Clinical trial results:
A phase II, open-label, randomized controlled study of PDR001 in patients with moderately differentiated/undifferentiated locally advanced recurrent or metastatic nasopharyngeal carcinoma who progressed on standard treatment

Summary

EudraCT number	2015-000454-38
Trial protocol	FR
Global end of trial date	19 February 2021

Results information

Result version number	v1
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification

Sponsor protocol code	CPDR001X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02605967
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.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	19 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of spartalizumab versus investigator’s choice of chemotherapy in subjects with moderately differentiated/ undifferentiated locally advanced recurrent or metastatic nasopharyngeal cancer (NPC) who progressed on or after first-line therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 April 2016
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	China: 8
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Hong Kong: 27
Country: Number of subjects enrolled	Singapore: 14
Country: Number of subjects enrolled	Taiwan: 33
Country: Number of subjects enrolled	Thailand: 18
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	122
EEA total number of subjects	15

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	103
From 65 to 84 years	19
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 19 investigative sites in 7 countries.

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. All screening evaluations were performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the study treatment. After screening, the treatment period started on Cycle 1 Day 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Spartalizumab 400 mg Q4W

Arm description:

anti-PD1 humanized monoclonal antibody. Participants treated with spartalizumab who remained on spartalizumab

Arm type	Experimental
Investigational medicinal product name	Spartalizumab
Investigational medicinal product code	PDR001
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Spartalizumab was administered via intravenous infusion at a dose of 400 mg every 4 weeks (Q4W).

Arm title	Chemotherapy

Arm description:

Commonly used chemotherapy as per investigator's choice

Arm type	Active comparator
Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Solution for infusion
Routes of administration	Oral use, Intravenous use

Dosage and administration details:

Commonly used chemotherapy as per investigator's choice. The dose and route of administration was the one described in each drug's label.

Number of subjects in period 1	Spartalizumab 400 mg Q4W	Chemotherapy
Started	82	40
Safety Set	82	39
Crossover to spartalizumab	0	27
Completed	0	0
Not completed	82	40
Adverse event, serious fatal	4	2
Physician decision	10	1
Adverse event, non-fatal	1	-
progressive disease	66	35
subject / guardian decision	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Spartalizumab 400 mg Q4W
Reporting group description: anti-PD1 humanized monoclonal antibody. Participants treated with spartalizumab who remained on spartalizumab	
Reporting group title	Chemotherapy
Reporting group description: Commonly used chemotherapy as per investigator's choice	

Reporting group values	Spartalizumab 400 mg Q4W	Chemotherapy	Total
Number of subjects	82	40	122
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	70	33	103
From 65-84 years	12	7	19
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.1	50.5	
standard deviation	± 11.54	± 12.32	-
Sex: Female, Male Units: participants			
Female	14	7	21
Male	68	33	101
Race/Ethnicity, Customized Units: Subjects			
Caucasian	12	2	14
Black	0	1	1
Asian	70	37	107

Subject analysis sets	
Subject analysis set title	Crossover to spartalizumab
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with chemotherapy who crossed over to spartalizumab	

Reporting group values	Crossover to spartalizumab		
Number of subjects	27		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	24		
From 65-84 years	3		
85 years and over	0		
Age Continuous Units: years			
arithmetic mean	49.2		
standard deviation	± 11.48		
Sex: Female, Male Units: participants			
Female	5		
Male	22		
Race/Ethnicity, Customized Units: Subjects			
Caucasian	1		
Black	1		
Asian	25		

End points

End points reporting groups

Reporting group title	Spartalizumab 400 mg Q4W
Reporting group description: anti-PD1 humanized monoclonal antibody. Participants treated with spartalizumab who remained on spartalizumab	
Reporting group title	Chemotherapy
Reporting group description: Commonly used chemotherapy as per investigator's choice	
Subject analysis set title	Crossover to spartalizumab
Subject analysis set type	Full analysis
Subject analysis set description: Patients treated with chemotherapy who crossed over to spartalizumab	

Primary: Progression-free survival (PFS) as per RECIST v 1.1 using central assessment – Number of participants with progression or death

End point title	Progression-free survival (PFS) as per RECIST v 1.1 using central assessment – Number of participants with progression or death[1]

End point description:

PFS is the time from the date of randomization to the date of event defined as the first documented confirmed progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Progressive disease is at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. Number of participants in each category (progression, death, censored) is reported in this record.

End point type	Primary

End point timeframe:

From randomization up to maximum 3.3 years

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: No statistical analysis were planned for this primary endpoint.

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: participants				
number of progression	62	32		
number of deaths	3	1		
number of censored	17	7		

Statistical analyses

No statistical analyses for this end point

Primary: Progression-free survival (PFS) as per RECIST v 1.1 using central assessment – Median PFS

End point title	Progression-free survival (PFS) as per RECIST v 1.1 using central assessment – Median PFS[2]

End point description:

PFS is the time from the date of randomization to the date of event defined as the first documented confirmed progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Progressive disease is at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline.

End point type	Primary

End point timeframe:

From randomization up to maximum 3.3 years

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: No statistical analysis were planned for this primary endpoint.

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: months				
median (confidence interval 95%)	1.9 (1.8 to 2.9)	5.6 (3.7 to 9.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival (OS) is defined as the time from date of randomization to date of death due to any cause. If a patient is not known to have died, survival is censored at the date of last known date the patient was alive.

End point type	Secondary

End point timeframe:

From randomization up to maximum 4.8 years.

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: months				
median (confidence interval 95%)	20.1 (13.6 to 25.5)	16.0 (8.8 to 22.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) as per RECIST v 1.1

End point title	Overall Response Rate (ORR) as per RECIST v 1.1

End point description:

ORR is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR). Tumor response was based on central review of overall lesion response according to RECIST 1.1.
For RECIST v1.1, CR=Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR= At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary

End point timeframe:

From randomization up to maximum 3.3 years

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: percentage of participants				
number (not applicable)	18.3	32.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as per RECIST v 1.1

End point title	Duration of Response (DOR) as per RECIST v 1.1

End point description:

DOR only applies to subjects for whom best overall response is complete response (CR) or partial response (PR) based on central review of overall lesion response according to RECIST 1.1. DOR is defined as the time between the date of first documented response (confirmed CR or confirmed PR) and the date of first documented disease progression or death due to underlying cancer. If a patient not had an event, duration was censored at the date of last adequate tumor assessment.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not available'). Therefore, not applicable values because of insufficient number of participants with events are indicated as '999'.

End point type	Secondary

End point timeframe:

From randomization up to maximum 3.3 years

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	13		
Units: months				
median (confidence interval 95%)	10.2 (7.4 to 999)	5.7 (3.7 to 7.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Progression (TTP) as per RECIST v 1.1

End point title	Time to Progression (TTP) as per RECIST v 1.1

End point description:

TTP is defined as time from date of randomization to the date of event defined as the first documented progression or death due to underlying cancer. If a subject did not had an event, TTP was censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was RECIST v1.1. Progressive disease is at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after

End point type	Secondary

End point timeframe:

From randomization up to maximum 3.3 years

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: months				
median (confidence interval 95%)	1.9 (1.8 to 2.9)	5.6 (3.7 to 9.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Immune-related progression-free survival (irPFS) as per irRC

End point title	Immune-related progression-free survival (irPFS) as per irRC

End point description:

irPFS is the time from the date of randomization to the date of event defined as the first documented progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was immune-related Response Criteria (irRC). Immune-related progressive disease is at least a 20% increase in the sum of diameters of all measured target lesions including new measurable lesions.

End point type	Secondary

End point timeframe:

From randomization up to maximum 3.3 years

End point values	Spartalizumab 400 mg Q4W	Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	0[3]		
Units: months				
median (confidence interval 95%)	1.9 (1.8 to 3.6)	(to)		

Notes:

[3] - Tumor scans for efficacy assessment as per irRC were not planned in this arm.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed serum concentration (Cmax) of spartalizumab

End point title	Maximum observed serum concentration (Cmax) of spartalizumab[4]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed serum concentration following a dose.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n=78)	116 (± 21.9)			
Cycle 3 (n=47)	149 (± 25.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum serum concentration (Tmax) of spartalizumab

End point title	Time to reach maximum serum concentration (Tmax) of spartalizumab[5]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) serum concentration following a dose. Actual recorded sampling times were considered for the calculations.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: hours				
median (full range (min-max))				
Cycle 1 (n=78)	1.57 (0.58 to 3.17)			
Cycle 3 (n=47)	1.57 (1.00 to 14.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the serum concentration-time curve from time zero to the end of the dosing interval tau (AUCtau) of spartalizumab

End point title	Area under the serum concentration-time curve from time zero to the end of the dosing interval tau (AUCtau) of spartalizumab[6]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. The duration of the dosing interval (tau) was 28 days.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: day*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n=73)	1340 (± 25.8)			

Cycle 3 (n=39)	2260 (± 30.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation ratio (Racc) of spartalizumab

End point title	Accumulation ratio (Racc) of spartalizumab[7]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Racc was calculated as the ratio between AUCtau Cycle 3 and AUCtau Cycle 1.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: ratio				
geometric mean (geometric coefficient of variation)	1.61 (± 19.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the serum concentration-time curve from time zero to infinity (AUCinf) of spartalizumab

End point title	Area under the serum concentration-time curve from time zero to infinity (AUCinf) of spartalizumab[8]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC calculation. The extrapolation of AUC to infinity could be calculated if the percentage of area extrapolated was less than 20% and the regression analysis of the terminal serum elimination phase met a pre-defined criteria of goodness of fit.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: day*ug/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 (n=6)	1180 (± 23.9)			
Cycle 3 (n=2)	1090 (± 84.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal elimination half-life (T1/2) of spartalizumab

End point title	Terminal elimination half-life (T1/2) of spartalizumab[9]

End point description:

Pharmacokinetic (PK) parameters were calculated based on spartalizumab serum concentrations by using non-compartmental methods. Elimination half-life (T1/2) values were calculated as 0.693/terminal elimination rate constant.

End point type	Secondary

End point timeframe:

pre-dose, 1, 24, 168, 336 and 672 hours post spartalizumab dose on Cycle 1 and Cycle 3. The duration of one cycle was 28 days.

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: days				
median (full range (min-max))				
Cycle 1 (n=79)	20.1 (7.35 to 41.5)			
Cycle 3 (n=48)	22.7 (5.29 to 48.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-spartalizumab antibodies

End point title	Number of participants with anti-spartalizumab antibodies[10]

End point description:

Validated immunoassays were used for screening and confirmation of the presence of anti-spartalizumab antibodies (ADA, anti-drug antibodies) in serum. Number of participants with each ADA status is reported in this record.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Cycle 1 Day 1) and post-baseline (assessed throughout the treatment up to maximum 655 days).

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Immunogenicity samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: participants				
ADA-negative at baseline (n=72)	66			
ADA-positive at baseline (n=72)	6			
ADA-negative at post-baseline (n=72)	59			
ADA-positive at post-baseline (n=72)	9			

Statistical analyses

No statistical analyses for this end point

Secondary: PD-L1 percent positive tumor

End point title	PD-L1 percent positive tumor[11]

End point description:

The expression of programmed cell death-ligand 1 (PD-L1) was measured in tumor samples by immunohistochemical methods. This record summarizes the PD-L1 positivity percentage in tumor samples.

End point type	Secondary

End point timeframe:

Baseline (screening), Cycle 3 Day 1. The duration of one cycle was 28 days.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: PD-L1 positivity percentage				
median (full range (min-max))				
Baseline (n=78)	20.00 (0 to 100)			

Cycle 3 Day 1 (n=1)	90.00 (90.00 to 90.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent marker area for CD8 expression in tumor samples

End point title	Percent marker area for CD8 expression in tumor samples[12]

End point description:

The expression of CD8 was measured in tumor samples by immunohistochemical methods. This record summarizes the percent marker area for CD8 expression in tumor samples.

End point type	Secondary

End point timeframe:

Baseline (screening), Cycle 3 Day 1. The duration of one cycle was 28 days.

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: CD8 percent marker area				
median (full range (min-max))				
Baseline (n=78)	4.23 (0.1 to 31.8)			
Cycle 3 Day 1 (n=1)	2.22 (2.22 to 2.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fold change from baseline in IFN-gamma levels in plasma

End point title	Fold change from baseline in IFN-gamma levels in plasma[13]

End point description:

The levels of interferon-gamma (IFN-gamma) were measured in plasma samples by immunoassay methods. This record summarizes the fold change from baseline in IFN-gamma levels in plasma.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Cycle 1 Day 1), Cycle 1 Day 15, Cycle 2 Day 15 and end of treatment (assessed up to maximum 4 years). The duration of one cycle was 28 days.

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: fold change				
median (full range (min-max))				
Cycle 1 Day 15 (n=65)	1.53 (0.2 to 14.3)			
Cycle 2 Day 15 (n=51)	1.31 (0.1 to 35.2)			
End of treatment (n=34)	1.11 (0.1 to 3.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: TIL count in tumor samples

End point title	TIL count in tumor samples[14]

End point description:

The count of tumor-infiltrating lymphocytes (TILs) was measured in baseline (screening) and post-baseline paired tumor samples by immunohistochemical methods. This record summarizes the TIL count in tumor samples.

End point type	Secondary

End point timeframe:

Baseline (screening), Cycle 3 Day 1. The duration of one cycle was 28 days.

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: TILs				
Baseline (n=1)	10			
Cycle 3 Day 1 (n=1)	15			

Statistical analyses

No statistical analyses for this end point

Secondary: Fold change from baseline in IL-6 levels in plasma

End point title	Fold change from baseline in IL-6 levels in plasma[15]

End point description:

The levels of interleukin-6 (IL-6) were measured in plasma samples by immunoassay methods. This record summarizes the fold change from baseline in IL-6 levels in plasma.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Cycle 1 Day 1), Cycle 1 Day 15, Cycle 2 Day 15 and end of treatment (assessed up to maximum 4 years). The duration of one cycle was 28 days.

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: fold change				
median (full range (min-max))				
Cycle 1 Day 15 (n=41)	1.10 (0.2 to 3.3)			
Cycle 2 Day 15 (n=30)	1.35 (0.2 to 6.3)			
End of treatment (n=26)	1.41 (0.2 to 7.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Fold change from baseline in TNF-alfa levels in plasma

End point title	Fold change from baseline in TNF-alfa levels in plasma[16]

End point description:

The levels of tumor necrosis factor-alpha (TNF-alfa) were measured in plasma samples by immunoassay methods. This record summarizes the fold change from baseline in TNF-alfa levels in plasma.

End point type	Secondary

End point timeframe:

Baseline (pre-dose on Cycle 1 Day 1), Cycle 1 Day 15, Cycle 2 Day 15 and end of treatment (assessed up to maximum 4 years). The duration of one cycle was 28 days.

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Biomarker samples were not collected in participants randomized to chemotherapy.

End point values	Spartalizumab 400 mg Q4W			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: fold change				
median (full range (min-max))				
Cycle 1 Day 15 (n=73)	1.32 (0.4 to 2.2)			
Cycle 2 Day 15 (n=62)	1.39 (0.3 to 3.1)			
End of treatment (n=45)	1.67 (0.3 to 3.7)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression-free survival (PFS) as per RECIST v 1.1 using central assessment in participants who crossed over – Number of participants with progression or death

End point title	Progression-free survival (PFS) as per RECIST v 1.1 using central assessment in participants who crossed over – Number of participants with progression or death

End point description:

PFS is the time from the date of first dose of spartalizumab to the date of event defined as the first documented confirmed progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Progressive disease is at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. Number of participants in each category (progression, death, censored) is reported in this record.

End point type	Post-hoc

End point timeframe:

From first dose of spartalizumab up to maximum 0.6 years

End point values	Crossover to spartalizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: participants				
number of progression	20			
number of deaths	5			
number of censored	2			

Statistical analyses

No statistical analyses for this end point

Post-hoc: Progression-free survival (PFS) as per RECIST v 1.1 using central assessment in participants who crossed over – Median PFS

End point title	Progression-free survival (PFS) as per RECIST v 1.1 using central assessment in participants who crossed over – Median PFS

End point description:

PFS is the time from the date of first dose of spartalizumab to the date of event defined as the first documented confirmed progression or death due to any cause. If a patient has not had an event, progression-free survival is censored at the date of last adequate tumor assessment.
Tumor response was based on central review of tumor scan and the assessment criteria was Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Progressive disease is at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline.

End point type	Post-hoc

End point timeframe:

From first dose of spartalizumab up to maximum 0.6 years

End point values	Crossover to spartalizumab			
Subject group type	Subject analysis set			
Number of subjects analysed	27			
Units: months				
median (confidence interval 95%)	1.7 (1.6 to 1.9)			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths

End point description:

On-treatment deaths were collected from the start of treatment up to 30 days after study drug discontinuation, for a maximum duration of 4.0 years. Post-treatment deaths were collected after the on-treatment period (starting at day 31 after last dose of study treatment), up to 4.8 years.
For the crossover patients, the deaths collected before crossing over are summarized in the chemotherapy arm and the deaths collected after the crossover are summarized in the crossover arm.

End point type	Post-hoc

End point timeframe:

Up to 4.0 years (on-treatment deaths) and 4.8 years (all deaths).

End point values	Spartalizumab 400 mg Q4W	Chemotherapy	Crossover to spartalizumab	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	82	39	27	
Units: participants				
Total Deaths	48	9	19	
Deaths on-treatment	5	3	3	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up to 30 days after last dose (max 4yrs). For crossover patients, safety data collected before crossing over is summarized in the chemotherapy arm and data collected after the crossover is summarized in the crossover arm

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Spartalizumab 400 mg Q4W

Reporting group description:

anti-PD1 humanized monoclonal antibody. Participants treated with spartalizumab who remained on spartalizumab

Reporting group title	All spartalizumab participants

Reporting group description:

All participants who received at least one dose of spartalizumab

Reporting group title	Crossover to spartalizumab

Reporting group description:

Patients treated with chemotherapy who crossed over to spartalizumab.

Reporting group title	Chemotherapy

Reporting group description:

Commonly used chemotherapy as per investigator's choice

Serious adverse events	Spartalizumab 400 mg Q4W	All spartalizumab participants	Crossover to spartalizumab
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 82 (34.15%)	40 / 109 (36.70%)	12 / 27 (44.44%)
number of deaths (all causes)	5	8	3
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	1 / 2	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	3 / 82 (3.66%)	4 / 109 (3.67%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 4	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Social circumstances			
Miscarriage of partner			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			

Acute respiratory failure			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 82 (0.00%)	2 / 109 (1.83%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal congestion			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	2 / 2	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Aspartate aminotransferase increased			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bilirubin conjugated increased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin unconjugated increased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Electrical burn			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Diplegia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normocytic anaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			

subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Brain abscess			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sepsis			
subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Septic shock			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinusitis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			

subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	1 / 2	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Chemotherapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 39 (38.46%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour associated fever			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Generalised oedema			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oedema peripheral			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			

subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Peripheral swelling				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Social circumstances				
Miscarriage of partner				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Dyspnoea				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nasal congestion				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Epistaxis				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pleural effusion				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia aspiration				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bilirubin conjugated increased				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin increased				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood bilirubin unconjugated increased				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Injury, poisoning and procedural complications			
Electrical burn			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pericardial effusion			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Diplegia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Spinal cord compression			
subjects affected / exposed	1 / 39 (2.56%)		
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	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	4 / 39 (10.26%)			
occurrences causally related to treatment / all	5 / 5			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Normocytic anaemia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Papilloedema				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ascites				

subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dysphagia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis acute			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			

Angioedema			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rash maculo-papular			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Brain abscess			

subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Conjunctivitis				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Sinusitis				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				

subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypercalcaemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Malnutrition			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Spartalizumab 400 mg Q4W	All spartalizumab participants	Crossover to spartalizumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 82 (92.68%)	101 / 109 (92.66%)	25 / 27 (92.59%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 82 (1.22%)	3 / 109 (2.75%)	2 / 27 (7.41%)
occurrences (all)	2	4	2
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	11 / 82 (13.41%)	12 / 109 (11.01%)	1 / 27 (3.70%)
occurrences (all)	15	16	1
Fatigue			
subjects affected / exposed	14 / 82 (17.07%)	19 / 109 (17.43%)	5 / 27 (18.52%)
occurrences (all)	16	22	6
Oedema peripheral			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Peripheral swelling			
subjects affected / exposed	0 / 82 (0.00%)	2 / 109 (1.83%)	2 / 27 (7.41%)
occurrences (all)	0	3	3
Pyrexia			
subjects affected / exposed	16 / 82 (19.51%)	24 / 109 (22.02%)	8 / 27 (29.63%)
occurrences (all)	25	33	8
Swelling face			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Malaise			
subjects affected / exposed	6 / 82 (7.32%)	7 / 109 (6.42%)	1 / 27 (3.70%)
occurrences (all)	7	8	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	17 / 82 (20.73%)	18 / 109 (16.51%)	1 / 27 (3.70%)
occurrences (all)	21	22	1
Dysphonia			
subjects affected / exposed	4 / 82 (4.88%)	4 / 109 (3.67%)	0 / 27 (0.00%)
occurrences (all)	4	4	0
Epistaxis			
subjects affected / exposed	10 / 82 (12.20%)	10 / 109 (9.17%)	0 / 27 (0.00%)
occurrences (all)	15	15	0
Dyspnoea			
subjects affected / exposed	12 / 82 (14.63%)	15 / 109 (13.76%)	3 / 27 (11.11%)
occurrences (all)	12	16	4
Nasal congestion			

subjects affected / exposed	3 / 82 (3.66%)	4 / 109 (3.67%)	1 / 27 (3.70%)
occurrences (all)	3	4	1
Pleural effusion			
subjects affected / exposed	2 / 82 (2.44%)	5 / 109 (4.59%)	3 / 27 (11.11%)
occurrences (all)	2	5	3
Productive cough			
subjects affected / exposed	1 / 82 (1.22%)	2 / 109 (1.83%)	1 / 27 (3.70%)
occurrences (all)	1	2	1
Rhinorrhoea			
subjects affected / exposed	2 / 82 (2.44%)	3 / 109 (2.75%)	1 / 27 (3.70%)
occurrences (all)	2	3	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	9 / 82 (10.98%)	12 / 109 (11.01%)	3 / 27 (11.11%)
occurrences (all)	9	12	3
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 82 (18.29%)	17 / 109 (15.60%)	2 / 27 (7.41%)
occurrences (all)	17	19	2
Alanine aminotransferase increased			
subjects affected / exposed	7 / 82 (8.54%)	8 / 109 (7.34%)	1 / 27 (3.70%)
occurrences (all)	8	9	1
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 82 (4.88%)	6 / 109 (5.50%)	2 / 27 (7.41%)
occurrences (all)	4	6	2
Blood creatinine increased			
subjects affected / exposed	5 / 82 (6.10%)	6 / 109 (5.50%)	1 / 27 (3.70%)
occurrences (all)	6	8	2
Platelet count decreased			
subjects affected / exposed	1 / 82 (1.22%)	3 / 109 (2.75%)	2 / 27 (7.41%)
occurrences (all)	1	3	2
Neutrophil count decreased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Lymphocyte count decreased			

subjects affected / exposed	3 / 82 (3.66%)	4 / 109 (3.67%)	1 / 27 (3.70%)
occurrences (all)	3	4	1
White blood cell count decreased			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Weight decreased			
subjects affected / exposed	9 / 82 (10.98%)	9 / 109 (8.26%)	0 / 27 (0.00%)
occurrences (all)	9	9	0
Blood thyroid stimulating hormone increased			
subjects affected / exposed	6 / 82 (7.32%)	6 / 109 (5.50%)	0 / 27 (0.00%)
occurrences (all)	7	7	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 82 (6.10%)	8 / 109 (7.34%)	3 / 27 (11.11%)
occurrences (all)	7	10	3
Headache			
subjects affected / exposed	12 / 82 (14.63%)	13 / 109 (11.93%)	1 / 27 (3.70%)
occurrences (all)	14	15	1
Hypoaesthesia			
subjects affected / exposed	4 / 82 (4.88%)	6 / 109 (5.50%)	2 / 27 (7.41%)
occurrences (all)	5	7	2
Neuropathy peripheral			
subjects affected / exposed	3 / 82 (3.66%)	5 / 109 (4.59%)	2 / 27 (7.41%)
occurrences (all)	3	5	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 82 (23.17%)	25 / 109 (22.94%)	6 / 27 (22.22%)
occurrences (all)	22	28	6
Lymphopenia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Neutropenia			

subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Leukopenia			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Thrombocytopenia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Abdominal pain			
subjects affected / exposed	5 / 82 (6.10%)	9 / 109 (8.26%)	4 / 27 (14.81%)
occurrences (all)	5	9	4
Abdominal distension			
subjects affected / exposed	5 / 82 (6.10%)	6 / 109 (5.50%)	1 / 27 (3.70%)
occurrences (all)	5	6	1
Abdominal pain upper			
subjects affected / exposed	8 / 82 (9.76%)	11 / 109 (10.09%)	3 / 27 (11.11%)
occurrences (all)	8	11	3
Constipation			
subjects affected / exposed	13 / 82 (15.85%)	16 / 109 (14.68%)	3 / 27 (11.11%)
occurrences (all)	17	21	4
Diarrhoea			
subjects affected / exposed	5 / 82 (6.10%)	6 / 109 (5.50%)	1 / 27 (3.70%)
occurrences (all)	7	8	1
Dry mouth			
subjects affected / exposed	3 / 82 (3.66%)	4 / 109 (3.67%)	1 / 27 (3.70%)
occurrences (all)	3	4	1
Dyspepsia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Mouth ulceration			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0

Nausea			
subjects affected / exposed	13 / 82 (15.85%)	17 / 109 (15.60%)	4 / 27 (14.81%)
occurrences (all)	15	19	4
Oral pain			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	14 / 82 (17.07%)	21 / 109 (19.27%)	7 / 27 (25.93%)
occurrences (all)	21	29	8
Stomatitis			
subjects affected / exposed	6 / 82 (7.32%)	6 / 109 (5.50%)	0 / 27 (0.00%)
occurrences (all)	6	6	0
Dysphagia			
subjects affected / exposed	5 / 82 (6.10%)	5 / 109 (4.59%)	0 / 27 (0.00%)
occurrences (all)	6	6	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Dry skin			
subjects affected / exposed	5 / 82 (6.10%)	7 / 109 (6.42%)	2 / 27 (7.41%)
occurrences (all)	6	8	2
Pruritus			
subjects affected / exposed	10 / 82 (12.20%)	14 / 109 (12.84%)	4 / 27 (14.81%)
occurrences (all)	14	18	4
Rash			
subjects affected / exposed	15 / 82 (18.29%)	16 / 109 (14.68%)	1 / 27 (3.70%)
occurrences (all)	21	22	1
Urticaria			
subjects affected / exposed	0 / 82 (0.00%)	0 / 109 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			

Urinary retention			
subjects affected / exposed	0 / 82 (0.00%)	2 / 109 (1.83%)	2 / 27 (7.41%)
occurrences (all)	0	2	2
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	10 / 82 (12.20%)	13 / 109 (11.93%)	3 / 27 (11.11%)
occurrences (all)	10	13	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 82 (10.98%)	14 / 109 (12.84%)	5 / 27 (18.52%)
occurrences (all)	11	17	6
Back pain			
subjects affected / exposed	9 / 82 (10.98%)	13 / 109 (11.93%)	4 / 27 (14.81%)
occurrences (all)	9	14	5
Musculoskeletal chest pain			
subjects affected / exposed	4 / 82 (4.88%)	4 / 109 (3.67%)	0 / 27 (0.00%)
occurrences (all)	4	4	0
Muscular weakness			
subjects affected / exposed	2 / 82 (2.44%)	2 / 109 (1.83%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Bone pain			
subjects affected / exposed	4 / 82 (4.88%)	5 / 109 (4.59%)	1 / 27 (3.70%)
occurrences (all)	4	5	1
Myalgia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 82 (3.66%)	3 / 109 (2.75%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Herpes zoster			
subjects affected / exposed	3 / 82 (3.66%)	3 / 109 (2.75%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Sinusitis			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	4	4	0

Upper respiratory tract infection			
subjects affected / exposed	9 / 82 (10.98%)	10 / 109 (9.17%)	1 / 27 (3.70%)
occurrences (all)	11	12	1
Urinary tract infection			
subjects affected / exposed	1 / 82 (1.22%)	1 / 109 (0.92%)	0 / 27 (0.00%)
occurrences (all)	4	4	0
Pneumonia			
subjects affected / exposed	3 / 82 (3.66%)	3 / 109 (2.75%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	16 / 82 (19.51%)	24 / 109 (22.02%)	8 / 27 (29.63%)
occurrences (all)	18	26	8
Dehydration			
subjects affected / exposed	3 / 82 (3.66%)	3 / 109 (2.75%)	0 / 27 (0.00%)
occurrences (all)	3	3	0
Hypoalbuminaemia			
subjects affected / exposed	6 / 82 (7.32%)	9 / 109 (8.26%)	3 / 27 (11.11%)
occurrences (all)	6	9	3
Hypokalaemia			
subjects affected / exposed	5 / 82 (6.10%)	9 / 109 (8.26%)	4 / 27 (14.81%)
occurrences (all)	7	12	5
Hypomagnesaemia			
subjects affected / exposed	7 / 82 (8.54%)	9 / 109 (8.26%)	2 / 27 (7.41%)
occurrences (all)	8	10	2
Hyponatraemia			
subjects affected / exposed	14 / 82 (17.07%)	18 / 109 (16.51%)	4 / 27 (14.81%)
occurrences (all)	19	24	5
Hypophosphataemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 109 (0.92%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Hyperglycaemia			
subjects affected / exposed	5 / 82 (6.10%)	5 / 109 (4.59%)	0 / 27 (0.00%)
occurrences (all)	9	9	0

Non-serious adverse events	Chemotherapy		
Total subjects affected by non-serious			

adverse events subjects affected / exposed	37 / 39 (94.87%)		
Vascular disorders Hypertension subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Peripheral swelling subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Swelling face subjects affected / exposed occurrences (all) Malaise subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 3 15 / 39 (38.46%) 16 5 / 39 (12.82%) 8 0 / 39 (0.00%) 0 3 / 39 (7.69%) 3 3 / 39 (7.69%) 3 2 / 39 (5.13%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dysphonia subjects affected / exposed occurrences (all) Epistaxis	 12 / 39 (30.77%) 15 2 / 39 (5.13%) 2		

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	5		
Dyspnoea			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Pleural effusion			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	4		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	12		
Alanine aminotransferase increased			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	14		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	3		
Platelet count decreased			

subjects affected / exposed	7 / 39 (17.95%)		
occurrences (all)	27		
Neutrophil count decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	6		
Lymphocyte count decreased			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	6		
White blood cell count decreased			
subjects affected / exposed	8 / 39 (20.51%)		
occurrences (all)	46		
Weight decreased			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	7		
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Hypoaesthesia			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Neuropathy peripheral			
subjects affected / exposed	5 / 39 (12.82%)		
occurrences (all)	5		
Peripheral sensory neuropathy			
subjects affected / exposed	4 / 39 (10.26%)		
occurrences (all)	5		
Blood and lymphatic system disorders			

Anaemia				
subjects affected / exposed	19 / 39 (48.72%)			
occurrences (all)	32			
Lymphopenia				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	4			
Neutropenia				
subjects affected / exposed	12 / 39 (30.77%)			
occurrences (all)	36			
Leukopenia				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences (all)	4			
Thrombocytopenia				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences (all)	3			
Gastrointestinal disorders				
Abdominal discomfort				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Abdominal pain				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences (all)	2			
Abdominal distension				
subjects affected / exposed	0 / 39 (0.00%)			
occurrences (all)	0			
Abdominal pain upper				
subjects affected / exposed	3 / 39 (7.69%)			
occurrences (all)	3			
Constipation				
subjects affected / exposed	7 / 39 (17.95%)			
occurrences (all)	8			
Diarrhoea				
subjects affected / exposed	5 / 39 (12.82%)			
occurrences (all)	7			
Dry mouth				

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Dyspepsia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Mouth ulceration			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	8 / 39 (20.51%)		
occurrences (all)	9		
Oral pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Vomiting			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Stomatitis			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	14		
Dysphagia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	9 / 39 (23.08%)		
occurrences (all)	9		
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		
Dry skin			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Pruritus			

subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Rash			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Urticaria			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 39 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	7		
Musculoskeletal chest pain			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Muscular weakness			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Bone pain			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
Myalgia			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Herpes zoster subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Sinusitis subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3			
Pneumonia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 3			
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	9 / 39 (23.08%) 12			
Dehydration subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2			
Hypokalaemia subjects affected / exposed occurrences (all)	13 / 39 (33.33%) 20			
Hypomagnesaemia subjects affected / exposed occurrences (all)	6 / 39 (15.38%) 6			
Hyponatraemia				

subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	8		
Hypophosphataemia			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	6		
Hyperglycaemia			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2015	To revise exclusion criteria to exclude subjects receiving systemic corticosteroids at dose of > 10mg/day prednisone; To specify in more detail guidelines and criteria about immune related and non-immune related AE management and study treatment recommendations; To clarify the criterion that subjects beyond initial RECIST v1.1 defined disease progression were allowed to continue study treatment; To specify more frequent evaluations may be performed at investigator's discretion or if recommended by drug product information.
21 January 2016	The primary purpose of this amendment was to introduce the RP2D of spartalizumab established in the Phase I (first-in-human) Study X2101. Based on PK and safety data from Study X2101, the RP2D for spartalizumab had been declared as a flat dose of 400 mg iv Q4W; The safety follow-up period had been extended to 90 days after the last dose of spartalizumab treatment (based on preliminary PK data from Study X2101 and the possibility of delayed appearance of immune-related AEs); Subjects who were HBV or HCV positive were eligible. As PD-1 blocking antibodies were not immunosuppressive, there was no specific contraindication to recruit subjects who were HBV and HCV positive, provided their active disease was adequately controlled by antiviral therapy; Subjects who had previously received CTLA-4-antagonists were eligible providing they did not have hepatic, diarrhea/colitis or endocrine AEs grade ≥ 2, any other non-laboratory immune-related AE grade ≥ 3. Subjects must have had minimum 8-week washout period between the last dose of anti-CTLA4 and the first dose of spartalizumab. The 8 weeks washout period was needed to resolve the anti-CTLA4 induced irAE, which could have a delayed onset; For monitoring of thyroid function, the measurement of free T4 a more specific parameter as compared to total T4 was included, whereas total T4 was removed; The tumor assessment should include the head and neck if clinically relevant.
27 July 2016	With the available PK data obtained from the single agent first-in-human Study X2101, an exploratory population PK (PopPK) analysis showed that the T1/2 of spartalizumab in man was 20 (17, 23) days (mean (90% CI)). Using 5 times the upper limit of the half-life of 23 days and an added safety margin, the protocol was amended to increase the duration of contraception and safety follow-up period post spartalizumab treatment from 90 days to 150 days. These changes were related to an Urgent Safety Measure communicated on 08-Jun-2016 to all investigators; This amendment also introduced the following key changes: Clarification of inclusion criterion 8: Specified that lesions in previously irradiated areas should not be considered measurable unless there was clear evidence of progression in such lesions since the radiotherapy; Modification of exclusion criterion 8: Subjects who had previously received an investigational therapeutic cancer vaccine could be eligible. This change had been introduced considering the limited efficacy evidence available for cancer vaccines and the high-unmet medical need in this subject population; Clarification of exclusion criterion 10: Subjects who had previously received an investigational therapeutic cancer vaccine were eligible providing there was a minimum 4-week washout period between the last dose of the vaccine and the first dose of spartalizumab; ECG monitoring plan was simplified to collection of ECGs at screening, C1D1, C3D1 and as clinically indicated, because no signal of QT interval prolongation was observed in the first in human Study X2101 or other currently approved anti-PD-1 antibodies. Concentration-QT analysis plan in Section 10.6.1 was removed accordingly.

07 December 2017	Addition of safety evaluations on 30 and 90 days to the 150-day safety follow-up visit, in order to ensure regular safety follow-up of subjects after the last administration of spartalizumab; To ensure a consistent approach in the reporting of the safety profile of study treatment, the main data analysis focused on the period from the first dose of study treatment to 30 days after the date of the last administration of study treatment. Data collected beyond this period (i.e. post-treatment period) were summarized separately; irAEs had been included in the AEs part as secondary endpoints. To avoid redundant description and reporting, the irAEs were removed as standalone secondary endpoint but continued to be analyzed as part of the AEs analysis (secondary endpoint); In order to explore the durability of disease control by spartalizumab in subjects with NPC, the analysis of long-term endpoints was added to the primary CSR. This analysis included all subjects data up to the date when each subject had reached a minimum of 12 months of follow-up after the first dose of study treatment or had lost to follow-up. There were no changes to the pre-defined study endpoints; In order to better characterize PK through population approach, one more sample collection was added for PK and IG at the 150-day safety follow-up visit for the spartalizumab arm subjects who come on site.
30 August 2018	After the occurrence of a case of Steven Johnson Syndrome in a study with spartalizumab in combination with another investigational agent, the dose modification guidelines for protocols using spartalizumab were updated to mandate permanent discontinuation of study treatment for subjects who experience Stevens–Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); The independent central review of imaging data were terminated for the whole study when both criteria were met, 1) decisions were made based on central review results for all the chemotherapy arm subjects on whether to crossover; 2) all subject had reached a minimum of 12 months follow-up after the first dose of study treatment (unless have been lost to follow-up). Because the purposes of applying the central review service had been fulfilled; Serology tests (anti-DNA antibodies (Abs), anti-nuclear abs, anti-phospholipid abs, antimitochondrial abs, c-Reactive protein (CRP), Rheumatoid factor (RF)) were no longer mandated. The available safety data from clinical studies indicate that spartalizumab was generally well tolerated; ECG was no longer centrally reviewed; PK and IG sample collection was terminated after the Cycle 4 samples were collected from all the spartalizumab arm subjects, as sufficient PK and IG samples had been collected for characterization of the PK and IG profile of spartalizumab in NPC subjects.
24 June 2019	The definition of end of study was revised to include the option for subjects still on study treatment and who in the opinion of the Investigator were still deriving clinical benefit at the time of end of study, to transfer to another study or to an alternative treatment option to continue providing study treatment to these subjects; In addition, the blood sample collection was removed for the assessment of serum cytokines used for retrospective analysis of a CRS AE. Blood samples for serum cytokines were included due to the unknown risk of CRS with IO agents alone and in combination, and to allow an assessment of any association between cytokines and clinical events. These samples were drawn at baseline and at the time of a potential CRS event, stored, and analyzed retrospectively. Due to this, results were not intended to be used to support clinical decision-making for subjects with possible CRS. There were no unexpected clinically assessed events of CRS observed across 19 studies including more than 2200 subjects. The risk of CRS in the current study was deemed to be low, thus supporting the removal of this blood sample collection.

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com for complete trial results.

Notes: