



Clinical trial results:

A phase II, multicenter, randomized, two-arm study of capmatinib (INC280, an oral MET inhibitor) and spartalizumab (PDR001, a PD-1 inhibitor) combination therapy versus docetaxel in pretreated adult patients with EGFR wild-type, ALK rearrangement negative locally advanced/metastatic non-small cell lung cancer.

Summary

EudraCT number	2018-001420-19
Trial protocol	DE ES GB BE FR GR BG NL IT RO
Global end of trial date	07 September 2020

Results information

Result version number	v1
This version publication date	24 June 2021
First version publication date	24 June 2021

Trial information

Trial identification

Sponsor protocol code	CINC280D2201
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03647488
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	07 September 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	07 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the safety and efficacy of capmatinib in combination with spartalizumab in adult participants with epidermal growth factor receptor (EGFR) wild type (for exon 19 deletions and exon 21 L858R substitution mutations), anaplastic lymphoma kinase (ALK) rearrangement negative in locally advanced (stage IIIB, not eligible for definitive chemo-radiation) or metastatic (stage IV) Non-small cell lung cancer (NSCLC) after failure of platinum doublet and checkpoint inhibitor treatment.

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:

In general, the use of any concomitant medication/therapy deemed necessary for the care of the participant (e.g. such as anti-emetics, anti-diarrhea) was permitted, except when specifically prohibited (e.g. such as CYP450 inducers, inhibitors, and substrates, gastric protecting agents, and other investigational and antineoplastic therapies).

Evidence for comparator: -

Actual start date of recruitment	26 December 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	Belgium: 3
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	18
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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	13
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Based on preliminary results of run-in part, the decision was not to open randomized part of the study. Therefore, no participants were enrolled in randomized part.

Period 1

Period 1 title	Run-in part (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Run-in part: capmatinib + spartalizumab
------------------	---

Arm description:

Participants (enrolled in the run-in part) were treated with capmatinib 400 mg twice daily (BID) and spartalizumab 400 mg intravenously (i.v.) once every 28 days

Arm type	Experimental
Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib 400 mg (tablets) orally taken twice daily. The orally administered film-coated tablet formulation was provided in up to two strengths of 150 mg and 200 mg free base equivalent.

Investigational medicinal product name	Spartalizumab
Investigational medicinal product code	PDR001
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Spartalizumab 400 mg via intravenous infusion once every 28 days

Number of subjects in period 1	Run-in part: capmatinib + spartalizumab
Started	18
Completed	0
Not completed	18
Clinical progression	2
Adverse event, non-fatal	5
Progressive disease	10
Refusal to take investigational product	1

Baseline characteristics

Reporting groups

Reporting group title	Run-in part: capmatinib + spartalizumab
-----------------------	---

Reporting group description:

Participants (enrolled in the run-in part) were treated with capmatinib 400 mg twice daily (BID) and spartalizumab 400 mg intravenously (i.v.) once every 28 days

Reporting group values	Run-in part: capmatinib + spartalizumab	Total	
Number of subjects	18	18	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	13	13	
From 65-84 years	5	5	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	61.2		
standard deviation	± 10.52	-	
Sex: Female, Male Units: Participants			
Female	7	7	
Male	11	11	
Race/Ethnicity, Customized Units: Subjects			
White	17	17	
Missing	1	1	

End points

End points reporting groups

Reporting group title	Run-in part: capmatinib + spartalizumab
Reporting group description: Participants (enrolled in the run-in part) were treated with capmatinib 400 mg twice daily (BID) and spartalizumab 400 mg intravenously (i.v.) once every 28 days	

Primary: Run-in part: Percentage of participants with Dose Limiting Toxicities (DLTs)

End point title	Run-in part: Percentage of participants with Dose Limiting Toxicities (DLTs) ^[1]
End point description: A DLT was defined as an adverse event or abnormal laboratory value assessed as unrelated to disease progression, inter-current illness, or concomitant medications that met certain criteria as defined in the protocol.	
End point type	Primary
End point timeframe: From the day of the first dose of study medication up to 56 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: No statistical analyses were planned for this endpoint	

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
number (not applicable)	5.56			

Statistical analyses

No statistical analyses for this end point

Primary: Run-in part: Percentage of participants with adverse events (AEs)

End point title	Run-in part: Percentage of participants with adverse events (AEs) ^[2]
End point description: Percentage of participants with AEs, including changes from baseline in vital signs and laboratory results qualifying and reported as AEs. AEs were assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0: Grade 1: mild; Grade 2: moderate; Grade 3: severe or medically significant; Grade 4: life-threatening consequences; Grade 5: Death.	
End point type	Primary
End point timeframe: From the day of the first dose of study medication to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib (whichever is later) up to maximum duration of approximately 1.7 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 analyses were planned for this endpoint

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of Participants				
number (not applicable)				
AEs- All grades	100			
AEs- Grade ≥ 3	61.11			
Treatment-related (TR) AEs- All grades	77.78			
TR AEs- Grade ≥ 3	5.56			
Serious AEs (SAEs)- All grades	55.56			
SAEs- Grade ≥ 3	38.89			
TR SAEs- All grades	16.67			
TR SAEs- Grade ≥ 3	0			
Fatal SAEs- All grades	5.56			
Fatal SAEs- Grade ≥ 3	5.56			
AEs leading to discontinuation- All grades	27.78			
AEs leading to discontinuation- Grade ≥ 3	16.67			
TR AEs leading to discontinuation- All grades	16.67			
TR AEs leading to discontinuation- Grade ≥ 3	5.56			
AEs leading to adjustment/interruption- All grades	50			
AEs leading to adjustment/interruption- Grade ≥ 3	27.78			
AEs requiring additional therapy- All grades	88.89			
AEs requiring additional therapy- Grade ≥ 3	44.44			

Statistical analyses

No statistical analyses for this end point

Primary: Run-in part: Percentage of participants with at least one dose reduction.

End point title	Run-in part: Percentage of participants with at least one dose reduction. ^[3]
-----------------	--

End point description:

Percentage of participants with at least one dose reduction. Dose reductions were only allowed for capmatinib

End point type	Primary
----------------	---------

End point timeframe:

From the day of the first dose of study medication to end of treatment, assessed up to maximum duration of 68 weeks

Notes:

[3] - 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 analyses were planned for this endpoint

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of Participants				
number (not applicable)	33.33			

Statistical analyses

No statistical analyses for this end point

Primary: Run-in part: Percentage of participants with at least one dose interruption

End point title	Run-in part: Percentage of participants with at least one dose interruption ^[4]
-----------------	--

End point description:

Percentage of participants with at least one dose interruption. Dose interruptions were allowed for capmatinib and spartalizumab.

End point type	Primary
----------------	---------

End point timeframe:

From the day of the first dose of study medication to end of treatment, assessed up to maximum duration of 68 weeks

Notes:

[4] - 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 analyses were planned for this endpoint

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of Participants				
number (not applicable)				
Capmatinib	44.44			
Spartalizumab	16.67			

Statistical analyses

No statistical analyses for this end point

Primary: Run-in part: Relative dose intensity received by participants

End point title	Run-in part: Relative dose intensity received by participants ^[5]
-----------------	--

End point description:

The relative dose intensity of capmatinib and spartalizumab is computed as the ratio of dose intensity and planned dose intensity, expressed as a percentage.

End point type	Primary
----------------	---------

End point timeframe:

From the day of the first dose of study medication to end of treatment, assessed up to maximum duration of 68 weeks

Notes:

[5] - 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 analyses were planned for this endpoint

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of dose received				
median (full range (min-max))				
Capmatinib	99.6 (27.8 to 100.0)			
Spartalizumab	100.0 (75.0 to 133.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR) based on RECIST 1.1 and as per investigator assessment

End point title	Objective response rate (ORR) based on RECIST 1.1 and as per investigator assessment
-----------------	--

End point description:

ORR is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 and as per investigator assessment.

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.

ORR results for randomized part are not available because randomized part never started.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment until end of treatment, assessed up to 68 weeks (run-in part)

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	0 (0.0 to 18.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) based on RECIST 1.1 and as per investigator assessment

End point title	Disease control rate (DCR) based on RECIST 1.1 and as per investigator assessment
-----------------	---

End point description:

DCR is defined as the proportion of subjects with best overall response of CR or PR or stable disease based on RECIST 1.1 and as per investigator assessment.

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.

Stable disease: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression.

DCR results for randomized part are not available because randomized part never started.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment until end of treatment, assessed up to 68 weeks (run-in part)

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Percentage of participants				
number (confidence interval 95%)	27.8 (9.7 to 53.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
-----------------	---------------------------------

End point description:

PFS is defined as the time from the date of start of treatment to the date of the first documented radiological progression or death due to any cause. For participants who had not progressed or died at the analysis cut-off date, PFS was censored at the date of the last adequate tumor evaluation date. An

adequate tumour assessment is a tumour assessment with an overall response other than unknown. Progression is defined using RECIST 1.1 and as per investigator assessment as 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. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

PFS results for randomized part are not available because randomized part never started.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment until the first documented radiological progression or death, whichever comes first, assessed up to 68 weeks (run-in part)

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Months				
median (confidence interval 95%)	1.9 (1.7 to 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) based on RECIST 1.1 and as per investigator assessment

End point title	Time to response (TTR) based on RECIST 1.1 and as per investigator assessment
-----------------	---

End point description:

TTR is defined as the time from the date of start of treatment to the first documented response of either CR or PR, which must be subsequently confirmed. TTR was evaluated according to RECIST 1.1 and as per investigator assessment.

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.

For run-in part, TTR results are not available because there were no participants achieving response (CR or PR)

For randomized part, TTR results are not available because randomized part never started.

End point type	Secondary
----------------	-----------

End point timeframe:

From start of treatment to the first documented response of either complete response or partial response, assessed up to 68 weeks (run-in part)

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[6]			
Units: Months				
number (confidence interval 95%)	(to)			

Notes:

[6] - No participants were analyzed because there were no participants achieving response (CR or PR)

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) based on RECIST 1.1 and as per investigator assessment

End point title	Duration of response (DOR) based on RECIST 1.1 and as per investigator assessment
-----------------	---

End point description:

DOR is the time between the date of first documented response (CR or PR) and the date of first documented progression or death due to underlying cancer based on RECIST 1.1 and as per investigator assessment. If progression or death has not occurred, the subject is censored at the date of last adequate tumor assessment. CR: Disappearance of all non-nodal target lesions and 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. Progression: 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. The sum must also demonstrate an absolute increase of at least 5 mm. Results are not available because there were no participants achieving response in the run-in part and randomized part never started

End point type	Secondary
----------------	-----------

End point timeframe:

From first documented response (CR or PR) to first documented progression or death, whichever came first, assessed up to 68 weeks (run-in part)

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[7]			
Units: Months				
median (confidence interval 95%)	(to)			

Notes:

[7] - No participants were analyzed because there were no participants achieving response (CR or PR)

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of capmatinib

End point title	AUClast of capmatinib
-----------------	-----------------------

End point description:

AUClast is the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration. AUClast was calculated using non-compartmental methods.

End point type	Secondary
End point timeframe:	
Cycle 3 day 1 at predose, 0.5 hours (h), 1h, 2h, 4h and 8h postdose. Each Cycle is 28 days	

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: nanogram*hour/milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	11500 (± 47.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of capmatinib

End point title	AUCtau of capmatinib
End point description:	
AUCtau is the area under the plasma concentration-time curve from time zero to the end of the dosing interval Tau. AUCtau was calculated using non-compartmental methods.	
End point type	Secondary
End point timeframe:	
Cycle 3 day 1 at predose, 0.5 hours (h), 1h, 2h, 4h and 8h postdose. Each Cycle is 28 days	

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: nanogram*hour/milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	12800 (± 48.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of capmatinib

End point title	Maximum plasma concentration (Cmax) of capmatinib
-----------------	---

End point description:

The maximum (peak) observed plasma concentration after single dose administration. Cmax was calculated using non-compartmental methods.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 3 day 1 at predose, 0.5 hours (h), 1h, 2h, 4h and 8h postdose. Each Cycle is 28 days

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	3260 ($\pm$ 44.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum (Tmax) plasma concentration of capmatinib

End point title	Time to reach maximum (Tmax) plasma concentration of capmatinib
-----------------	---

End point description:

Tmax is the time to reach maximum (peak) plasma concentration of capmatinib after single dose administration (time). Tmax was calculated using non-compartmental methods.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 3 day 1 at predose, 0.5 hours (h), 1h, 2h, 4h and 8h postdose. Each Cycle is 28 days

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hour (h)				
median (full range (min-max))	1.42 (0.983 to 2.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of spartlizumab

End point title	AUClast of spartlizumab
End point description: AUClast is the area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration. AUClast was calculated using non-compartmental methods.	
End point type	Secondary
End point timeframe: Cycle 3 day 1 at predose and 1h postdose. Each Cycle is 28 days	

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: microgram*day/milliliter (µg*day/mL)				
geometric mean (geometric coefficient of variation)	1720 (± 64.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of spartlizumab

End point title	AUCtau of spartlizumab
End point description: AUCtau is the area under the plasma concentration-time curve from time zero to the end of the dosing interval Tau. AUCtau was calculated using non-compartmental methods.	
End point type	Secondary
End point timeframe: Cycle 3 day 1 at predose and 1h postdose. Each Cycle is 28 days	

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: microgram*day/milliliter (µg*day/mL)				
geometric mean (geometric coefficient of variation)	2110 (± 35.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum plasma concentration (Cmax) of spartlizumab

End point title	Maximum plasma concentration (Cmax) of spartlizumab
-----------------	---

End point description:

The maximum (peak) observed plasma concentration after single dose administration. Cmax was calculated using non-compartmental methods.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 3 day 1 at predose and 1h postdose. Each Cycle is 28 days

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: microgram/milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)	138 (± 23.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum (Tmax) plasma concentration of spartlizumab

End point title	Time to reach maximum (Tmax) plasma concentration of spartlizumab
-----------------	---

End point description:

Tmax is the time to reach maximum (peak) plasma concentration of spartlizumab after single dose administration (time). Tmax was calculated using non-compartmental methods.

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 3 day 1 at predose and 1h postdose. Each Cycle is 28 days

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hour (h)				
median (full range (min-max))	1.13 (1.00 to 1.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spartalizumab antidrug antibodies (ADA) prevalence at baseline

End point title	Spartalizumab antidrug antibodies (ADA) prevalence at baseline
-----------------	--

End point description:

ADA prevalence at baseline was calculated as the proportion of participants who had an ADA positive result at baseline

End point type	Secondary
----------------	-----------

End point timeframe:

Cycle 1 Day 1 at predose. Each Cycle is 28 days

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	17			
Units: Participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Spartalizumab ADA Incidence On-treatment

End point title	Spartalizumab ADA Incidence On-treatment
-----------------	--

End point description:

ADA incidence on treatment was calculated as the proportion of participants who were treatment-induced ADA positive (post-baseline ADA positive with ADA-negative sample at baseline) and treatment-boosted ADA positive (post-baseline ADA positive with titer that is at least the fold titer change greater than the ADA-positive baseline titer)

End point type	Secondary
----------------	-----------

End point timeframe:

Predose at Cycle (C)1 Day (D)1, C2D1, C3D1, C4D1, C6D1, C8D1, C10D1, C12D1, thereafter every 6 cycles until discontinuation, and end of treatment (EOT), 30-day and 150-day after EOT

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Participants	3			

Statistical analyses

No statistical analyses for this end point

Post-hoc: All Collected Deaths

End point title	All Collected Deaths
-----------------	----------------------

End point description:

Deaths on-treatment were collected from first dose of study medication to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib, whichever is later, up to a maximum duration of approximately 1.7 years.

Total deaths were collected from first dose of study treatment until end of post-treatment efficacy or survival follow, up to maximum duration of approximately 1.7 years

End point type	Post-hoc
----------------	----------

End point timeframe:

On-treatment: up to approximately 1.7 years. All deaths: up to approximately 1.7 years

End point values	Run-in part: capmatinib + spartalizumab			
Subject group type	Reporting group			
Number of subjects analysed	18			
Units: Participants				
Total Deaths	12			
Deaths on-treatment	5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from first dose of study medication to 150 days after the last dose of spartalizumab, or 30 days after the last dose of capmatinib, whichever is later, up to a maximum duration of approximately 1.7 years.

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	23.0
--------------------	------

Reporting groups

Reporting group title	Run-in part: capmatinib + spartalizumab
-----------------------	---

Reporting group description:

Participants (enrolled in the run-in part) were treated with capmatinib 400 mg twice daily (BID) and spartalizumab 400 mg intravenously (i.v.) once every 28 days

Serious adverse events	Run-in part: capmatinib + spartalizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 18 (55.56%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular arrhythmia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Drug hypersensitivity			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial obstruction			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			

subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Run-in part: capmatinib + spartalizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Vascular disorders Hypotension subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) Axillary pain subjects affected / exposed occurrences (all) Chest pain subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pain subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	4 / 18 (22.22%) 4 1 / 18 (5.56%) 1 2 / 18 (11.11%) 2 4 / 18 (22.22%) 4 4 / 18 (22.22%) 4 1 / 18 (5.56%) 1 4 / 18 (22.22%) 5		
Reproductive system and breast disorders Nipple pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Respiratory, thoracic and mediastinal disorders			

Bronchospasm			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dysphonia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dyspnoea			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	5		
Dyspnoea exertional			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Productive cough			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Confusional state			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Sleep disorder			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Amylase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	6		
Blood magnesium decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Lipase increased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Lymphocyte count decreased			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Weight decreased			

subjects affected / exposed occurrences (all)	3 / 18 (16.67%) 3		
Cardiac disorders			
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Stress cardiomyopathy subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Dysgeusia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Headache subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Lethargy subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Somnolence subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2		
Eye disorders			
Eyelid oedema subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Gastrointestinal disorders			
Abdominal pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		

Cheilitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	6		
Dry mouth			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	7 / 18 (38.89%)		
occurrences (all)	7		
Stomatitis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 18 (27.78%)		
occurrences (all)	5		
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 18 (11.11%)		
occurrences (all)	2		
Rash macular			

subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Renal and urinary disorders Renal pain subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Muscle spasms subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Infections and infestations Herpes zoster subjects affected / exposed occurrences (all) Osteomyelitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all)	1 / 18 (5.56%) 1 1 / 18 (5.56%) 1 1 / 18 (5.56%) 1		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Dehydration subjects affected / exposed occurrences (all)	2 / 18 (11.11%) 2 1 / 18 (5.56%) 3		

Hyperglycaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	1 / 18 (5.56%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported