median OS (19 Jan 2020) was 18.9 months (95% CI 13.3, 22.1) for patients treated with avelumab plus BSC and for BSC 13.4 months (95% CI 10.4, 17.3), with a HR 0.83 (95% CI 0.603, 1.131). There were no signs of a detrimental effect on OS in patients with PD-L1-negative tumours treated with avelumab plus BSC compared to BSC. PFS by BICR assessment for patients with PD-L1-negative tumours was prolonged for patients treated with avelumab in combination with BSC (3.0 months (95% CI 2.0, 3.7)) compared to BSC (1.9 months (95% CI 1.9, 2.1), HR 0.63 (95% CI 0.474, 0.847).

3.3. Uncertainties and limitations about favourable effects

The efficacy data from patients with PD-L1-unknown tumours are challenging to interpret due to very low patient numbers. However, no evident detrimental effect on PFS or OS is seemingly detected in patients with PD-L1-unknown tumours.

Patients with PD-L1-negative tumours, on a group level, display a modest prolongation of PFS with avelumab plus BSC compared with BSC alone and no signs of a detrimental effect on OS. The OS subgroup analyses in patients with PD-L1-negative tumours generally present with HR of ≤1, albeit with large confidence intervals due to small patient samples and more heterogeneity compared to the PFS subgroup results. No conclusion can be drawn that any patient population display a detrimental effect on OS that would motivate an exclusion of this patient population from the indication. It is noted that for the subgroups where HR for OS is ≥1, the HR for PFS is <1.

Due to the low number of patients with PD-L1-negative tumours achieving objective response rate (ORR) and also the lack of information regarding follow-up time for these responses, firm conclusions cannot be drawn. Hence, the duration of the response in PD-L1-negative tumours is uncertain.

3.4. Unfavourable effects

Nearly all patients treated with avelumab reported adverse event (AE), in line with the known safety profile. The proportion of patients that reported AE of grade 3 or higher was lower in study B9991001 compared to the safety set, 47.4% compared to 58.9% respectively.

The proportion of patients that interrupted the treatment with avelumab was almost double for patients in study B9991001 compared to the pooled safety set, 40.7% compared to 20.9 %. The exposure-adjusted incident rate per 100 patient months AE analysis shows a slightly higher incident rate for patients with AE leading to interruption of avelumab treatment in study B9991001. Incidence rate per 100 patient months was 6.1 compared to the pooled safety population 5.0. This is not as pronounced as the non-adjusted analysis.

The proportion of patients that discontinued treatment due to an AE was quite similar between the groups, 11.9% for study B9991001 and 14.0% for the pooled safety set. Exposure adjusted analysis incident rate per 100 patient months show a lower treatment (about half) discontinuation rate of avelumab in study B9991001 compared to the Pooled Safety Set (1.3 vs. 2.9). Immune-related adverse events (irAE) were more common in study B9991001 for patients treated with avelumab plus BSC, 29.4% compared to the pooled safety set where 14.2% presented with irAEs. The exposure adjusted incident rate per 100 patient months of irAEs is higher in study B9991001 compared to the pooled population, 4.1 compared to 3.3. However, the increase when analysed adjusted for exposure raises no major concern in relation to the benefit risk assessment.

Most common cause of death, both in study B9991001 and the pooled safety set was disease progression. Deaths related to study treatment toxicity was 0.6% in study B9991001 compared to 0.2% in the pooled safety set. Considering that avelumab in study B9991001 is used in a maintenance setting this increased rate of deaths related to study treatment toxicity could be of concern. However, the absolute number of deaths assessed by the investigator to be related to study treatment is low and the reported cases display several confounding factors that do not support a clear relationship to study treatment. The frequency of deaths not attributed to disease progression in study B9991001 does not raise new safety concerns for avelumab treatment in patients treated with avelumab plus BSC with advanced urothelial carcinoma that did not progress on first-line platinum-based chemotherapy.

3.5. Uncertainties and limitations about unfavourable effects

Compared to the pooled safety set an increased frequency of deaths was reported in study B9991001 although the absolute numbers were low.

In relation to the BSC patients, a considerably higher incidence of AE of grade 3 and above was reported along with the irAE increase and increase in serious AE compared to patients treated with avelumab plus BSC.

3.6. Effects Table

Table 70. Effects Table for Bavencio as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) whose disease has not progressed with first-line platinum-based induction chemotherapy (Study B9991001, data cut-off: 21 October 2019 (efficacy), 19 January 2020 (updated OS and safety)).

Effect	Short description	Unit	Avelumab +BSC	BSC	Uncertainties / Strength of evidence	Ref
Favourable Effects						
OS		Months	22.1	14.6	The OS-results for patients with PD-L1-negative tumours display no signs of detrimental OS effect (HR 0.83 (95% CI 0.603, 1.131)).	
		HR (95% CI)	0,70 (0.564, 0.862)			
PFS	BIRC, RECIST v1.1	Months	3.7	2.0		
		HR (95% CI)	0.62 (0.519, 0.751)			

Effect	Short description	Unit	Avelumab +BSC	BSC	Uncertainties / Strength of evidence	Ref
OR	BIRC, RECIST v1.1	n (%)	34 (9.7)	5 (1.4)		
Unfavourable Effects						
Any AE		%	98.0	77.7	Median treatment duration*: Avelumab+BSC: 25.3 weeks (range: 2.0, 173.9) BSC: 13.1 weeks (range: 0.1, 168.4)	
grade≥3 AE		%	47.4	25.2		
SAE		%	27.9	20.0		
Any irAE		%	29.4	1.4		
grade≥3 irAE		%	7.0	0.3		
AEs leading to treatment dis-continuation		%	11.9	0		
Death: Cause of death study treatment toxicity		%	0.6	0		

*DCO: 19 Jan. 2020

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The interim OS-analysis from study B9991001 demonstrated a statistically significant and clinically relevant prolonged OS of 7.1 months for all included patients and also for patients with PD-L1-positive tumours. The updated OS-analysis demonstrated a prolonged OS of 7.5 months for all included patients. The benefit of the addition of avelumab to BSC for patients with PD-L1-negative tumours is less pronounced, nevertheless, patients with PD-L1-negative tumours, on a group level, display a modest increase of PFS and no signs of a detrimental effect on OS that would otherwise motivate exclusion of this patient population from the indication.

Overall, the safety profile of avelumab in the pivotal study B9991001 is similar, regardless of PD-L1-status, to the previously reported safety profile of avelumab monotherapy. No new safety concerns were raised, and the safety profile is considered manageable.

3.7.2. Balance of benefits and risks

Efficacy has been demonstrated in all patients independent of PD-L1-status and the safety profile is manageable. Hence, the benefit-risk balance is positive.

3.7.3. Additional considerations on the benefit-risk balance

Exposure comparisons between the 10 mg/kg dosing and a flat 800 mg dose based on simulations from population PK models are the justification for the change of the posology to flat-dosing for the treatment of aUC patients. The benefit-risk balance for the 800 mg Q2W flat-dose posology is considered unchanged compared to the 10 mg/kg Q2W posology since the flat-dose exposure range is comparable to the weight-based dosing exposure range.

3.8. Conclusions

The overall B/R of avelumab is positive in the new sought indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, II and IIIB

Extension of indication to include a new indication for Bavencio in the treatment as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum based chemotherapy; as a consequence, sections 4.1 , 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.0 of the RMP has also been submitted. The MAH took also the occasion to include some editorial changes in the PI.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Bavencio-H-C-4338-II-0018.