Clinical trial results:
Open-label, Phase I/II study to evaluate pharmacokinetics, pharmacodynamics, safety, and anticancer activity of avelumab in pediatric subjects from birth to less than 18 years of age with refractory or relapsed solid tumors and lymphoma

Summary

EudraCT number	2017-002985-28
Trial protocol	BE DK
Global end of trial date	31 May 2021

Results information

Result version number	v1 (current)
This version publication date	09 February 2022
First version publication date	09 February 2022

Trial information

Trial identification

Sponsor protocol code	MS100070_0306

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03451825
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA, Darmstadt, Germany
Sponsor organisation address	Frankfurter Strasse 250, Darmstadt, Germany, 64293
Public contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151 72 5200, service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001849-PIP02-15
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 May 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study to evaluate the dose, safety and tolerability, antitumor activity, pharmacokinetic and pharmacodynamics of avelumab in pediatric subjects 0 to less than 18 years of age with refractory or relapsed malignant solid tumors (including central nervous system tumors) and lymphoma for which no standard therapy is available or for which the subject is not eligible for the existing therapy.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Korea, Republic of: 15
Worldwide total number of subjects	21
EEA total number of subjects	1

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	11

Adolescents (12-17 years)	10
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 26 subjects were screened for participation in the Phase I part of the study, out of which 21 subjects were eligible received the study treatment.

Pre-assignment

Screening details:

The study was planned to be conducted in 2 parts: the dose-finding part (Phase I) and the tumor-specified expansion part (Phase II). However, Phase II was cancelled due to limited clinical benefit of Programmed death ligand 1 (PD-L1) monotherapy in pediatric subjects.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Avelumab 10 miligram per kilogram (mg/kg)

Arm description:

Subjects received an intravenous infusion of avelumab 10mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an intravenous infusion of avelumab 10mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Arm title	Avelumab 20 mg/kg

Arm description:

Subjects received an intravenous infusion of avelumab 20 mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received an intravenous infusion of avelumab 20mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Number of subjects in period 1	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg
Started	6	15
Completed	6	15

Baseline characteristics

Reporting groups	
Reporting group title	Avelumab 10 miligram per kilogram (mg/kg)
Reporting group description:	
Subjects received an intravenous infusion of avelumab 10mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.	
Reporting group title	Avelumab 20 mg/kg
Reporting group description:	
Subjects received an intravenous infusion of avelumab 20 mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.	

Reporting group values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg	Total
Number of subjects	6	15	21
Age Categorical Units: Subjects			
Children (2-11 years)	3	8	11
Adolescents (12-17 years)	3	7	10
Gender Categorical Units: Subjects			
Female	2	8	10
Male	4	7	11
Race (NIH/OMB) Units: Subjects			
Asian	6	9	15
White	0	4	4
Not Collected at Site	0	2	2

End points

End points reporting groups

Reporting group title	Avelumab 10 miligram per kilogram (mg/kg)
Reporting group description:	
Subjects received an intravenous infusion of avelumab 10mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.	
Reporting group title	Avelumab 20 mg/kg
Reporting group description:	
Subjects received an intravenous infusion of avelumab 20 mg/kg IV once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.	

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) as per Severity With Grade 3 or Higher According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs) as per Severity With Grade 3 or Higher According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)[1]

End point description:

Adverse event (AE) was defined as any untoward medical occurrence in a subject, which does not necessarily have causal relationship with treatment. A serious AE was defined as an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged in participant hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAEs were those events with onset dates occurring during the on-treatment period for the first time, or if the worsening of an event was during the on-treatment period. TEAEs included both serious TEAEs and non-serious TEAEs. Severity of grade 3 or higher TEAEs were graded using NCI-CTCAE v4.03 toxicity grades, as follows: Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. Number of subjects with TEAEs as per severity with Grade 3 and higher were reported. Safety analysis set included all subjects who received any dose of avelumab.

End point type	Primary

End point timeframe:

Baseline up to 1182 days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned for this endpoint.

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
Subjects with TEAEs - Grade 3	4	6		
Subjects with TEAEs - Grade 4	0	2		
Subjects with TEAEs - Grade 5	1	3		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects Experiencing Dose-Limiting Toxicities (DLTs)

End point title	Number of Subjects Experiencing Dose-Limiting Toxicities (DLTs)[2]

End point description:

DLT was defined as severity of AEs were graded according to NCI_CTCAE version 4.03. Hematologic: Grade 4 neutropenia for more than 7 days in duration; Grade greater than or equal to (>=) 3 neutropenic infection; Grade >= 3 thrombocytopenia with bleeding; Grade 4 thrombocytopenia > 7 days and Grade 4 anemia. Nonhematologic: Any Grade >= 3 toxicity, except for any of the following: Transient (less than or equal to (<=) 72 hours; Grade 3 flu-like symptoms or fever, which was controlled with medical management; Transient (<= 72 hours) Grade 3 fatigue, local reactions, headache, nausea, or emesis that resolved to Grade <= 1 or to Baseline. Grade 3 diarrhea or Grade 3 skin toxicity that resolved to Grade <= 1 in less than 7 days after medical management (immunosuppressant treatment) had been initiated. Grade >= 3 amylase or lipase abnormality that was not associated with clinical manifestations of pancreatitis. DLTs analysis: all subjects received all study drug in DLT evaluation period.

End point type	Primary

End point timeframe:

Baseline up to 28 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive data was planned for this endpoint.

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Subjects	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point title	Number of Subjects With Confirmed Best Overall Response (BOR) as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point description:

Confirmed BOR was evaluated based on RECIST v1.1 and Investigator's assessments and defined as best response of any of confirmed complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) recorded from date of study treatment until disease progression/recurrence. CR: Disappearance of all evidence of target/non-target lesions. PR: At least 30 percent (%) reduction from baseline in sum of longest diameter (SLD) of all lesions. SD: Neither sufficient increase to qualify for PD nor sufficient shrinkage to qualify for PR. PD: at least a 20% increase in SLD, taking as reference smallest SLD recorded from baseline/appearance of 1or more new lesions and unequivocal progression of non-target lesions. Full analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Baseline up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
Complete Response (CR)	0	0		
Partial Response (PR)	0	0		
Stable Disease (SD)	0	4		
Non-CR/Non-PR	0	0		
Progressive Disease (PD)	5	9		
Not Evaluable	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point title	Duration of Response (DOR) as per Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point description:

Duration of response was defined for subjects with confirmed objective response (OR), as the time from first documentation of objective response (Complete Response or Partial Response) to the date of first documentation of objective PD or death due to any cause, whichever occurred first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 % increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DOR was determined according to RECIST v1.1 and assessed by Investigator. Full analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Time from first documentation of objective response up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[3]	0[4]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[3] - Analyses of DOR were not conducted in the absence of any responders (For CR and PR).

[4] - Analyses of DOR were not conducted in the absence of any responders (For CR and PR).

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point title	Time to Response According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point description:

Time to response (TTR) was defined, for subjects with an objective response, as the time from the start date of study treatment to the first documentation of OR (CR or PR) which was subsequently confirmed. Full analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Time from start of study treatment up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[5]	0[6]		
Units: Months				
median (full range (min-max))	(to)	(to)		

Notes:

[5] - Analyses of Time to response were not conducted in the absence of any responders (For CR and PR).
[6] - Analyses of Time to response were not conducted in the absence of any responders (For CR and PR).

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point title	Progression-Free Survival According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) and as Adjudicated by the Investigator

End point description:

Progression-Free survival was defined as the time from first administration of study treatment until the first documentation of disease progression (PD) or death due to any cause, whichever occurred first. PD: At least a 20 % increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. PFS was measured using Kaplan-Meier (KM) estimates. Full analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Time from first administration of study drug until the first documentation of PD or death, assessed up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Weeks				
median (full range (min-max))	7.5 (6.57 to 8.14)	7.7 (0.14 to 131.86)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival was defined as the time from date of first dose of study drug to the date of death due to any cause. For subjects who were still alive at the time of data analysis or who were lost to follow-up, OS time was censored at the date of last contact. OS was measured using Kaplan-Meier (KM) estimates. Full analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Time from first administration of study drug up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Months				
median (full range (min-max))	4.4 (1.51 to 14.36)	7.0 (0.85 to 31.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-Emergent Adverse Events, Adverse Events of Special Interest (AESI) and Treatment-related Adverse Events According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point title	Number of Subjects With Treatment-Emergent Adverse Events, Adverse Events of Special Interest (AESI) and Treatment-related Adverse Events According to National Cancer Institute-Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03)

End point description:

Adverse Event (AE) was defined any untoward medical occurrence in a subject administered with a study drug, which does not necessarily had a causal relationship with this treatment. Serious AE was defined AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAEs: TEAEs was defined as events with onset date or worsening during the on-treatment period. TEAEs included serious AEs and non-serious AEs. Treatment-related TEAEs: reasonably related to the study intervention. AESIs included Infusion-related reactions (IRRs) and Immune-related AE (irAEs). The safety analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Baseline up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
Subject with any TEAEs	6	15		
Subjects with any Serious TEAEs	4	12		
Subjects with Treatment-emergent irAE	0	1		
Subjects with Treatment-emergent IRR	2	7		
Subjects with Study-drug related AEs	3	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Grade 3 or Higher Laboratory Abnormalities According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03

End point title	Number of Subjects With Grade 3 or Higher Laboratory Abnormalities According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 4.03

End point description:

The total number of subjects with laboratory test abnormalities were assessed. Clinical laboratory tests included hematology and biochemistry abnormalities. The on-treatment hematology and biochemistry abnormalities (by worst on-treatment NCI-CTCAE Grade 3 and Grade 4) were reported. Safety analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Baseline up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
Grade 3: Anemia:	1	1		
Grade 3: lymphocyte count decreased	1	2		
Grade 4: platelet count decreased	0	1		
Grade 3: hyponatremia	1	3		
Grade 3: hyperkalemia	1	0		
Grade 3: creatinine increased	1	0		
Grade 3: alkaline phosphatase increased	1	1		
Grade 3: hypokalemia	0	2		
Grade 3: serum amylase increased	0	1		
Grade 4: Hyperkalemia	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-Time Curve From Time Zero to the 336 Hours Post-Dose (AUC 0-336 hours) of Avelumab

End point title	Area Under the Serum Concentration-Time Curve From Time Zero to the 336 Hours Post-Dose (AUC 0-336 hours) of Avelumab

End point description:

The AUC from time zero (= dosing time) to the last sampling time (tlast) at which the concentration was at or above the lower limit of quantification. Calculated using the mixed loglinear trapezoidal rule (linear up, log down). The PK analysis set included all subjects who received at least one dose of avelumab, had no important protocol deviations or important events affecting PK, and provided at least one measurable post-dose concentration.

End point type	Secondary

End point timeframe:

Pre-dose, end of infusion (1 hour), 3 hours post-dose on Day 1, cycle 1 (each cycle.is for 14 days)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: microgram*hour per mililiter (mcg•h/mL)				
geometric mean (geometric coefficient of variation)	18800 (± 29.2)	43500 (± 21.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax) of Avelumab

End point title	Maximum Observed Serum Concentration (Cmax) of Avelumab

End point description:

Cmax is the maximum observed serum concentration obtained directly from the concentration versus time curve. The Pharmacokinetic (PK) analysis set included all subjects who received at least one dose of avelumab, had no important protocol deviations or important events affecting PK, and provided at least one measurable post-dose concentration.

End point type	Secondary

End point timeframe:

Pre-dose, end of infusion (1 hour), 3 hours post-dose on Day 1, cycle 1 (each cycle.is for 14 days)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: microgram per mililiter (mcg/mL)				
geometric mean (geometric coefficient of variation)	190 (± 34.5)	384 (± 27.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Terminal Half life (t1/2) of Avelumab

End point title	Apparent Terminal Half life (t1/2) of Avelumab

End point description:

Apparent terminal half-life was defined as the time required for the plasma concentration of drug to decrease 50 percent in the final stage of its elimination. Apparent terminal half-life. t1/2 = log (ln) 2/lambdaz (λz). PK analysis set included all subjects who received at least one dose of avelumab, had no important protocol deviations or important events affecting PK, and provided at least one measurable post-dose concentration. Here, number of subject analyzed signifies those subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, end of infusion (1 hour), 3 hours post-dose on Day 1, cycle 1 (each cycle.is for 14 days)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	7		
Units: hours				
geometric mean (geometric coefficient of variation)	85.9 (± 15.1)	119 (± 73.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Serum Post-dose Trough (Ctrough) Concentration of Avelumab

End point title	Minimum Serum Post-dose Trough (Ctrough) Concentration of Avelumab

End point description:

The concentration observed immediately before next dosing (corresponding to predose or trough concentration for multiple dosing) was calculated. PK analysis set included all subjects who received at least one dose of avelumab, had no important protocol deviations or important events affecting PK, and provided at least one measurable post-dose concentration. Here :Number of subject analyzed" signifies those who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose at Day 15

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	14		
Units: microgram per ml (mcg/mL)				
geometric mean (geometric coefficient of variation)	11.2 (± 44.9)	34.8 (± 77.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Treatment Emergent Anti-drug Antibodies (ADA) and Neutralizing Antibodies (Nabs)

End point title	Number of Subjects With Positive Treatment Emergent Anti-drug Antibodies (ADA) and Neutralizing Antibodies (Nabs)

End point description:

Serum samples were analyzed by a validated electrochemiluminesce immunoassay to detect the presence of anti-drug antibodies and neutralizing antibodies. Samples that screened positive were subsequently tested in a confirmatory assay. Those confirmed positive were titered for a quasi-

quantitative result. Number of subjects with positive treatment emergent anti-drug antibodies and neutralizing antibodies were reported. Subjects not positive prior to treatment with avelumab and with at least one positive result in the human-Antihuman Antibodies assay were characterized as treatment-emergent. Immunogenicity Analysis Set included all subjects who received any dose of avelumab and have at least one valid ADA result.

End point type	Secondary

End point timeframe:

Baseline up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
Subject With Anti-drug Antibodies	1	0		
Subjects With Neutralizing Antibodies	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Positive Tumor Programmed death ligand 1 (PD-L1) Expression

End point title	Number of Subjects With Positive Tumor Programmed death ligand 1 (PD-L1) Expression

End point description:

Number of subjects with positive tumor programmed death ligand 1 (PDL-1) with cut off >=1%, >= 5%, >=25%, >=50% and >=80% expression were reported. Biomarker Analysis Set included all subjects who received any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment visit (27.5 weeks)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects				
PD-L1 expression:greater than or equal to (>=)1%	0	5		
PD-L1 expression at cut-off of >=5%	0	4		
PD-L1 expression at cut-off of >=25%	0	3		
PD-L1 expression at cut-off of >=50%	0	2		

PD-L1 expression at cut-off of >=80%	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for Tumor-Infiltrating T-cell Levels

End point title	Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for Tumor-Infiltrating T-cell Levels

End point description:

Number of Subjects with substantial, sustained, or significant changes from baseline for Tumor-Infiltrating T-cell Levels were reported. We were only able to analyze tumor tissue from baseline samples. Only one subject provided post treatment tumor samples and this sample could not be analyzed, therefore this secondary variable could not be analyzed. Biomarker Analysis Set included all subjects who received any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments. Tumor-Infiltrating T-cell Levels were observed.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment visit (27.5 weeks)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[7]	0[8]		
Units: Subjects				

Notes:

[7] - This endpoint was not analyzed.

[8] - This endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for T-cell Population in Blood

End point title	Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for T-cell Population in Blood

End point description:

Number of subjects with substantial, sustained, or significant changes from baseline for T-cell population in blood were reported. Due to limited data (small number of subjects with baseline plus on treatment samples), no conclusions of substantial, sustained, or significant changes in blood T cells could be made. Biomarker Analysis Set included all subjects who received any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment visit (27.5 weeks)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[9]	0[10]		
Units: Subjects				

Notes:

[9] - This endpoint was not analyzed..

[10] - This endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for T-cell, B-cell and NK-cell in Blood

End point title	Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for T-cell, B-cell and NK-cell in Blood

End point description:

Number of subjects with substantial, sustained, or significant changes from baseline for T-cell, B-cell and NK-cell in blood were reported. Due to limited data (small number of subjects with baseline plus on treatment samples), no conclusions of substantial, sustained, or significant changes in blood T, B, NK cells could be made. Biomarker Analysis Set included all subjects who received any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment visit (27.5 weeks)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[11]	0[12]		
Units: Subjects				

Notes:

[11] - This endpoint was not analyzed.

[12] - This endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for Vaccination-Related Antibody Concentrations

End point title	Number of Subjects With Substantial, Sustained, or Significant Changes From Baseline for Vaccination-Related Antibody Concentrations

End point description:

Samples for the testing of vaccination-related antibody concentrations for diphtheria, tetanus, and pneumococcal conjugate (PCV-7) were to be collected at Cycle 1/Day 1 (pretreatment), Cycle 7/Day 85 and at the End-of-Treatment visit. Due to limited data (small # of pts with baseline + on treatment samples), no conclusions of substantial, sustained, or significant changes in vaccination related antibodies could be made. Biomarker Analysis Set included all subjects who received any dose of avelumab and who have provided at least one blood, serum, plasma, or tumor sample for biomarker assessments.

End point type	Secondary

End point timeframe:

Baseline up to end of treatment visit (27.5 weeks)

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Subjects				

Notes:

[13] - This endpoint was not analyzed.

[14] - This endpoint was not analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs Related to Vital Signs that Resulted in Treatment Discontinuation

End point title	Number of Subjects with TEAEs Related to Vital Signs that Resulted in Treatment Discontinuation

End point description:

Vital signs included: Heart Rate, Blood pressure, respiratory rate. Vital signs were measured in semi-supine position after 5 minutes rest for the subjects. The safety analysis set included all subjects who received any dose of avelumab.

End point type	Secondary

End point timeframe:

Baseline up to 1182 days

End point values	Avelumab 10 miligram per kilogram (mg/kg)	Avelumab 20 mg/kg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	15		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 1182 days

Adverse event reporting additional description:

The safety analysis set included all subjects who received any dose of avelumab. The AEs reported under non-serious AEs are the TEAEs (including non-serious as well as serious AEs) as no separate non-serious AEs were generated per planned analysis. All fatal AEs were related to progression of disease. No treatment related death.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Avelumab 20 mg/kg

Reporting group description:

Subjects received an intravenous infusion of avelumab 20mg/kg administered intravenously (IV) once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Reporting group title	Avelumab 10 miligram per kilogram (mg/kg)

Reporting group description:

Subjects received an intravenous infusion of avelumab 10mg/kg administered intravenously (IV) once every 2 weeks until confirmed progression, death, unacceptable toxicity, or any criterion for withdrawal occurred.

Serious adverse events	Avelumab 20 mg/kg	Avelumab 10 miligram per kilogram (mg/kg)	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 15 (80.00%)	4 / 6 (66.67%)	
number of deaths (all causes)	12	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pseudoprogression			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Post procedural inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopaenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Disease progression	Additional description: All fatal AEs were related to progression of disease.		
subjects affected / exposed	5 / 15 (33.33%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 1	
Influenza like illness			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypophagia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Avelumab 20 mg/kg	Avelumab 10 miligram per kilogram (mg/kg)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	6 / 6 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lip and/or oral cavity cancer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Malignant pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Tumour haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Tumour pseudoprogression			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypotension			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypertension			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	

Catheter site pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Chills			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Influenza like illness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	6 / 15 (40.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gait disturbance			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Disease progression			
subjects affected / exposed	5 / 15 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Malaise			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oedema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	10 / 15 (66.67%)	4 / 6 (66.67%)	
occurrences (all)	0	0	
Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Cough			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dyspnoea exertional			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Rhinorrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pleural effusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pharyngeal inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Increased bronchial secretion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypoxia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Product issues			

Device occlusion			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	0	
Amylase increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Blood creatinine increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Lymphocyte count decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
C-reactive protein increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood phosphorus increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Platelet count decreased			

subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urine output decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Weight decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ligament sprain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Limb injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Post procedural inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Procedural pain			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dizziness postural			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Headache			

subjects affected / exposed	5 / 15 (33.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hemiparesis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hydrocephalus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Intracranial pressure increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Lethargy			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Memory impairment			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nystagmus			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Seizure			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Paraesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Coagulopathy			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Anaemia			
subjects affected / exposed	5 / 15 (33.33%)	2 / 6 (33.33%)	
occurrences (all)	0	0	

Thrombocytopenia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diplopia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Ascites			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Abdominal pain			
subjects affected / exposed	3 / 15 (20.00%)	2 / 6 (33.33%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	5 / 15 (33.33%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Dental caries			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dry mouth			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dysphagia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastric haemorrhage			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal ulcer			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	6 / 15 (40.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	6 / 15 (40.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Stomatitis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Decubitus ulcer			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Dermatitis atopic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Erythema			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pain of skin			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pruritus allergic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rash			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rash maculo-papular			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urticaria			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Cystitis noninfective			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Acute kidney injury			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Urinary retention			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Renal tubular disorder			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Nephritis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Haematuria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Muscular weakness			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Groin pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Flank pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Arthralgia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Pain in extremity			

subjects affected / exposed	4 / 15 (26.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Fungal skin infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hordeolum			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oral candidiasis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Oral herpes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Otitis media			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Pyuria			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	

Tonsillitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Skin infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 15 (6.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Dehydration			
subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hyperkalaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hyperuricaemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypokalaemia			
subjects affected / exposed	2 / 15 (13.33%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypophosphataemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypophagia			
subjects affected / exposed	3 / 15 (20.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hyponatraemia			
subjects affected / exposed	2 / 15 (13.33%)	1 / 6 (16.67%)	
occurrences (all)	0	0	
Hypomagnesaemia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
Hypoalbuminaemia			
subjects affected / exposed	4 / 15 (26.67%)	1 / 6 (16.67%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 September 2017	non-substantial changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was planned to be conducted in 2 parts: the dose-finding part (Phase I) and the tumor-specified expansion part (Phase II). However, Phase II was cancelled due to limited clinical benefit of PD-L1 monotherapy in pediatric subjects.

Notes: