



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 (\pm 40.8) | | | |

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 ^[3] |
|-----------------|--|

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:

[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: hours | | | | |
| median (full range (min-max)) | 3.00 (1.00 to 6.00) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of 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 ^[4] |
|-----------------|---|

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:

[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: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 5560 (\pm 42.8) | | | |

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 ^[5] |
|-----------------|---|

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:

[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 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 (\pm 48.8) | | | |

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 ^[6] |
|-----------------|---|

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:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: 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 ^[7] | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 6190 (\pm 83.9) | () | | |

Notes:

[7] - 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 ^[8] |
|-----------------|--|

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:

[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: hours | | | | |
| median (full range (min-max)) | 0.983 (0.667 to 1.08) | (to) | | |

Notes:

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

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 ^[10] |
|-----------------|--|

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:

[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: hr*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | 19300 (± 97.5) | () | | |

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

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|--|-----------------|-----------------|-----------------|
| 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 | | | |

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|-------------------------------|-----------------|-----------------|----------------|
| 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 | | | |

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

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|-----------------------------|-----------------|----------------|----------------|
| 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 | | | |

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|-----------------------------|----------------|-----------------|-----------------|
| 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 occurrences (all) | 2 / 18 (11.11%) 4 | 0 / 16 (0.00%) 0 | 1 / 30 (3.33%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 2 / 16 (12.50%) 2 | 1 / 30 (3.33%) 1 |
| Metabolism and nutrition disorders | | | |
| Cell death subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 30 (0.00%) 0 |
| Decreased appetite subjects affected / exposed occurrences (all) | 6 / 18 (33.33%) 6 | 2 / 16 (12.50%) 3 | 9 / 30 (30.00%) 9 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 30 (0.00%) 0 |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 1 / 16 (6.25%) 2 | 0 / 30 (0.00%) 0 |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 4 | 0 / 16 (0.00%) 0 | 2 / 30 (6.67%) 3 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 18 (0.00%) 0 | 2 / 16 (12.50%) 3 | 9 / 30 (30.00%) 10 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 2 / 18 (11.11%) 2 | 0 / 16 (0.00%) 0 | 2 / 30 (6.67%) 3 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 3 / 18 (16.67%) 4 | 2 / 16 (12.50%) 2 | 7 / 30 (23.33%) 16 |
| Hypochloraemia subjects affected / exposed occurrences (all) | 1 / 18 (5.56%) 1 | 0 / 16 (0.00%) 0 | 0 / 30 (0.00%) 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 occurrences (all) | 2 / 46 (4.35%) 2 | | |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 3 | | |
| Suicidal ideation subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Product issues Device occlusion subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Thrombosis in device subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 7 / 46 (15.22%) 9 | | |
| Amylase increased subjects affected / exposed occurrences (all) | 15 / 46 (32.61%) 34 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 6 / 46 (13.04%) 10 | | |
| Bilirubin conjugated increased subjects affected / exposed occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 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 | 1 / 46 (2.17%) | | |
| occurrences (all) | 2 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Speech disorder | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 11 / 46 (23.91%) | | |
| occurrences (all) | 16 | | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | | |
| occurrences (all) | 3 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | | |
| occurrences (all) | 2 | | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 1 | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | | |
| occurrences (all) | 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 | | |
| Onychoclasia | | | |
| 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 occurrences (all) | 1 / 46 (2.17%) 1 | | |
| Renal failure subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 3 | | |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Endocrine disorders Hyperthyroidism subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | | |
| Hypophysitis subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 0 | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 2 | | |
| Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all) | 2 / 46 (4.35%) 3 | | |
| Arthralgia subjects affected / exposed occurrences (all) | 9 / 46 (19.57%) 15 | | |
| Back pain subjects affected / exposed occurrences (all) | 6 / 46 (13.04%) 7 | | |
| Bone pain subjects affected / exposed occurrences (all) | 3 / 46 (6.52%) 4 | | |
| Muscle contracture subjects affected / exposed occurrences (all) | 0 / 46 (0.00%) 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 | | |

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