EU Clinical Trials Register

Clinical trial results:
A Phase IIa, single-arm, multicenter study to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in participants with advanced squamous non-small-cell lung cancer

Summary

EudraCT number	2018-001529-24
Trial protocol	HU ES
Global end of trial date	27 May 2021

Results information

Result version number	v1 (current)
This version publication date	29 May 2022
First version publication date	29 May 2022

Trial information

Trial identification

Sponsor protocol code	MS201944-0170

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03717155
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
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?	No

Notes:

Results analysis stage

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

Global end of trial reached?	Yes
Global end of trial date	27 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study was to investigate the clinical activity and safety of avelumab in combination with cetuximab plus gemcitabine and cisplatin in subjects with treatment-naïve advanced non-small-cell lung cancer (NSCLC).

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	30 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Serbia: 17
Worldwide total number of subjects	43
EEA total number of subjects	26

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)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	23

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 43 subjects were enrolled in this study at different sites in Hungary, Serbia and Spain.

Period 1

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

Arms

Arm title	Avelumab and Cetuximab

Arm description:

Subjects received 800 milligrams Avelumab, 1250 milligrams per square meter (mg/m^2) gemcitabine on Day 1 and Day 8, cisplatin at a dose of 75 mg/m^2 on Day 1 along with 250 mg/m2 body surface area Cetuximab on Day 1 and 500 mg/m2 body surface area on Day 8 of each cycle as intravenous (IV) infusions up to maximum of 4 cycles (each cycle is of 3 weeks) until disease progression or unacceptable toxicities. In case of cisplatin toxicities, subjects were switched to carboplatin at a dose of target area under the serum concentration-time curve of 5 (AUC 5) on Day 1 for the remainder of cycles. Subsequently subjects were administered with avelumab and cetuximab as IV infusion at the dose of 800 mg and 500 mg/m^2 respectively, every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.

Arm type	Experimental
Investigational medicinal product name	Avelumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received avelumab intravenous infusions at a dose of 800 milligram (mg) on Day 1 and Day 8 of each 3-week cycle for the first 4 cycles. Thereafter, administered every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.

Investigational medicinal product name	Cetuximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cetuximab intravenous infusions at a dose of 250 milligram per meter square (mg/m^2) body surface area on Day 1 and 500 mg/m^2 body surface area on Day 8 of first 4 cycles of concurrent chemotherapy. Thereafter, administered given at a dose of 500 mg/m^2 intravenous every 2 weeks in the Maintenance phase, until disease progression or unacceptable toxicities.

Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received gemcitabine intravenous infusions at a dose of 1250 mg/m^2 body surface area on Day 1 and Day 8 in 3-week cycles up to a maximum of 4 cycles, until disease progression or unacceptable toxicities.

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received cisplatin intravenous infusions at a dose of 75 mg/m^2 body surface area on Day 1 of 3-week cycles up to a maximum of 4 cycles, until disease progression or unacceptable toxicities.

Investigational medicinal product name	Carboplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

In case of cisplatin toxicities, subjects were switched to carboplatin at a dose of target area under the serum concentration-time curve of 5 (AUC 5) on Day 1 for the remainder of cycles.

Number of subjects in period 1	Avelumab and Cetuximab
Started	43
Completed	43

Baseline characteristics

Reporting groups

Reporting group title	Avelumab and Cetuximab

Reporting group description:

Subjects received 800 milligrams Avelumab, 1250 milligrams per square meter (mg/m^2) gemcitabine on Day 1 and Day 8, cisplatin at a dose of 75 mg/m^2 on Day 1 along with 250 mg/m2 body surface area Cetuximab on Day 1 and 500 mg/m2 body surface area on Day 8 of each cycle as intravenous (IV) infusions up to maximum of 4 cycles (each cycle is of 3 weeks) until disease progression or unacceptable toxicities. In case of cisplatin toxicities, subjects were switched to carboplatin at a dose of target area under the serum concentration-time curve of 5 (AUC 5) on Day 1 for the remainder of cycles. Subsequently subjects were administered with avelumab and cetuximab as IV infusion at the dose of 800 mg and 500 mg/m^2 respectively, every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.

Reporting group values	Avelumab and Cetuximab	Total	
Number of subjects	43	43	
Age categorical			
Units: Subjects			
Age Continuous			
Units: Years			
arithmetic mean	63		
standard deviation	± 7.2	-	
Sex: Female, Male			
Units: subjects			
Female	8	8	
Male	35	35	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	43	43	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Avelumab and Cetuximab

Reporting group description:

Subjects received 800 milligrams Avelumab, 1250 milligrams per square meter (mg/m^2) gemcitabine on Day 1 and Day 8, cisplatin at a dose of 75 mg/m^2 on Day 1 along with 250 mg/m2 body surface area Cetuximab on Day 1 and 500 mg/m2 body surface area on Day 8 of each cycle as intravenous (IV) infusions up to maximum of 4 cycles (each cycle is of 3 weeks) until disease progression or unacceptable toxicities. In case of cisplatin toxicities, subjects were switched to carboplatin at a dose of target area under the serum concentration-time curve of 5 (AUC 5) on Day 1 for the remainder of cycles. Subsequently subjects were administered with avelumab and cetuximab as IV infusion at the dose of 800 mg and 500 mg/m^2 respectively, every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.

Primary: Percentage of Subjects With Confirmed Best Objective Response (BOR) According to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 Assessed by Investigator

End point title	Percentage of Subjects With Confirmed Best Objective Response (BOR) According to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 Assessed by Investigator[1]

End point description:

Confirmed BOR was defined as the percentage of subjects who achieved confirmed CR or PR, according to RECIST version 1.1 assessed by Investigator.CR: Disappearance of all evidence of target & non-target lesions. PR: At least 30% reduction from baseline in 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 or appearance of 1 or more new lesions. Confirmed CR=as at least two determinations of CR at least 4 weeks apart with no PD. Confirmed PR=as at least 2 determinations of PR or better (PR followed by PR or PR followed by CR), at least 4 weeks apart (not qualifying for a CR) with no PD in between. Full analysis set includes all subjects who received at least one non-zero dose of any study treatment. Full analysis set includes all subjects who received at least one non-zero dose of any study treatment.

End point type	Primary

End point timeframe:

Time from the first dose of study drug until occurrence of PD, death due to any cause (assessed up to 612 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 summary statistics was planned for this endpoint.

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: percentage of subjects				
number (confidence interval 95%)	34.9 (21.0 to 50.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Adverse Events (AEs), Treatment-Related Grade >=3 AEs and Immune-related AEs (irAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs), Treatment-Related Adverse Events (AEs), Treatment-Related Grade >=3 AEs and Immune-related AEs (irAEs)

End point description:

AE was defined as any unfavorable & unintended sign (including an abnormal laboratory finding), symptom, or disease associated with use of study drug, whether or not considered related to study drug or worsening of pre-existing medical condition, whether or not related to study drug. SAE was an AE that resulted in any of the following outcomes: death; life threatening; significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect or was otherwise considered medically important. TEAE is defined as AEs starting or worsening after first intake of study drug. TEAEs include both Serious & non-serious TEAEs. irAEs included AEs that matches a preferred term on list of pre-selected MedDRA terms. AEs with relationship to study treatment are reported as Treatment-related AEs. Treatment related AEs with grade 3 or more is also reported. Safety analysis set included all subjects who received at least one non-zero dose of any study treatment.

End point type	Secondary

End point timeframe:

Time from the first dose of study drug assessed up to (941 days)

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: subjects				
TEAEs	41			
Treatment-Related AEs	38			
Treatment Related Grade>=3 TEAEs	24			
irTEAEs	13			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) Time Per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

End point title	Progression-Free Survival (PFS) Time Per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1

End point description:

Progression free survival (PFS) is defined as the time (in months) from first treatment day to the date of the first documentation of objective progression of disease (PD) according to RECIST version 1.1 assessed by Investigator, or death due to any cause, whichever occurs first. PD is defined as at least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Full analysis set includes all subjects who received at least one non-zero dose of any study treatment.

End point type	Secondary

End point timeframe:

Time from the first dose of study drug until occurrence of PD, death due to any cause (assessed up to 737 days)

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Months				
median (confidence interval 95%)	6.1 (4.3 to 9.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

DOR is defined for subjects with confirmed complete response (CR) or partial response (PR), as the time from first documentation of confirmed response to the date of first documentation of progression of disease (PD) according to RECIST version 1.1 (assessed by Investigator) or death due to any cause. Duration of objective response was assessed using Kaplan-Meier analysis. 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 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Full analysis set included all subjects who receive at least one non-zero dose of any study treatment. Here "Overall number of subjects analyzed" signifies those subjects who had confirmed CR or PR.

End point type	Secondary

End point timeframe:

Time from the first dose of study drug until occurrence of PD, death due to any cause (assessed up to 612 days)

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	15			
Units: Months				
median (confidence interval 95%)	7.1 (4.2 to 12.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immediate Observed Serum Concentration at End of Infusion (Ceoi) of Avelumab

End point title	Immediate Observed Serum Concentration at End of Infusion (Ceoi) of Avelumab

End point description:

Ceoi is the serum concentration observed immediately at the end of infusion. This was taken directly from the observed Avelumab concentration-time data. Pharmacokinetic (PK) analysis set included all subjects who received at least one dose of avelumab and/or cetuximab, have no important events affecting PK, and provide at least one measurable post-dose concentration. Number of Subjects Analyzed=subjects evaluable for this endpoint & n=subjects evaluated at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 2 hours after end of infusion on Day 1, 8, 22 and 29; Pre-dose, 30 minutes after the end of infusion on Day 43, 50, 64, 71; Pre-dose, 3 hours after end of infusion on Day 85, 99, 113, 127, 169, 253, and 337

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=40)	206 (± 26.6)			
Day 8 (n=36)	243 (± 23.8)			
Day 22 (n=29)	234 (± 24.1)			
Day 29 (n=31)	282 (± 26.8)			
Day 43 (n=22)	237 (± 30.5)			
Day 50 (n=32)	259 (± 38.9)			
Day 64 (n=22)	214 (± 67.6)			
Day 71 (n=28)	244 (± 43.8)			
Day 85 (n=25)	223 (± 33.3)			
Day 99 (n=25)	202 (± 62.4)			
Day 113 (n=27)	234 (± 29.7)			
Day 127 (n=20)	222 (± 55.1)			
Day 169 (n=21)	245 (± 20.8)			
Day 253 (n=10)	249 (± 28.7)			
Day 337 (n=09)	246 (± 38.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Immediate Observed Serum Concentration at End of Infusion (Ceoi) of Cetuximab

End point title	Immediate Observed Serum Concentration at End of Infusion (Ceoi) of Cetuximab

End point description:

Ceoi is the serum concentration observed immediately at the end of infusion. This was taken directly from the observed cetuximab concentration-time data. PK analysis set included all subjects who received at least one dose of avelumab and/or cetuximab, have no important events affecting PK, and provide at least one measurable post-dose concentration. Here, n=subjects evaluated at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose, 2 hours after end of infusion on Day 1, 8, 22 and 29; Pre-dose, 30 minutes after the end of infusion on Day 43, 50, 64, 71; Pre-dose, 3 hours after end of infusion on Day 85, 99, 113, 127, 169, 253, and 337

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1 (n=43)	109 (± 50.7)			
Day 8 (n=35)	198 (± 86.6)			
Day 22 (n=28)	124 (± 54.4)			
Day 29 (n=30)	260 (± 25.0)			
Day 43 (n=22)	154 (± 32.7)			
Day 50 (n=30)	238 (± 28.9)			
Day 64 (n=21)	159 (± 36.1)			
Day 71 (n=27)	262 (± 25.1)			
Day 85 (n=25)	239 (± 38.4)			
Day 99 (n=25)	252 (± 21.1)			
Day 113 (n=26)	250 (± 20.4)			
Day 127 (n=21)	245 (± 55.8)			
Day 169 (n=20)	297 (± 29.2)			
Day 253 (n=10)	269 (± 34.4)			
Day 337 (n=09)	304 (± 37.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough Concentration Levels (Ctrough) of Avelumab

End point title	Serum Trough Concentration Levels (Ctrough) of Avelumab

End point description:

Ctrough is the serum concentration observed immediately before next dosing. PK analysis set included all subjects who received at least one dose of avelumab and/or cetuximab, have no important events affecting PK, and provide at least one measurable post-dose concentration. Number of Subjects Analyzed=subjects evaluable for this endpoint and n=subjects evaluated at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose: Day 8, Day 22, Day 29, Day 43, Day 50, Day 64, Day 71, Day 85, Day 99, Day 113, Day 127, Day 169, Day 253 and Day 337

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	35			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 8 (n=35)	28.8 (± 82.7)			
Day 22 (n=29)	13.6 (± 97.1)			
Day 29 (n=31)	42.4 (± 147.8)			
Day 43 (n=22)	15.6 (± 115.1)			
Day 50 (n=32)	56.4 (± 77.9)			
Day 64 (n=22)	19.7 (± 145.7)			
Day 71 (n=27)	58.2 (± 62.5)			
Day 85 (n=25)	21.5 (± 70.9)			
Day 99 (n=25)	21.2 (± 75.4)			
Day 113 (n=27)	19.4 (± 78.5)			
Day 127 (n=21)	18.1 (± 107.6)			
Day 169 (n=21)	19.3 (± 67.2)			
Day 253 (n=10)	17.0 (± 80.1)			
Day 337 (n=10)	20.8 (± 55.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Trough Concentration Levels (Ctrough) of Cetuximab

End point title	Serum Trough Concentration Levels (Ctrough) of Cetuximab

End point description:

Ctrough is the serum concentration observed immediately before next dosing. PK analysis set included all subjects who received at least one dose of avelumab and/or cetuximab, have no important events affecting PK, and provide at least one measurable post-dose concentration. Number of Subjects Analyzed=subjects evaluable for this endpoint and n=subjects evaluated at specified time point.

End point type	Secondary

End point timeframe:

Pre-dose: Day 8, Day 22, Day 29, Day 43, Day 50, Day 64, Day 71, Day 85, Day 99, Day 113, Day 127, Day 169, Day 253 and Day 337

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 8 (n=32)	12.1 (± 90.0)			
Day 22 (n=26)	12.8 (± 63.7)			
Day 29 (n=29)	22.8 (± 73.3)			
Day 43 (n=20)	25.6 (± 103.7)			

Day 50 (n=30)	23.9 (± 118.1)			
Day 64 (n=20)	17.2 (± 157.9)			
Day 71 (n=27)	35.4 (± 110.4)			
Day 85 (n=22)	26.5 (± 119.4)			
Day 99 (n=22)	22.6 (± 117.3)			
Day 113 (n=23)	35.0 (± 59.0)			
Day 127 (n=18)	38.0 (± 63.6)			
Day 169 (n=19)	40.4 (± 62.2)			
Day 253 (n=10)	31.9 (± 237.7)			
Day 337 (n=09)	28.9 (± 204.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from the first treatment day to the date of death due to any cause. Overall survival was assessed using Kaplan-Meier analysis. Full analysis set includes all subjects who received at least one non-zero dose of any study treatment. Here, n=subjects evaluated at specified time point.

End point type	Secondary

End point timeframe:

Time from the first dose of study drug until occurrence of death due to any cause (assessed up to 941 days)

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Months				
median (confidence interval 95%)	10.1 (8.6 to 14.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Positive Anti-Drug Antibody (ADA) of Avelumab

End point title	Number of Subjects with Positive Anti-Drug Antibody (ADA) of Avelumab

End point description:

The detection of antibodies to avelumab was performed using a validated immunoassay method with tiered testing of screening, confirmatory and titration. Number of participants with positive anti-drug antibody (ADA) of avelumab were reported. ADA analysis set included all subjects who received at least 1 dose of avelumab and/or cetuximab and have at least 1 valid ADA result.

End point type	Secondary

End point timeframe:

Pre-dose up to 149 days

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Subjects	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Positive for Anti-Drug Antibody (ADA) of Cetuximab

End point title	Number of Subjects Positive for Anti-Drug Antibody (ADA) of Cetuximab

End point description:

The detection of antibodies to cetuximab was performed using a validated immunoassay method with tiered testing of screening, confirmatory and titration. Number of participants with positive anti-drug antibody (ADA) of cetuximab were reported. ADA analysis set included all subjects who receive at least 1 dose of avelumab and/or cetuximab and have at least 1 valid ADA result.

End point type	Secondary

End point timeframe:

Pre-dose up to 149 days

End point values	Avelumab and Cetuximab			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Subjects	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:	
Time from the first dose of study drug until 941 days.	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Avelumab and Cetuximab

Reporting group description:

Subjects received 800 milligrams Avelumab, 1250 milligrams per square meter (mg/m^2) gemcitabine on Day 1 and Day 8, cisplatin at a dose of 75 mg/m^2 on Day 1 along with 250 mg/m2 body surface area Cetuximab on Day 1 and 500 mg/m2 body surface area on Day 8 of each cycle as intravenous (IV) infusions up to maximum of 4 cycles (each cycle is of 3 weeks) until disease progression or unacceptable toxicities. In case of cisplatin toxicities, subjects were switched to carboplatin at a dose of target area under the serum concentration-time curve of 5 (AUC 5) on Day 1 for the remainder of cycles. Subsequently subjects were administered with avelumab and cetuximab as IV infusion at the dose of 800 mg and 500 mg/m^2 respectively, every 2 weeks in the Maintenance phase until disease progression or unacceptable toxicities.

Serious adverse events	Avelumab and Cetuximab		
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 43 (46.51%)		
number of deaths (all causes)	30		
number of deaths resulting from adverse events			
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Dry gangrene			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral artery embolism			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Peripheral artery thrombosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Tachycardia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Disease progression			

subjects affected / exposed	4 / 43 (9.30%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal impairment			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lower respiratory tract infection			

subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Dehydration				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypomagnesaemia				
subjects affected / exposed	1 / 43 (2.33%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Avelumab and Cetuximab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 43 (90.70%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	6		
Amylase increased			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Blood creatinine increased			

subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Neutrophil count decreased			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Transaminases increased			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 43 (44.19%)		
occurrences (all)	19		
Leukopenia			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Neutropenia			
subjects affected / exposed	15 / 43 (34.88%)		
occurrences (all)	15		
Thrombocytopenia			
subjects affected / exposed	10 / 43 (23.26%)		
occurrences (all)	10		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	12 / 43 (27.91%)		
occurrences (all)	12		
Fatigue			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	7		
Oedema peripheral			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Pyrexia			
subjects affected / exposed	6 / 43 (13.95%)		
occurrences (all)	6		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Nausea			
subjects affected / exposed	12 / 43 (27.91%)		
occurrences (all)	12		
Vomiting			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Cough			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Dry skin			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Erythema			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	22 / 43 (51.16%)		
occurrences (all)	22		
Dermatitis acneiform			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		

Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	7 / 43 (16.28%)		
occurrences (all)	7		
Hypocalcaemia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Hypomagnesaemia			
subjects affected / exposed	16 / 43 (37.21%)		
occurrences (all)	16		
Hyponatraemia			
subjects affected / exposed	5 / 43 (11.63%)		
occurrences (all)	5		
Hypophosphataemia			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 August 2019	update of inclusion criterion number 1 regarding the upper age limit. In addition, switch to on-study anticancer therapy with carboplatin will be allowed for participants who cannot tolerate treatment with cisplatin.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported