Clinical trial results:
A randomized, open label, multicenter phase II study evaluating the efficacy and safety of capmatinib (INC280) plus pembrolizumab versus pembrolizumab alone as first line treatment for locally advanced or metastatic non-small cell lung cancer with PD-L1 50%

Summary

EudraCT number	2019-002660-27
Trial protocol	GB FR BE ES GR DE NL IT
Global end of trial date	07 February 2023

Results information

Result version number	v1 (current)
This version publication date	31 January 2024
First version publication date	31 January 2024

Trial information

Trial identification

Sponsor protocol code	CINC280I12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04139317
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis, 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 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	07 February 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the efficacy of capmatinib plus pembrolizumab in comparison to pembrolizumab alone.

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	22 January 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	India: 7
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 2
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Thailand: 5
Worldwide total number of subjects	76
EEA total number of subjects	41

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)	33
From 65 to 84 years	43
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 36 investigative sites in 16 countries.

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. Screening evaluations were performed within 28 days prior to the first dose of 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	Capmatinib 400mg BID + pembrolizumab 200mg Q3W

Arm description:

Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)

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

Dosage and administration details:

Pembrolizumab (100 mg concentrate for solution for infusion or 50 mg lyophilized power for reconstitution for infusion) was administered intravenously at 200 mg once every 21 days.

Investigational medicinal product name	Capmatinib
Investigational medicinal product code	INC280
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Capmatinib tablets were administered orally on a continuous twice daily (BID) dosing schedule at a dose level of 400 mg, from Day 1 until Day 21 of each 21-day cycle. Based on lack of tolerability observed in the capmatinib plus pembrolizumab arm, the study enrollment was halted per sponsor's decision. Immediately following the enrollment halt, capmatinib treatment was discontinued in subjects on the combination arm and all ongoing participants were allowed to continue receiving pembrolizumab single agent treatment.

Arm title	Pembrolizumab 200mg Q3W

Arm description:

Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)

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

Dosage and administration details:

Pembrolizumab (100 mg concentrate for solution for infusion or 50 mg lyophilized power for reconstitution for infusion) was administered intravenously at 200 mg once every 21 days.

Number of subjects in period 1	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W
Started	51	25
Entered post-treatment follow-up	38	20
Completed	10	7
Not completed	41	18
Physician decision	3	1
Subject Decision	2	2
Adverse Event	10	2
Death	6	4
Progressive Disease	19	9
Lost to follow-up	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Capmatinib 400mg BID + pembrolizumab 200mg Q3W
Reporting group description:	
Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	
Reporting group title	Pembrolizumab 200mg Q3W
Reporting group description:	
Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	

Reporting group values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W	Total
Number of subjects	51	25	76
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)	23	10	33
From 65-84 years	28	15	43
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	64.7	66.6	
standard deviation	± 7.59	± 8.80	-
Sex: Female, Male Units: participants			
Female	16	9	25
Male	35	16	51
Race/Ethnicity, Customized Units: Subjects			
White	25	16	41
Asian	22	8	30
Unknown	4	1	5

End points

End points reporting groups

Reporting group title	Capmatinib 400mg BID + pembrolizumab 200mg Q3W
Reporting group description:	
Capmatinib (INC280) 400 mg orally twice daily (BID) in combination with pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	
Reporting group title	Pembrolizumab 200mg Q3W
Reporting group description:	
Pembrolizumab 200 mg intravenously every 3 weeks (Q3W)	

Primary: Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1

End point title	Progression-Free Survival (PFS) by investigator assessment as per RECIST 1.1[1]

End point description:

PFS is defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. Tumor response was based on investigator assessment per RECISTv1.1.
If a patient did not have an event, PFS was censored at the date of the last adequate tumor assessment, the start of a subsequent anti-neoplastic therapy (if any) or the date of sponsor's decision to discontinue capmatinib (applicable only to subjects on the combination arm).
Due to the discontinuation of one of the investigational drugs (capmatinib) in all subjects in the combination arm, PFS was censored on 21-Jan-2021 or the last adequate tumor assessment prior to that date for the capmatinib plus pembrolizumab arm.
PFS was analyzed using Kaplan-Meier estimates.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating not available). Therefore, NA values because of insufficient number of participants with events are indicated as 999

End point type	Primary

End point timeframe:

Up to 1.3 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 endpoint.

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: months				
median (confidence interval 95%)	5.2 (2.0 to 999)	5.1 (2.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1

End point title	Disease Control Rate (DCR) by investigator assessment as per RECIST 1.1

End point description:

Tumor response was based on local investigator assessment per RECIST v1.1. DCR is defined as the percentage of participants with a BOR of Complete Response (CR), Partial Response (PR), Stable Disease (SD), and non-CR/non-progressive disease (for subjects without target lesions). For the capmatinib plus pembrolizumab arm, 21-Jan-2021 or any last adequate tumor assessment prior to that date was considered as the end of evaluation period for BOR.
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; SD= Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progression).

End point type	Secondary

End point timeframe:

Up to 1.3 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: percentage of participants				
number (confidence interval 95%)	37.3 (24.1 to 51.9)	60.0 (38.7 to 78.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1

End point title	Overall Response Rate (ORR) by investigator assessment as per RECIST 1.1

End point description:

Tumor response was based on local investigator assessment as RECIST v1.1. ORR per RECIST v1.1 is defined as the percentage of participants with a best overall response (BOR) of Complete Response (CR) or Partial Response (PR). For the capmatinib plus pembrolizumab arm, 21-Jan-2021 or any last adequate tumor assessment prior to that date was considered as the end of evaluation period for BOR.
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:

Up to 1.3 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: Percentage of participants				
number (confidence interval 95%)	9.8 (3.3 to 21.4)	40.0 (21.1 to 61.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS is defined as the time from the date of randomization to date of death due to any cause.
The requirement for survival follow-up period was removed following the discontinuation of one of the investigational drugs (capmatinib) in all subjects in the combination arm and the implementation of Protocol Amendment 03.
OS was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not available'). Therefore, not available values because of insufficient number of participants with events are indicated as '999'.

End point type	Secondary

End point timeframe:

Up to 2.1 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by investigator assessment as per RECIST 1.1

End point title	Duration of Response (DOR) by investigator assessment as per RECIST 1.1

End point description:

DOR only applies to patients for whom best overall response is complete response (CR) or partial

response (PR) based on local investigator assessment of overall lesion response according to RECIST v1.1. DOR is defined as the time from the date of first documented response (confirmed CR or confirmed PR) to the date of first documented disease progression or death due to any cause. If a patient not had an event, duration was censored at the date of last adequate tumor assessment before the start of a new anticancer therapy, if any.
DOR was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not available'). Therefore, not available values because of insufficient number of participants with events are indicated as '999'.

End point type	Secondary

End point timeframe:

Up to 1.3 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	10		
Units: months				
median (confidence interval 95%)	999 (999 to 999)	999 (999 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) by investigator assessment as per RECIST 1.1

End point title	Time to response (TTR) by investigator assessment as per RECIST 1.1

End point description:

TTR is defined as the time from the date of randomization to the first documented response of either complete response or partial response, which must be subsequently confirmed (although initial date of response is used, not date of confirmation).
TTR was analyzed using the Kaplan-Meier method as defined in the statistical analysis plan.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not available'). Therefore, not available values because of insufficient number of participants with events are indicated as '999'.

End point type	Secondary

End point timeframe:

Up to 1.3 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: months				
median (confidence interval 95%)	999 (999 to	999 (999 to		

999)	999)

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

Number of participants with AEs (any AE regardless of seriousness) and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.

End point type	Secondary

End point timeframe:

From first dose of study treatment to 30 days after last dose, up to 2.1 years

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: participants				
AEs	49	25		
Treatment-related AEs	45	18		
SAEs	31	13		
Treatment-related SAEs	18	1		
AEs leading to discontinuation	18	5		
Treatment-related AEs leading to discontinuation	17	2		
AEs leading to dose reduction/interruption	34	7		
Treat-rel. AEs leading to dose reduction/interrup.	24	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) of capmatinib

End point title	Maximum observed plasma concentration (Cmax) of capmatinib[2]

End point description:

Pharmacokinetic (PK) parameters were calculated based on capmatinib plasma concentrations by using

non-compartmental methods. Cmax is defined as the maximum (peak) observed plasma concentration following a dose.

End point type	Secondary

End point timeframe:

pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 days.

Notes:

[2] - 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: This endpoint is only applicable to capmatinib + pembrolizumab arm

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	2730 (± 155.9)			

Statistical analyses

No statistical analyses for this end point

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

End point title	Time to reach maximum plasma concentration (Tmax) of capmatinib[3]

End point description:

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

End point type	Secondary

End point timeframe:

pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 days.

Notes:

[3] - 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: This endpoint is only applicable to capmatinib + pembrolizumab arm

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: hours				
median (full range (min-max))	1.33 (0 to 4.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib

End point title	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of capmatinib[4]

End point description:

PK parameters were calculated based on capmatinib plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUClast calculation.

End point type	Secondary

End point timeframe:

pre-dose and 1, 2, 4 and 8 hours after morning dose on Cycle 2 Day 1. The duration of one cycle was 21 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: This endpoint is only applicable to capmatinib + pembrolizumab arm

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	4210 (± 232.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough serum concentration (Ctrough) of pembrolizumab

End point title	Trough serum concentration (Ctrough) of pembrolizumab

End point description:

PK parameters were calculated based on pembrolizumab serum concentrations by using non-compartmental methods. Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary

End point timeframe:

pre-dose on Cycle 2 Day 1, Cycle 3 Day 1, Cycle 6 Day 1 and Cycle 12 Day 1. The duration of one cycle was 21 days.

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	18		
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1 (n=32, 18)	11.8 (± 37.5)	10.6 (± 34.8)		
Cycle 3 Day 1 (n=29, 18)	18.9 (± 51.9)	18.2 (± 32.3)		
Cycle 6 Day 1 (n=14, 8)	27.6 (± 66.5)	36.8 (± 26.0)		
Cycle 12 Day 1 (n=0, 2)	999 (± 999)	49.7 (± 10.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with anti-pembrolizumab antibodies

End point title	Number of participants with anti-pembrolizumab antibodies

End point description:

Immunogenicity (IG) was evaluated in serum samples. The assay to quantify and assess the IG was a validated homogeneous enzyme-linked immunosorbent assay (ELISA).
• ADA-negative at baseline: ADA-negative sample at baseline
• ADA-positive at baseline: ADA-positive sample at baseline
• ADA-negative post-baseline: patient with ADA-negative sample at baseline and at least 1 post baseline determinant sample, all of which are ADA-negative samples
• ADA-positive post-baseline: patient with at least 1 ADA-positive sample post baseline

End point type	Secondary

End point timeframe:

Baseline (pre-dose), up to 8 months

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	20		
Units: participants				
ADA-negative at baseline	37	18		
ADA-positive at baseline	5	2		
ADA-negative post-baseline	36	18		
ADA-positive post-baseline	6	2		

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 start of treatment to 30 days after last dose.
Post-treatment survival follow-up deaths were collected from day 31 after last dose of study treatment until the requirement for survival follow-up was removed following the discontinuation of capmatinib in the combination arm (protocol amendment 03).
All deaths refer to the sum of on-treatment deaths plus post-treatment survival follow-up deaths.

End point type	Post-hoc

End point timeframe:

On-treatment: Up to 2.1 years after start of treatment. Post-treatment survival follow-up: Up to 1.3 years after start of treatment.

End point values	Capmatinib 400mg BID + pembrolizumab 200mg Q3W	Pembrolizumab 200mg Q3W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	25		
Units: participants				
On-treatment deaths (n=51, 25)	10	3		
Post-treatment survival FU deaths (n=38, 20)	6	5		
All deaths (n=51, 25)	16	8		

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 treatment to 30 days after last dose, up to 2.1 years after start of treatment. Patients were analyzed according to the treatment they actually received.

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	25.0

Reporting groups

Reporting group title	Capmatinib + pembrolizumab – On-treatment

Reporting group description:

Capmatinib 400 mg BID in combination with pembrolizumab 200 mg Q3W. AEs collected during on-treatment period (up to 30 days after last dose).

Reporting group title	Pembrolizumab – On-treatment

Reporting group description:

Pembrolizumab single agent 200 mg Q3W from study start. AEs collected during on-treatment period (up to 30 days after last dose).

Reporting group title	Pembrolizumab after combination treatment – On-treatment

Reporting group description:

Pembrolizumab single agent 200 mg Q3W after discontinuing capmatinib. AEs collected during on-treatment period (up to 30 days after last dose).

Serious adverse events	Capmatinib + pembrolizumab – On-treatment	Pembrolizumab – On-treatment	Pembrolizumab after combination treatment – On-treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 51 (50.98%)	13 / 25 (52.00%)	9 / 51 (17.65%)
number of deaths (all causes)	8	3	2
number of deaths resulting from adverse events	4	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pericardial effusion malignant			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral ischaemia			

subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	3 / 51 (5.88%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			

subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	0 / 51 (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 / 51 (1.96%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Vocal cord polyp			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Radiation pneumonitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anastomotic stenosis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Nervous system disorders			
Brain oedema			

subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 51 (0.00%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 51 (0.00%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin reaction			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 51 (3.92%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis listeria			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Encephalitis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelitis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 51 (3.92%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 51 (3.92%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Septic shock			

subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	0 / 51 (0.00%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Capmatinib + pembrolizumab – On-treatment	Pembrolizumab – On-treatment	Pembrolizumab after combination treatment – On-treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 51 (80.39%)	24 / 25 (96.00%)	29 / 51 (56.86%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 51 (1.96%)	6 / 25 (24.00%)	0 / 51 (0.00%)
occurrences (all)	1	6	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 51 (7.84%)	5 / 25 (20.00%)	1 / 51 (1.96%)
occurrences (all)	4	5	1
Chest pain			
subjects affected / exposed	2 / 51 (3.92%)	3 / 25 (12.00%)	2 / 51 (3.92%)
occurrences (all)	2	3	1
Fatigue			

subjects affected / exposed	2 / 51 (3.92%)	5 / 25 (20.00%)	3 / 51 (5.88%)
occurrences (all)	2	6	3
Chills			
subjects affected / exposed	3 / 51 (5.88%)	0 / 25 (0.00%)	0 / 51 (0.00%)
occurrences (all)	4	0	0
Oedema peripheral			
subjects affected / exposed	14 / 51 (27.45%)	1 / 25 (4.00%)	6 / 51 (11.76%)
occurrences (all)	17	1	6
Pyrexia			
subjects affected / exposed	9 / 51 (17.65%)	5 / 25 (20.00%)	2 / 51 (3.92%)
occurrences (all)	12	6	2
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Productive cough			
subjects affected / exposed	0 / 51 (0.00%)	3 / 25 (12.00%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Cough			
subjects affected / exposed	2 / 51 (3.92%)	4 / 25 (16.00%)	3 / 51 (5.88%)
occurrences (all)	2	6	4
Dyspnoea			
subjects affected / exposed	5 / 51 (9.80%)	3 / 25 (12.00%)	5 / 51 (9.80%)
occurrences (all)	5	3	5
Haemoptysis			
subjects affected / exposed	1 / 51 (1.96%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	1	2	3
Nasal congestion			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Psychiatric disorders			

Insomnia			
subjects affected / exposed	4 / 51 (7.84%)	4 / 25 (16.00%)	3 / 51 (5.88%)
occurrences (all)	4	5	3
Investigations			
Blood bilirubin increased			
subjects affected / exposed	6 / 51 (11.76%)	1 / 25 (4.00%)	1 / 51 (1.96%)
occurrences (all)	7	1	1
Amylase increased			
subjects affected / exposed	4 / 51 (7.84%)	2 / 25 (8.00%)	3 / 51 (5.88%)
occurrences (all)	4	2	3
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 51 (9.80%)	1 / 25 (4.00%)	0 / 51 (0.00%)
occurrences (all)	6	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 51 (21.57%)	3 / 25 (12.00%)	2 / 51 (3.92%)
occurrences (all)	13	3	2
Alanine aminotransferase increased			
subjects affected / exposed	11 / 51 (21.57%)	3 / 25 (12.00%)	4 / 51 (7.84%)
occurrences (all)	12	3	2
Lipase increased			
subjects affected / exposed	2 / 51 (3.92%)	2 / 25 (8.00%)	2 / 51 (3.92%)
occurrences (all)	4	3	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 51 (7.84%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	4	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 51 (5.88%)	0 / 25 (0.00%)	1 / 51 (1.96%)
occurrences (all)	5	0	1
Blood creatinine increased			
subjects affected / exposed	7 / 51 (13.73%)	1 / 25 (4.00%)	1 / 51 (1.96%)
occurrences (all)	7	2	2
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 51 (1.96%)	0 / 25 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	4

SARS-CoV-2 test negative			
subjects affected / exposed	4 / 51 (7.84%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	6	3	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 51 (5.88%)	3 / 25 (12.00%)	1 / 51 (1.96%)
occurrences (all)	3	3	2
Dizziness			
subjects affected / exposed	1 / 51 (1.96%)	3 / 25 (12.00%)	1 / 51 (1.96%)
occurrences (all)	2	3	0
Hypoaesthesia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 25 (12.00%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Paraesthesia			
subjects affected / exposed	1 / 51 (1.96%)	4 / 25 (16.00%)	1 / 51 (1.96%)
occurrences (all)	1	4	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	0	3	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 25 (0.00%)	2 / 51 (3.92%)
occurrences (all)	6	0	2
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	3 / 51 (5.88%)	1 / 25 (4.00%)	3 / 51 (5.88%)
occurrences (all)	3	1	3
Abdominal pain			
subjects affected / exposed	1 / 51 (1.96%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	1	2	2
Vomiting			
subjects affected / exposed	14 / 51 (27.45%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	18	4	1

Nausea			
subjects affected / exposed	13 / 51 (25.49%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	16	3	2
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 51 (1.96%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	1	2	0
Diarrhoea			
subjects affected / exposed	8 / 51 (15.69%)	6 / 25 (24.00%)	4 / 51 (7.84%)
occurrences (all)	9	9	6
Constipation			
subjects affected / exposed	5 / 51 (9.80%)	4 / 25 (16.00%)	7 / 51 (13.73%)
occurrences (all)	5	8	8
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Dermatitis acneiform			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Ecchymosis			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	1 / 51 (1.96%)	2 / 25 (8.00%)	2 / 51 (3.92%)
occurrences (all)	1	4	2
Rash			
subjects affected / exposed	5 / 51 (9.80%)	3 / 25 (12.00%)	5 / 51 (9.80%)
occurrences (all)	7	6	7
Rash maculo-papular			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	4	0
Erythema			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Pruritus			

subjects affected / exposed	5 / 51 (9.80%)	8 / 25 (32.00%)	7 / 51 (13.73%)
occurrences (all)	6	14	8
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 51 (1.96%)	1 / 25 (4.00%)	6 / 51 (11.76%)
occurrences (all)	1	1	5
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Myalgia			
subjects affected / exposed	3 / 51 (5.88%)	3 / 25 (12.00%)	0 / 51 (0.00%)
occurrences (all)	4	4	0
Muscular weakness			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	1 / 51 (1.96%)
occurrences (all)	0	2	1
Back pain			
subjects affected / exposed	4 / 51 (7.84%)	3 / 25 (12.00%)	2 / 51 (3.92%)
occurrences (all)	4	4	2
Arthralgia			
subjects affected / exposed	3 / 51 (5.88%)	6 / 25 (24.00%)	5 / 51 (9.80%)
occurrences (all)	4	10	7
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 51 (0.00%)	2 / 25 (8.00%)	0 / 51 (0.00%)
occurrences (all)	0	2	0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	5 / 51 (9.80%)	0 / 25 (0.00%)	3 / 51 (5.88%)
occurrences (all)	6	0	2
Hypoalbuminaemia			
subjects affected / exposed	6 / 51 (11.76%)	2 / 25 (8.00%)	2 / 51 (3.92%)
occurrences (all)	7	2	2
Decreased appetite			
subjects affected / exposed	5 / 51 (9.80%)	5 / 25 (20.00%)	2 / 51 (3.92%)
occurrences (all)	7	5	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2019	The main purpose of this amendment was to address HAs' requests to provide specific recommendations of concomitant medications to treat diarrhea and nausea toxicities. Free T3 testing was removed from thyroid function monitoring and total T3 was to be tested if abnormal thyroid function was suspected. Unintended references to central ECG monitoring for cardiac toxicity follow up were removed to reflect study conduct.
17 February 2020	The main purpose of this amendment was to address HAs' requests to: • add background clinical pharmacology information for capmatinib, • exclude subjects with active infection or history of allogeneic tissue/organ transplantation and to provide the recommended treatment modifications for pembrolizumab in details, in order to align with the EU SmPC for pembrolizumab, • interrupt capmatinib treatment in case of hypersensitivity reactions, as SAEs of hypersensitivity have been reported as suspected to be related to study treatment in the capmatinib IB, • clarify that SAE reporting is required for any progression of malignancy suspected to be related to study treatment and meeting the SAE definition and • conduct a safety review by DMC after the first 6 randomized patients have been followed up for at least 6 weeks from randomization or have discontinued earlier. Dose modification guidelines for protocols using capmatinib in combination with PD-1 inhibitors were updated to mandate permanent discontinuation of study treatment in case of myocarditis grade ≥2 or other cardiac event grade ≥3. Further HCV RNA testing was not required if a subject's HCV Ab test was negative.
21 April 2021	The main purpose of this amendment was to modify the study conduct and data analysis following the enrollment halt on 21-Jan-2021 due to lack of tolerability observed in the capmatinib plus pembrolizumab arm. The decision to halt enrollment, supported by the DMC, was made based on the observation that subjects who received capmatinib plus pembrolizumab combination treatment had higher rates of SAEs/AEs leading to dose interruption and/or discontinuation of both study treatments compared to subjects in the pembrolizumab single agent arm. Procedural changes included discontinuation of capmatinib treatment in the combination arm, release of randomization to the CTT, termination of PK, biomarker and IG samples. All ongoing subjects continued to receive single-agent pembrolizumab, a registered and commercialized treatment for the study indication. Subjects who remained in the study were allowed to continue receiving pembrolizumab single agent treatment as per investigator's discretion until unacceptable toxicity, or disease progression, or up to 35 cycles of treatment, whichever occurred first. Treatment beyond disease progression was no longer to be allowed. Other significant changes included: • All efficacy assessments were performed according to each institution's standard of care. • All safety assessments were performed according to each institution's standard of care. • Except AEs, efficacy and safety assessment results were not captured in the eCRF. • End of study definition was refined as the earliest occurrence of discontinuation of study treatment and completed safety follow-up, death or withdrawn consent or lost to follow-up. • Independent review of safety and efficacy data was no longer required after release of randomization information to the CTT and the DMC was disbanded. • Originally planned administrative interim analysis was canceled. • Disease progression follow-up and survival follow-up were not performed.

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/#/

Notes: