Clinical trial results:
A phase II, multicenter, open-label study of EGF816 in combination with Nivolumab in adult patients with EGFR mutated non-small cell lung cancer and of INC280 in combination with Nivolumab in adult patients with cMet positive non-small cell lung cancer

Summary

EudraCT number	2014-003731-20
Trial protocol	DE ES NL IT
Global end of trial date	05 February 2021

Results information

Result version number	v1 (current)
This version publication date	16 February 2022
First version publication date	16 February 2022

Trial information

Trial identification

Sponsor protocol code	CEGF816X2201C

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02323126
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	05 February 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 February 2021
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 estimate the clinical activity of nivolumab in combination with EGF816 or INC280.

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	09 February 2015
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	Australia: 8
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	64
EEA total number of subjects	43

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)	33
From 65 to 84 years	30
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Participants took part in 13 investigative sites in 8 countries.

Pre-assignment

Screening details:

In the molecular pre-screening, tumor tissue was collected for determination and/or confirmation of protocol specific pre-requisite genetic alterations. After the molecular pre-screening, screening evaluations were performed within 28 days prior to the first dose of study medication. 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	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Nivolumab and EGF816

Arm description:

Group 1: EGF816 150 mg QD + Nivolumab 3 mg/kg Q2W

Arm type	Experimental
Investigational medicinal product name	EGF816
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

EGF816 150 mg once daily (QD) administered orally

Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab 3 mg/kg every 2 weeks (Q2W) administered by intravenous infusion

Arm title	Nivolumab and INC280, high cMet

Arm description:

Group 2A: INC280 400 mg BID, High cMET + Nivolumab 3 mg/kg Q2W

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

Dosage and administration details:

Nivolumab 3 mg/kg every 2 weeks (Q2W) administered by intravenous infusion

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

Dosage and administration details:

INC280 400 mg twice daily (BID) administered orally

Arm title	Nivolumab and INC280, low cMet

Arm description:

Group 2B: INC280 400 mg BID, Low cMet + Nivolumab 3 mg/kg Q2W

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

Dosage and administration details:

Nivolumab 3 mg/kg every 2 weeks (Q2W) administered by intravenous infusion

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

Dosage and administration details:

INC280 400 mg twice daily (BID) administered orally

Number of subjects in period 1	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet
Started	18	16	30
Completed	0	0	0
Not completed	18	16	30
Adverse event, serious fatal	1	1	4
Patient / guardian decision	-	1	2
Physician decision	-	1	3
Adverse event, non-fatal	3	5	7
Progressive disease	14	8	14

Baseline characteristics

Reporting groups	
Reporting group title	Nivolumab and EGF816
Reporting group description:	
Group 1: EGF816 150 mg QD + Nivolumab 3 mg/kg Q2W	
Reporting group title	Nivolumab and INC280, high cMet
Reporting group description:	
Group 2A: INC280 400 mg BID, High cMET + Nivolumab 3 mg/kg Q2W	
Reporting group title	Nivolumab and INC280, low cMet
Reporting group description:	
Group 2B: INC280 400 mg BID, Low cMet + Nivolumab 3 mg/kg Q2W	

Reporting group values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet
Number of subjects	18	16	30
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)	11	8	14
From 65-84 years	7	8	15
85 years and over	0	0	1
Age Continuous Units: years			
arithmetic mean	62.6	63.8	64.9
standard deviation	± 8.77	± 13.05	± 8.45
Sex: Female, Male Units: participants			
Female	12	8	15
Male	6	8	15
Race/Ethnicity, Customized Units: Subjects			
Asian	4	1	2
Caucasian	14	14	26
Other	0	0	1
Unknown	0	1	1

Reporting group values	Total		
Number of subjects	64		
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)	33		
From 65-84 years	30		
85 years and over	1		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	35		
Male	29		
Race/Ethnicity, Customized			
Units: Subjects			
Asian	7		
Caucasian	54		
Other	1		
Unknown	2		

End points

End points reporting groups

Reporting group title	Nivolumab and EGF816
Reporting group description:	
Group 1: EGF816 150 mg QD + Nivolumab 3 mg/kg Q2W	
Reporting group title	Nivolumab and INC280, high cMet
Reporting group description:	
Group 2A: INC280 400 mg BID, High cMET + Nivolumab 3 mg/kg Q2W	
Reporting group title	Nivolumab and INC280, low cMet
Reporting group description:	
Group 2B: INC280 400 mg BID, Low cMet + Nivolumab 3 mg/kg Q2W	

Primary: Progression-Free Survival (PFS) rate at 6 months per RECIST v1.1

End point title	Progression-Free Survival (PFS) rate at 6 months per RECIST v1.1[1]

End point description:

PFS rate represents the percentage of participants without a first documented progression or death due to any cause after the start of study treatment. Tumor response was based on local investigator assessment as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
PFS was modeled using a Weibull distribution and the PFS rate at 6 months was estimated from the posterior distribution.

End point type	Primary

End point timeframe:

6 months

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	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: percentage of participants				
number (confidence interval 95%)	63.4 (45.7 to 79.2)	68.9 (48.5 to 85.7)	50.9 (35.6 to 66.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR) per RECIST v1.1

End point title	Overall Response Rate (ORR) per RECIST v1.1

End point description:

Tumor response was based on local investigator assessment as per RECIST v1.1. ORR per RECIST 1.1 is defined as the percentage of participants with a best overall response of Complete Response (CR) or Partial Response (PR).

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 start of treatment until end of treatment, assessed up to 4.7 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: percentage of participants				
number (not applicable)	38.9	25.0	16.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR) per RECIST v1.1

End point title	Disease Control Rate (DCR) per RECIST v1.1

End point description:

Tumor response was based on local investigator assessment as per RECIST v1.1. DCR per RECIST 1.1 is defined as the percentage of participants with a best overall response of Complete Response (CR), Partial Response (PR) or Stable Disease (SD).
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 diameters 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:

From start of treatment until end of treatment, assessed up to 4.7 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: percentage of participants				
number (not applicable)	94.4	81.3	43.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Progression-Free Survival (PFS) per RECIST v1.1

End point title	Median Progression-Free Survival (PFS) per RECIST v1.1

End point description:

PFS is the time from the date of start of treatment 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. The median PFS was estimated using the Kaplan-Meier method.
Tumor response was based on local investigator assessment as per RECIST v1.1

End point type	Secondary

End point timeframe:

From start of treatment to first documented progression or death, assessed up to 5 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: months				
median (confidence interval 95%)	7.4 (3.7 to 11.1)	6.2 (3.5 to 19.2)	4.2 (1.8 to 7.4)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) rate at 3 months per RECIST v1.1

End point title	Progression-Free Survival (PFS) rate at 3 months per RECIST v1.1

End point description:

PFS rate represents the percentage of participants without a first documented progression or death due to any cause after the start of study treatment. Tumor response was based on local investigator assessment as per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1).
The PFS rate at 3 months was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

3 months

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: percentage of participants				
number (confidence interval 95%)	83.3 (56.8 to 94.3)	86.7 (56.4 to 96.5)	53.8 (33.3 to 70.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at 1 year

End point title	Overall Survival (OS) at 1 year

End point description:

OS represents the percentage of participants who are alive after the start of study treatment. OS at 1 year was estimated using the Kaplan-Meier method.

End point type	Secondary

End point timeframe:

1 year

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: percentage of participants				
number (confidence interval 95%)	55.6 (30.5 to 74.8)	72.3 (41.5 to 88.7)	32.5 (15.8 to 50.5)	

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 and SAEs, including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
AE grades were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

End point type	Secondary

End point timeframe:

From first dose of study medication up to 100 days after last dose of study medication, with a maximum duration of 5 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: participants				
AEs	18	16	30	
Treatment-related AEs	17	16	27	
AEs with grade 3/4	18	14	24	
Treatment-related AEs with grade 3/4	13	12	16	
SAEs	14	8	18	
Treatment-related SAEs	6	4	7	
Fatal SAEs	4	1	4	
Treatment related fatal SAEs	2	0	0	
AEs leading to discontinuation	5	7	11	
Treatment-related AEs leading to discontinuation	5	7	9	
AEs leading to dose adjustment/interruption	15	14	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with dose reductions and dose interruptions of EGF816, INC280 and nivolumab

End point title	Number of participants with dose reductions and dose interruptions of EGF816, INC280 and nivolumab

End point description:

Number of participants with at least one dose reduction of EGF816, INC280 or nivolumab and number of participants with at least one dose interruption of EGF816, INC280 or nivolumab.
Dose reduction was not allowed for nivolumab in this study.
Due to EudraCT system limitations, data fields cannot be blank if the number of subjects analyzed in the corresponding column is greater than 0. Therefore, not applicable values (eg. dose reduction or interruption of EGF816 in Groups 2A and 2B) are indicated as '999'.

End point type	Secondary

End point timeframe:

From first dose of study treatment until last dose of study treatment, up to maximum 4.7 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: participants				
EGF816, dose reduction (n=18, 0, 0)	5	999	999	
EGF816, dose interruption (n=18, 0, 0)	14	999	999	
INC280, dose reduction (n=0, 16, 30)	999	7	10	
INC280, dose interruption (n=0, 16, 30)	999	14	25	

Nivolumab, dose reduction (n=18, 16, 30)	0	0	0	
Nivolumab, dose interruption (n=18, 16, 30)	12	10	15	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity of EGF816 and INC280

End point title	Dose intensity of EGF816 and INC280

End point description:

Dose intensity (mg/day) of EGF816 and INC280 was calculated as actual cumulative dose in milligrams divided by duration of exposure in days.
Due to EudraCT system limitations, data fields cannot be blank if the number of subjects analyzed in the corresponding column is greater than 0. Therefore, not applicable values (eg. dose intensity of EGF816 in Groups 2A and 2B) are indicated as '999'.

End point type	Secondary

End point timeframe:

From first dose of study treatment until last dose of study treatment, up to maximum 4.7 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: mg/day				
median (full range (min-max))				
EGF816 (n=18, 0, 0)	141.5 (81 to 150)	999 (999 to 999)	999 (999 to 999)	
INC280 (n=0, 16, 30)	999 (999 to 999)	609.4 (254 to 800)	636.7 (240 to 800)	

Statistical analyses

No statistical analyses for this end point

Secondary: Dose intensity of nivolumab

End point title	Dose intensity of nivolumab

End point description:

Dose intensity (mg/kg biweekly) of nivolumab was calculated as actual cumulative dose in mg/kg divided by duration of exposure in days and then multiplied by 14 days (2 weeks).

End point type	Secondary

End point timeframe:

From first dose of study treatment until last dose of study treatment, up to maximum 4.7 years

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	16	30	
Units: mg/kg/2-week				
median (full range (min-max))	3.0 (3 to 3)	3.0 (3 to 3)	3.0 (3 to 3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) of EGF816

End point title	Maximum observed plasma concentration (Cmax) of EGF816[2]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 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, 1, 3, 6 and 8 hours post EGF816 dose on Cycle 1 Day 15. The duration of one cycle was 28 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 for Group 1.

End point values	Nivolumab and EGF816			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	935 (± 40.8)			

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 EGF816

End point title	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of EGF816[3]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 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, 1, 3, 6 and 8 hours post EGF816 dose on Cycle 1 Day 15. The duration of one cycle was 28 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 for Group 1.

End point values	Nivolumab and EGF816			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	5560 (± 42.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration (Tmax) of EGF816

End point title	Time to reach maximum plasma concentration (Tmax) of EGF816[4]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) plasma concentration following a dose.

End point type	Secondary

End point timeframe:

pre-dose, 1, 3, 6 and 8 hours post EGF816 dose on Cycle 1 Day 15. 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: This endpoint is only applicable for Group 1.

End point values	Nivolumab and EGF816			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: hours				
median (full range (min-max))	3.00 (1.00 to 6.00)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) of INC280

End point title	Maximum observed plasma concentration (Cmax) of INC280[5]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 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, 1, 3, 6 and 8 hours post INC280 dose on Cycle 1 Day 15. 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: This endpoint is only applicable for Groups 2A and 2B.

End point values	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	0[6]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	6190 (± 83.9)	()		

Notes:

[6] - In the Group 2B, no patients provided an INC280 evaluable PK profile.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum observed plasma concentration (Cmin) of EGF816

End point title	Minimum observed plasma concentration (Cmin) of EGF816[7]

End point description:

Pharmacokinetic (PK) parameters were calculated based on EGF816 plasma concentrations by using non-compartmental methods. Cmin is defined as the minimum observed plasma concentration following a dose.

End point type	Secondary

End point timeframe:

pre-dose, 1, 3, 6 and 8 hours post EGF816 dose on Cycle 1 Day 15. 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: This endpoint is only applicable for Group 1.

End point values	Nivolumab and EGF816			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	398 (± 48.8)			

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 INC280

End point title	Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of INC280[8]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 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, 1, 3, 6 and 8 hours post INC280 dose on Cycle 1 Day 15. 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: This endpoint is only applicable for Groups 2A and 2B.

End point values	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	0[9]		
Units: hr*ng/mL				
geometric mean (geometric coefficient of variation)	19300 (± 97.5)	()		

Notes:

[9] - In the Group 2B, no patients provided an INC280 evaluable PK profile.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum plasma concentration (Tmax) of INC280

End point title	Time to reach maximum plasma concentration (Tmax) of INC280[10]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 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, 1, 3, 6 and 8 hours post INC280 dose on Cycle 1 Day 15. The duration of one cycle was 28 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: This endpoint is only applicable for Groups 2A and 2B.

End point values	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	0[11]		
Units: hours				
median (full range (min-max))	0.983 (0.667 to 1.08)	(to)		

Notes:

[11] - In the Group 2B, no patients provided an INC280 evaluable PK profile.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum observed plasma concentration (Cmin) of INC280

End point title	Minimum observed plasma concentration (Cmin) of INC280[12]

End point description:

Pharmacokinetic (PK) parameters were calculated based on INC280 plasma concentrations by using non-compartmental methods. Cmin is defined as the minimum observed plasma concentration following a dose.

End point type	Secondary

End point timeframe:

pre-dose, 1, 3, 6 and 8 hours post INC280 dose on Cycle 1 Day 15. 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: This endpoint is only applicable for Groups 2A and 2B.

End point values	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	0[13]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	428 (± 105)	()		

Notes:

[13] - In the Group 2B, no patients provided an INC280 evaluable PK profile.

Statistical analyses

No statistical analyses for this end point

Secondary: Pre-dose serum concentration of nivolumab

End point title	Pre-dose serum concentration of nivolumab

End point description:

Nivolumab serum concentrations were assessed in samples taken at pre-dose. Pre-dose samples were collected before the next dose administration.
Due to EudraCT system limitations, data fields cannot be blank if the number of subjects analyzed in the corresponding column is greater than 0. Therefore, not applicable values (eg. nivolumab concentration when n=0) are indicated as '999'. Additionally, in Cycle 1 Day 1, '0' indicates that the values were below the lower limit of quantification (<0.20 ng/mL).

End point type	Secondary

End point timeframe:

pre-dose on Cycle 1 Day 1 (groups 2A and 2B only) and pre-dose on Cycle 1 Day 15 and Cycle 2 Day 1 (all groups). The duration of one cycle was 28 days.

End point values	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	15	29	
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1 (n=0, 7, 16)	999 (± 999)	0 (± 0)	0 (± 0)	
Cycle 1 Day 15 (n=17, 13, 23)	17.2 (± 28.6)	18.6 (± 45.3)	19.5 (± 35.6)	
Cycle 2 Day 1 (n=15, 10, 22)	21.3 (± 54.6)	35.7 (± 26.6)	26.4 (± 77.1)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study medication up to 100 days after last dose of study medication, with a maximum duration of 5 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	23.1

Reporting groups

Reporting group title	Nivolumab and EGF816

Reporting group description:

Group 1: EGF816 150 mg QD + Nivolumab 3 mg/kg Q2W

Reporting group title	Nivolumab and INC280, high cMet

Reporting group description:

Group 2A: INC280 400 mg BID, High cMET + Nivolumab 3 mg/kg Q2W

Reporting group title	Nivolumab and INC280, low cMet

Reporting group description:

Group 2B: INC280 400 mg BID, Low cMet + Nivolumab 3 mg/kg Q2W

Reporting group title	Nivolumab and INC280, high+low cMet

Reporting group description:

Group 2A+2B (low and high cMet): INC280 400 mg BID + Nivolumab 3 mg/kg Q2W

Serious adverse events	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 18 (77.78%)	8 / 16 (50.00%)	18 / 30 (60.00%)
number of deaths (all causes)	8	4	10
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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			
Giant cell arteritis			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Fatigue			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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
General physical health deterioration			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pyrexia			
subjects affected / exposed	4 / 18 (22.22%)	1 / 16 (6.25%)	3 / 30 (10.00%)
occurrences causally related to treatment / all	2 / 4	1 / 1	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contrast media allergy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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

Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Interstitial lung disease			
subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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
Pulmonary oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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 failure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Tachypnoea			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			

subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Dysaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Dysarthria			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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
Headache			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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
Hemiparesis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			

subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lethargy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
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			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (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
Abdominal pain upper			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	2 / 30 (6.67%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash macular			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stevens-Johnson syndrome			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myositis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Bacterial infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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
Hyperamylasaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (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

Serious adverse events	Nivolumab and INC280, high+low cMet		
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 46 (56.52%)		
number of deaths (all causes)	14		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Condition aggravated			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gait disturbance			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pyrexia			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Contrast media allergy			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 2		

Interstitial lung disease				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumothorax				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary oedema				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachypnoea				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				

Confusional state			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Angina pectoris			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sinus tachycardia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Ataxia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cerebral ischaemia			

subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cerebrovascular accident				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysaesthesia				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dysarthria				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hemiparesis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ischaemic stroke				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Lethargy				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Somnolence				

subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Disseminated intravascular coagulation				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Eye disorders				
Diplopia				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Abdominal pain				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal pain upper				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Colitis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Diarrhoea				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrooesophageal reflux disease				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancreatitis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 46 (6.52%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic function abnormal				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Pruritus				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Rash macular				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Rash maculo-papular			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 46 (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	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Back pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myositis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal wall abscess			

subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bacterial infection				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bronchitis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Pneumonia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Diabetic ketoacidosis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hyperamylasaemia				

subjects affected / exposed	0 / 46 (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	Nivolumab and EGF816	Nivolumab and INC280, high cMet	Nivolumab and INC280, low cMet
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 18 (100.00%)	16 / 16 (100.00%)	29 / 30 (96.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Benign neoplasm			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Infected naevus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Metastases to meninges			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hypertension			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Peripheral ischaemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	7 / 18 (38.89%)	6 / 16 (37.50%)	10 / 30 (33.33%)
occurrences (all)	11	10	15
Chest discomfort			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Catheter site swelling			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Face oedema			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	3 / 18 (16.67%)	5 / 16 (31.25%)	4 / 30 (13.33%)
occurrences (all)	3	6	4
Gait disturbance			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Influenza like illness			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	4
Non-cardiac chest pain			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Oedema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Oedema peripheral			
subjects affected / exposed	1 / 18 (5.56%)	8 / 16 (50.00%)	8 / 30 (26.67%)
occurrences (all)	1	14	16
Pain			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	1 / 18 (5.56%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	2	2	0
Pyrexia			
subjects affected / exposed	10 / 18 (55.56%)	6 / 16 (37.50%)	3 / 30 (10.00%)
occurrences (all)	18	6	6
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Cystocele			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Genital ulceration			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pelvic pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Perineal fistula			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal pruritus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal discomfort			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 18 (22.22%)	3 / 16 (18.75%)	4 / 30 (13.33%)
occurrences (all)	7	3	4
Dysphonia			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dyspnoea			
subjects affected / exposed	4 / 18 (22.22%)	2 / 16 (12.50%)	7 / 30 (23.33%)
occurrences (all)	7	2	10
Dyspnoea exertional			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Haemoptysis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Epistaxis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nasal dryness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Pleural effusion			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	2 / 30 (6.67%)
occurrences (all)	0	2	2
Pneumonitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Insomnia			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	1 / 30 (3.33%)
occurrences (all)	2	2	1
Suicidal ideation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

Product issues			
Device occlusion			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Thrombosis in device			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	5 / 30 (16.67%)
occurrences (all)	0	2	7
Amylase increased			
subjects affected / exposed	6 / 18 (33.33%)	9 / 16 (56.25%)	6 / 30 (20.00%)
occurrences (all)	11	20	14
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	5 / 30 (16.67%)
occurrences (all)	0	1	9
Bilirubin conjugated increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Blood albumin decreased			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	6 / 30 (20.00%)
occurrences (all)	0	0	8
Blood creatinine increased			
subjects affected / exposed	0 / 18 (0.00%)	6 / 16 (37.50%)	9 / 30 (30.00%)
occurrences (all)	0	12	13
Blood glucose increased			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Blood triglycerides increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 18 (0.00%)	3 / 16 (18.75%)	0 / 30 (0.00%)
occurrences (all)	0	5	0
C-reactive protein increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Lipase increased			
subjects affected / exposed	4 / 18 (22.22%)	7 / 16 (43.75%)	6 / 30 (20.00%)
occurrences (all)	5	14	6
Lymphocyte count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Platelet count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Transaminases increased			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	2 / 30 (6.67%)
occurrences (all)	0	1	2
Weight decreased			
subjects affected / exposed	3 / 18 (16.67%)	2 / 16 (12.50%)	2 / 30 (6.67%)
occurrences (all)	3	2	2
White blood cell count decreased			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Limb injury			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Muscle injury			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Procedural pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Tachycardia			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Cerebral ischaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Dysaesthesia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Dizziness			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	3 / 30 (10.00%)
occurrences (all)	3	1	5
Dysgeusia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Essential tremor			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	4 / 18 (22.22%)	5 / 16 (31.25%)	0 / 30 (0.00%)
occurrences (all)	5	6	0
Hydrocephalus			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Lethargy			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Nervous system disorder			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Paraesthesia			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	3	1	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Presyncope			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Seizure			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Speech disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Tremor			

subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Spinal cord compression			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 18 (22.22%)	4 / 16 (25.00%)	7 / 30 (23.33%)
occurrences (all)	4	5	11
Leukopenia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Neutropenia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	2 / 30 (6.67%)
occurrences (all)	1	1	2
Thrombocytopenia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	2
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Tinnitus			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Uveitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vision blurred			
subjects affected / exposed	1 / 18 (5.56%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	3	0	2
Abdominal pain upper			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	3 / 30 (10.00%)
occurrences (all)	2	3	3
Anal haemorrhage			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Ascites			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	3 / 18 (16.67%)	5 / 16 (31.25%)	2 / 30 (6.67%)
occurrences (all)	5	9	2
Diarrhoea			
subjects affected / exposed	9 / 18 (50.00%)	5 / 16 (31.25%)	6 / 30 (20.00%)
occurrences (all)	17	10	18
Dry mouth			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dysphagia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Faeces discoloured			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	1 / 30 (3.33%)
occurrences (all)	0	2	1
Oesophageal pain			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0

Nausea			
subjects affected / exposed	5 / 18 (27.78%)	13 / 16 (81.25%)	12 / 30 (40.00%)
occurrences (all)	7	20	22
Stomatitis			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	2 / 30 (6.67%)
occurrences (all)	6	1	2
Toothache			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	5 / 18 (27.78%)	9 / 16 (56.25%)	7 / 30 (23.33%)
occurrences (all)	5	11	9
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hepatic pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Alopecia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dermatitis acneiform			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dry skin			
subjects affected / exposed	4 / 18 (22.22%)	2 / 16 (12.50%)	2 / 30 (6.67%)
occurrences (all)	4	2	2
Dermatitis exfoliative			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Ecchymosis			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Erythema			
subjects affected / exposed	2 / 18 (11.11%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	2	1	0
Eczema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyperhidrosis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Lichenoid keratosis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Nail dystrophy			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Onychoclasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pain of skin			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Palmar erythema			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	6 / 18 (33.33%)	2 / 16 (12.50%)	4 / 30 (13.33%)
occurrences (all)	14	3	4
Rash			
subjects affected / exposed	12 / 18 (66.67%)	3 / 16 (18.75%)	4 / 30 (13.33%)
occurrences (all)	20	4	5
Rash erythematous			

subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Rash maculo-papular			
subjects affected / exposed	3 / 18 (16.67%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	15	1	0
Rash pruritic			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Skin exfoliation			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Skin fissures			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Urticaria			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Pollakiuria			
subjects affected / exposed	3 / 18 (16.67%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	3	0	0
Renal impairment			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Renal failure			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Urinary incontinence			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Hypophysitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hypothyroidism			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	1	1	1
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 18 (0.00%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	3
Arthralgia			
subjects affected / exposed	4 / 18 (22.22%)	5 / 16 (31.25%)	4 / 30 (13.33%)
occurrences (all)	4	8	7
Back pain			
subjects affected / exposed	1 / 18 (5.56%)	3 / 16 (18.75%)	3 / 30 (10.00%)
occurrences (all)	2	3	4
Bone pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	2 / 30 (6.67%)
occurrences (all)	1	1	3
Muscle contracture			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	2 / 18 (11.11%)	2 / 16 (12.50%)	1 / 30 (3.33%)
occurrences (all)	2	3	1
Muscular weakness			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			

subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Musculoskeletal stiffness			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 18 (0.00%)	3 / 16 (18.75%)	3 / 30 (10.00%)
occurrences (all)	0	3	3
Pain in extremity			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	3 / 30 (10.00%)
occurrences (all)	2	1	3
Spinal pain			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Candida infection			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Cystitis bacterial			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Dermatitis infected			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0

Herpes zoster			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	0	1	1
Herpes simplex			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	2	0	0
Lower respiratory tract infection			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Nasopharyngitis			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	1	1	0
Oesophageal candidiasis			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Oral candidiasis			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	2	0	1
Pulpitis dental			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Respiratory tract infection viral			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	0	2	0

Upper respiratory tract infection			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	1 / 30 (3.33%)
occurrences (all)	4	0	1
Urinary tract infection			
subjects affected / exposed	1 / 18 (5.56%)	2 / 16 (12.50%)	1 / 30 (3.33%)
occurrences (all)	1	2	1
Metabolism and nutrition disorders			
Cell death			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Decreased appetite			
subjects affected / exposed	6 / 18 (33.33%)	2 / 16 (12.50%)	9 / 30 (30.00%)
occurrences (all)	6	3	9
Hypercalcaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 18 (0.00%)	1 / 16 (6.25%)	0 / 30 (0.00%)
occurrences (all)	0	2	0
Hyperuricaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	4	0	3
Hypoalbuminaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	9 / 30 (30.00%)
occurrences (all)	0	3	10
Hypocalcaemia			
subjects affected / exposed	2 / 18 (11.11%)	0 / 16 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	3
Hypokalaemia			
subjects affected / exposed	3 / 18 (16.67%)	2 / 16 (12.50%)	7 / 30 (23.33%)
occurrences (all)	4	2	16
Hypochloraemia			
subjects affected / exposed	1 / 18 (5.56%)	0 / 16 (0.00%)	0 / 30 (0.00%)
occurrences (all)	1	0	0
Hypomagnesaemia			

subjects affected / exposed	1 / 18 (5.56%)	2 / 16 (12.50%)	3 / 30 (10.00%)
occurrences (all)	1	2	3
Hyponatraemia			
subjects affected / exposed	1 / 18 (5.56%)	1 / 16 (6.25%)	1 / 30 (3.33%)
occurrences (all)	1	1	2
Hypophosphataemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	0	3	0
Hypoproteinaemia			
subjects affected / exposed	0 / 18 (0.00%)	2 / 16 (12.50%)	0 / 30 (0.00%)
occurrences (all)	0	3	0

Non-serious adverse events	Nivolumab and INC280, high+low cMet		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 46 (97.83%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Benign neoplasm			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Infected naevus			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Metastases to meninges			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Giant cell arteritis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	2		
Haematoma			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Hypertension			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Peripheral ischaemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	16 / 46 (34.78%)		
occurrences (all)	25		
Chest discomfort			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Catheter site swelling			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	10		
Gait disturbance			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Influenza like illness			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	4		
Non-cardiac chest pain			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Oedema			

subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Oedema peripheral			
subjects affected / exposed	16 / 46 (34.78%)		
occurrences (all)	30		
Pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	12		
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Cystocele			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Genital ulceration			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Pelvic pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Perineal fistula			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Vulvovaginal pruritus			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Vulvovaginal discomfort			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	7		
Dysphonia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Dyspnoea			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	12		
Dyspnoea exertional			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Haemoptysis			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Epistaxis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Nasal dryness			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Pleural effusion			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
Pneumonitis			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Sleep apnoea syndrome			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Psychiatric disorders			

Anxiety			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Insomnia			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Suicidal ideation			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Product issues			
Device occlusion			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Thrombosis in device			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	9		
Amylase increased			
subjects affected / exposed	15 / 46 (32.61%)		
occurrences (all)	34		
Aspartate aminotransferase increased			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	10		
Bilirubin conjugated increased			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Blood albumin decreased			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Blood bilirubin increased			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Blood alkaline phosphatase increased			

subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Blood creatine phosphokinase increased				
subjects affected / exposed	6 / 46 (13.04%)			
occurrences (all)	8			
Blood creatinine increased				
subjects affected / exposed	15 / 46 (32.61%)			
occurrences (all)	25			
Blood glucose increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	3			
Blood triglycerides increased				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Gamma-glutamyltransferase increased				
subjects affected / exposed	3 / 46 (6.52%)			
occurrences (all)	5			
C-reactive protein increased				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Lipase increased				
subjects affected / exposed	13 / 46 (28.26%)			
occurrences (all)	20			
Lymphocyte count decreased				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	3			
Platelet count decreased				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	3			
Transaminases increased				
subjects affected / exposed	3 / 46 (6.52%)			
occurrences (all)	3			
Weight decreased				

subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
White blood cell count decreased			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Limb injury			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Lumbar vertebral fracture			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Muscle injury			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Procedural pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Extrasystoles			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Cerebral ischaemia			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Dysaesthesia			

subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Dizziness				
subjects affected / exposed	4 / 46 (8.70%)			
occurrences (all)	6			
Dysgeusia				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Essential tremor				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Headache				
subjects affected / exposed	5 / 46 (10.87%)			
occurrences (all)	6			
Hydrocephalus				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Lethargy				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Nervous system disorder				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	2			
Paraesthesia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Peripheral sensory neuropathy				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Presyncope				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Sciatica				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Somnolence				

subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 2		
Seizure subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Speech disorder subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Tremor subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Spinal cord compression subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	11 / 46 (23.91%) 16		
Leukopenia subjects affected / exposed occurrences (all)	0 / 46 (0.00%) 0		
Neutropenia subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3		
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2		
Ear and labyrinth disorders			
Deafness subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Tinnitus subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1		
Eye disorders			

Dry eye			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Uveitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Vision blurred			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	6		
Anal haemorrhage			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Aphthous ulcer			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Ascites			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	11		
Diarrhoea			
subjects affected / exposed	11 / 46 (23.91%)		
occurrences (all)	28		
Dry mouth			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Dysphagia			

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Faeces discoloured			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Oesophageal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	25 / 46 (54.35%)		
occurrences (all)	42		
Stomatitis			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	16 / 46 (34.78%)		
occurrences (all)	20		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Hepatic pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Alopecia			

subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Dermatitis acneiform				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Dry skin				
subjects affected / exposed	4 / 46 (8.70%)			
occurrences (all)	4			
Dermatitis exfoliative				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Ecchymosis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Erythema				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Eczema				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Hyperhidrosis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Nail disorder				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Lichenoid keratosis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Nail dystrophy				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Onychoclasis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Pain of skin				

subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Palmar erythema			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	7		
Rash			
subjects affected / exposed	7 / 46 (15.22%)		
occurrences (all)	9		
Rash erythematous			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Rash maculo-papular			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Rash pruritic			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Skin exfoliation			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Skin fissures			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Urticaria			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Pollakiuria			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		

Renal impairment			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Renal failure			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Urinary incontinence			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Hypophysitis			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Hypothyroidism			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Arthralgia			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	15		
Back pain			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	7		
Bone pain			
subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	4		
Muscle contracture			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Muscle spasms			

subjects affected / exposed	3 / 46 (6.52%)		
occurrences (all)	4		
Muscular weakness			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Musculoskeletal chest pain			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Musculoskeletal stiffness			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	6 / 46 (13.04%)		
occurrences (all)	6		
Pain in extremity			
subjects affected / exposed	4 / 46 (8.70%)		
occurrences (all)	4		
Spinal pain			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Candida infection			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		
Cellulitis			
subjects affected / exposed	1 / 46 (2.17%)		
occurrences (all)	1		

Conjunctivitis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Cystitis bacterial				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Dermatitis infected				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Herpes zoster				
subjects affected / exposed	2 / 46 (4.35%)			
occurrences (all)	2			
Herpes simplex				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	2			
Nasopharyngitis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Oesophageal candidiasis				
subjects affected / exposed	0 / 46 (0.00%)			
occurrences (all)	0			
Oral candidiasis				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Paronychia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			
Pneumonia				
subjects affected / exposed	1 / 46 (2.17%)			
occurrences (all)	1			

Pulpitis dental subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1			
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1			
Sinusitis subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 2			
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1			
Urinary tract infection subjects affected / exposed occurrences (all)	3 / 46 (6.52%) 3			
Metabolism and nutrition disorders Cell death subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1			
Decreased appetite subjects affected / exposed occurrences (all)	11 / 46 (23.91%) 12			
Hypercalcaemia subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 1			
Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 46 (2.17%) 2			
Hyperuricaemia subjects affected / exposed occurrences (all)	2 / 46 (4.35%) 3			
Hypoalbuminaemia subjects affected / exposed occurrences (all)	11 / 46 (23.91%) 13			
Hypocalcaemia				

subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	9 / 46 (19.57%)		
occurrences (all)	18		
Hypochloraemia			
subjects affected / exposed	0 / 46 (0.00%)		
occurrences (all)	0		
Hypomagnesaemia			
subjects affected / exposed	5 / 46 (10.87%)		
occurrences (all)	5		
Hyponatraemia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Hypophosphataemia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		
Hypoproteinaemia			
subjects affected / exposed	2 / 46 (4.35%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2015	Provided additional guidelines for hepatic AE management for EGF816 and INC280; update contraception guidance following nivolumab treatment and prohibited concomitant medications and updated exclusion criteria; and implemented HIV testing at screening for patients in Germany.
16 October 2015	Clarified the definition of toxicity as independent of study drug; modified guideline for hepatotoxicity for cases meeting Hy's law criteria; and provided guidelines for dose modification or discontinuation for EGF816-related interstitial lung disease.
15 February 2016	Implemented changes that were introduced with 2 Urgent Safety Measures, including enrollment halt into Group 1 (EGF816 + nivolumab), nivolumab permanent discontinuation for all ongoing patients in Group 1, and dose escalation guidelines update for EGF816 and INC280 and skin-toxicity management guidelines.
19 May 2016	Expanded the eligibility of Group 2 patients (INC280 plus nivolumab) to include patients with NSCLC without high cMet levels (i.e., any level of cMet was permitted); allowed the exploration of the immunomodulatory activity of INC280 in patients with NSCLC by introducing new biomarker tests; added the provision for study treatment to be temporarily interrupted for palliative treatment of symptomatic CNS or bone lesions with non-invasive therapy; decreased the frequency of radiological efficacy assessments after Cycle 24; provided additional guidance for management to liver toxicities; and updated eligibility criteria and dose modification guidelines for amylase and lipase, and permitted and prohibited concomitant medications for INC280.
13 April 2017	Introduced the INC280 dose strength of 150 mg; made updates based on the new edition of INC280 investigator brochure; and updated exclusion criteria and requirement for pregnancy tests.
29 January 2018	Added recommendations for management of myotoxicity of nivolumab and pneumonitis/intestinal lung disease as a potential risk of INC280; updated administration instruction of INC280 and prohibited and permitted concomitant medications for Group 2; and clarified recommendations for discontinuing patients from study treatment versus from only one study drug in the setting of specific AEs.
21 June 2018	Updated guidelines for EGF816/INC280 dose modification/discontinuation in the context of non-infectious pneumonitis/interstitial lung disease.
12 March 2020	Introduced the timing for primary CSR; modified the duration of disease progression follow-up; streamlined study assessment to reduce the assessment burden of patients; refined the definition of end of study; updated the dose modification algorithm and AE management; and implemented a maximum duration of 2 years for nivolumab treatment

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: