



Clinical trial results:

A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Nivolumab or Nivolumab plus Cisplatin, in Combination with Radiotherapy in Participants with Cisplatin Ineligible and Cisplatin Eligible Locally Advanced Squamous Cell Carcinoma of the Head and Neck (SCCHN).

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2017-002676-87 |
| Trial protocol | ES GB PL IT |
| Global end of trial date | 14 October 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 29 October 2020 |
| First version publication date | 29 October 2020 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | CA209-9TM |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 14 October 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 October 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Following implementation of Revised Protocol 03, only safety assessments were conducted.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 December 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Japan: 25 |
| Country: Number of subjects enrolled | Poland: 2 |
| Country: Number of subjects enrolled | Korea, Republic of: 8 |
| Country: Number of subjects enrolled | Russian Federation: 4 |
| Country: Number of subjects enrolled | Spain: 17 |
| Country: Number of subjects enrolled | Taiwan: 6 |
| Country: Number of subjects enrolled | Turkey: 1 |
| Country: Number of subjects enrolled | United States: 36 |
| Worldwide total number of subjects | 111 |
| EEA total number of subjects | 31 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |

| | |
|--|----|
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 64 |
| From 65 to 84 years | 45 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

74 Randomized and 73 Treated

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Randomized |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|------------------|
| Arm title | Arm A (Cohort 1) |
|------------------|------------------|

Arm description:

Nivolumab + Radiotherapy

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravascular use |

Dosage and administration details:

10 mg/mL – 100 mg fill volume, 240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses

| | |
|--|---|
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week

| | |
|------------------|------------------|
| Arm title | Arm B (Cohort 1) |
|------------------|------------------|

Arm description:

Cetuximab + Radiotherapy

| | |
|--|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week

| | |
|---|---|
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 5 mg/mL - 500 mg fill volume, 400 mg/m ² IV x 1 dose then 250 mg/m ² IV x 7 doses | |
| Arm title | Arm C (Cohort 2) |
| Arm description: | |
| Cisplatin + Nivolumab + Radiotherapy | |
| Arm type | Active comparator |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravascular use |
| Dosage and administration details: | |
| 10 mg/mL – 100 mg fill volume, 240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses | |
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |
| Dosage and administration details: | |
| IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week | |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravascular use |
| Dosage and administration details: | |
| 1 mg/mL – 100 mg fill volume, 100 mg/m ² IV x 3 doses | |
| Arm title | Arm D (Cohort 2) |
| Arm description: | |
| Cisplatin + Radiotherapy | |
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravascular use |
| Dosage and administration details: | |
| 1 mg/mL – 100 mg fill volume, 100 mg/m ² IV x 3 doses | |
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |
| Dosage and administration details: | |
| IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 | |

| Number of subjects in period 1^[1] | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) |
|---|------------------|------------------|------------------|
| Started | 12 | 10 | 27 |
| Completed | 12 | 10 | 27 |

| Number of subjects in period 1^[1] | Arm D (Cohort 2) |
|---|------------------|
| Started | 25 |
| Completed | 25 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 74 Randomized and 73 Treated

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Arm A (Cohort 1) |

Arm description:

Nivolumab + Radiotherapy

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravascular use |

Dosage and administration details:

10 mg/mL – 100 mg fill volume, 240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses

| | |
|--|---|
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |

| | |
|--------------------------|-----------------------|
| Routes of administration | Intravenous bolus use |
|--------------------------|-----------------------|

Dosage and administration details:

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week

| | |
|------------------|------------------|
| Arm title | Arm B (Cohort 1) |
|------------------|------------------|

Arm description:

Cetuximab + Radiotherapy

| | |
|--|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

5 mg/mL - 500 mg fill volume, 400 mg/m² IV x 1 dose then 250 mg/m² IV x 7 doses

| | |
|--|---|
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week

| | |
|------------------|------------------|
| Arm title | Arm C (Cohort 2) |
|------------------|------------------|

Arm description:

Cisplatin + Nivolumab + Radiotherapy

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravascular use |

Dosage and administration details:

1 mg/mL – 100 mg fill volume, 100 mg/m² IV x 3 doses

| | |
|--|-------------------|
| Investigational medicinal product name | Nivolumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravascular use |

Dosage and administration details:

10 mg/mL – 100 mg fill volume, 240 mg IV x 1 dose then 360 mg IV x 3 doses then 480 mg IV x 6 doses

| | |
|--|---|
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |

Dosage and administration details:

IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week

| | |
|---|---|
| Arm title | Arm D (Cohort 2) |
| Arm description: Cisplatin + Radiotherapy | |
| Arm type | Active comparator |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravascular use |
| Dosage and administration details: 1 mg/mL – 100 mg fill volume, 100 mg/m ² IV x 3 doses | |
| Investigational medicinal product name | Radiotherapy |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Radiopharmaceutical precursor, solution |
| Routes of administration | Intravenous bolus use |
| Dosage and administration details: IMRT will be given in 35 fractions over 7 weeks beginning at Day 1 Cycle 3 for Cohort 1 or Day 1 Cycle 2 for Cohort 2, 5 fractions per week | |

| Number of subjects in period 2^[2] | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) |
|---|------------------|------------------|------------------|
| Started | 12 | 10 | 27 |
| Completed | 0 | 0 | 0 |
| Not completed | 12 | 10 | 27 |
| Adverse event, serious fatal | - | - | 1 |
| completed | 6 | - | 18 |
| Adverse event unrelated to Study Drug | 2 | 1 | 1 |
| Other Reason | 2 | - | 2 |
| Study Drug Toxicity | 1 | - | 1 |
| admin reason by sponsor | - | 7 | - |
| Disease Progression | - | 2 | - |
| participant request to discontinue | - | - | 4 |
| participant withdrew consent | 1 | - | - |

| Number of subjects in period 2^[2] | Arm D (Cohort 2) |
|---|------------------|
| Started | 24 |
| Completed | 0 |
| Not completed | 24 |
| Adverse event, serious fatal | - |
| completed | 1 |
| Adverse event unrelated to Study Drug | 1 |

| | |
|------------------------------------|----|
| Other Reason | 1 |
| Study Drug Toxicity | 1 |
| admin reason by sponsor | 19 |
| Disease Progression | 1 |
| participant request to discontinue | - |
| participant withdrew consent | - |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 74 Randomized and 73 Treated

Baseline characteristics

Reporting groups

| | |
|--------------------------------------|------------------|
| Reporting group title | Arm A (Cohort 1) |
| Reporting group description: | |
| Nivolumab + Radiotherapy | |
| Reporting group title | Arm B (Cohort 1) |
| Reporting group description: | |
| Cetuximab + Radiotherapy | |
| Reporting group title | Arm C (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Nivolumab + Radiotherapy | |
| Reporting group title | Arm D (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Radiotherapy | |

| Reporting group values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) |
|---|------------------|------------------|------------------|
| Number of subjects | 12 | 10 | 27 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 2 | 1 | 24 |
| From 65-84 years | 8 | 9 | 3 |
| 85 years and over | 2 | 0 | 0 |
| Age Continuous | | | |
| Units: Years | | | |
| arithmetic mean | 74.5 | 74.7 | 59.0 |
| standard deviation | ± 8.3 | ± 6.5 | ± 6.6 |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 2 | 2 | 3 |
| Male | 10 | 8 | 24 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 3 | 4 | 6 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 2 |
| White | 8 | 5 | 16 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 1 | 1 | 3 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 0 |
| Not Hispanic or Latino | 5 | 4 | 9 |
| Unknown or Not Reported | 7 | 6 | 18 |

| Reporting group values | Arm D (Cohort 2) | Total | |
|------------------------|------------------|-------|--|
| Number of subjects | 25 | 74 | |

| | | | |
|---|-------|----|--|
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 19 | 46 | |
| From 65-84 years | 6 | 26 | |
| 85 years and over | 0 | 2 | |
| Age Continuous Units: Years | | | |
| arithmetic mean | 60.8 | | |
| standard deviation | ± 7.0 | - | |
| Sex: Female, Male Units: participants | | | |
| Female | 2 | 9 | |
| Male | 23 | 65 | |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 15 | 28 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 2 | |
| White | 7 | 36 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 3 | 8 | |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | |
| Not Hispanic or Latino | 2 | 20 | |
| Unknown or Not Reported | 23 | 54 | |

End points

End points reporting groups

| | |
|--------------------------------------|------------------|
| Reporting group title | Arm A (Cohort 1) |
| Reporting group description: | |
| Nivolumab + Radiotherapy | |
| Reporting group title | Arm B (Cohort 1) |
| Reporting group description: | |
| Cetuximab + Radiotherapy | |
| Reporting group title | Arm C (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Nivolumab + Radiotherapy | |
| Reporting group title | Arm D (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Radiotherapy | |
| Reporting group title | Arm A (Cohort 1) |
| Reporting group description: | |
| Nivolumab + Radiotherapy | |
| Reporting group title | Arm B (Cohort 1) |
| Reporting group description: | |
| Cetuximab + Radiotherapy | |
| Reporting group title | Arm C (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Nivolumab + Radiotherapy | |
| Reporting group title | Arm D (Cohort 2) |
| Reporting group description: | |
| Cisplatin + Radiotherapy | |

Primary: Number of Participants with an Adverse Event (AE)

| | |
|--|--|
| End point title | Number of Participants with an Adverse Event (AE) ^[1] |
| End point description: | |
| Number of Participants with an Adverse Event | |
| End point type | Primary |
| End point timeframe: | |
| 30 days | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | 12 | 10 | 27 | 24 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with an Serious Adverse Event (SAE)

| | |
|-----------------|---|
| End point title | Number of Participants with an Serious Adverse Event (SAE) ^[2] |
|-----------------|---|

End point description:

Number of Participants with an Serious Adverse Event (SAE)

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

End point timeframe:

30 days

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | 5 | 5 | 9 | 6 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with an Adverse Event Leading to Discontinuation

| | |
|-----------------|--|
| End point title | Number of Participants with an Adverse Event Leading to Discontinuation ^[3] |
|-----------------|--|

End point description:

Number of Participants with an Adverse Event Leading to Discontinuation

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

End point timeframe:

30 days

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | 2 | 3 | 8 | 4 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with an Adverse Event Leading to dose modification

| | |
|-----------------|--|
| End point title | Number of Participants with an Adverse Event Leading to dose modification ^[4] |
|-----------------|--|

End point description:

Number of Participants with an Adverse Event Leading to dose modification Here '9999' signifies data not available as does modification did not take place

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

End point timeframe:

30 days

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | 9999 | 9999 | 9999 | 9999 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with select adverse events

| | |
|-----------------|--|
| End point title | Number of Participants with select adverse events ^[5] |
|-----------------|--|

End point description:

Number of Participants with select adverse events. Select Adverse events include: gastrointestinal, hepatic, hypersensitivity/infusion reaction, pulmonary, renal, or skin.

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

End point timeframe:

30 days

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | | | | |
| Gastrointestinal | 4 | 3 | 3 | 1 |
| Hepatic | 1 | 2 | 2 | 3 |
| Hypersensitivity/Infusion Reaction | 1 | 3 | 0 | 0 |
| Pulmonary | 0 | 0 | 0 | 0 |
| Renal | 2 | 1 | 13 | 6 |
| Skin | 7 | 7 | 12 | 11 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants with an immune-mediated adverse event (IMAE)

| | |
|-----------------|--|
| End point title | Number of Participants with an immune-mediated adverse event (IMAE) ^[6] |
|-----------------|--|

End point description:

Number of Participants with an immune-mediated adverse event (IMAE)

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

End point timeframe:

100 days

Notes:

[6] - 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 performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | | | | |
| Non-Endocrine related IMAE | 1 | 0 | 3 | 0 |
| Endocrine related IMAE | 0 | 0 | 4 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Time to onset and time to resolution of immune-related adverse events

| | |
|-----------------|--|
| End point title | Time to onset and time to resolution of immune-related adverse events ^[7] |
|-----------------|--|

End point description:

Time to onset and time to resolution of immune-related adverse events

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

End point timeframe:

100 days

Notes:

[7] - 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 performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|---|------------------|------------------|-------------------|-------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | 0 ^[10] | 0 ^[11] |
| Units: Weeks | | | | |
| arithmetic mean (confidence interval 95%) | | | | |
| Endocrine IMAE | (to) | (to) | (to) | (to) |
| Non Endocrine IMAE | (to) | (to) | (to) | (to) |

Notes:

[8] - Too few subjects, can risk subject identification

[9] - Too few subjects, can risk subject identification

[10] - Too few subjects, can risk subject identification

[11] - Too few subjects, can risk subject identification

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who experienced death

| | |
|------------------------|--|
| End point title | Number of Participants who experienced death ^[12] |
| End point description: | Number of Participants who experienced death |
| End point type | Primary |
| End point timeframe: | 100 days |

Notes:

[12] - 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 performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | 2 | 2 | 2 | 1 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with an abnormality in specific thyroid tests

| | |
|------------------------|--|
| End point title | Number of participants with an abnormality in specific thyroid tests ^[13] |
| End point description: | Number of participants with an abnormality in specific thyroid tests |
| End point type | Primary |
| End point timeframe: | 30 Days |

Notes:

[13] - 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 performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|--|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 27 | 23 |
| Units: participants | | | | |
| TSH > ULN | 5 | 1 | 7 | 1 |
| TSH > ULN WITH TSH ≤ ULN AT BASELINE | 5 | 1 | 7 | 1 |
| TSH >ULN WITH ATLEAST ONE FT3/FT4 TEST VALUE <LLN | 4 | 0 | 4 | 0 |
| TSH >ULN WITH ALL OTHER FT3/FT4 TEST VALUES ≥ LLN | 0 | 0 | 2 | 1 |
| TSH > ULN WITH FT3/FT4 TEST MISSING | 1 | 1 | 1 | 0 |
| TSH < LLN | 4 | 3 | 16 | 13 |
| TSH <LLN WITH TSH ≥ LLN AT BASELINE | 3 | 3 | 13 | 13 |
| TSH <LLN WITH ATLEAST ONE FT3/FT4 TEST VALUE > ULN | 0 | 0 | 9 | 2 |
| TSH <LLN WITH ALL OTHER FT3/FT4 TEST VALUES ≤ ULN | 4 | 1 | 6 | 7 |
| TSH < LLN WITH FT3/FT4 TEST MISSING | 0 | 2 | 1 | 4 |

Statistical analyses

No statistical analyses for this end point

Primary: Number of participants with an abnormality in specific liver tests

| | |
|-----------------|--|
| End point title | Number of participants with an abnormality in specific liver tests ^[14] |
|-----------------|--|

End point description:

Number of participants with an abnormality in specific liver tests

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

End point timeframe:

30 days

Notes:

[14] - 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 performed due to the type of endpoint

| End point values | Arm A (Cohort 1) | Arm B (Cohort 1) | Arm C (Cohort 2) | Arm D (Cohort 2) |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 12 | 10 | 27 | 24 |
| Units: participants | | | | |
| ALT OR AST > 3XULN | 2 | 0 | 0 | 0 |
| ALT OR AST> 5XULN | 1 | 0 | 0 | 0 |
| ALT OR AST> 10XULN | 0 | 0 | 0 | 0 |

| | | | | |
|---|---|---|---|---|
| ALT OR AST > 20XULN | 0 | 0 | 0 | 0 |
| TOTAL BILIRUBIN > 2XULN | 0 | 0 | 0 | 0 |
| ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>2XULN IN 1 DAY | 0 | 0 | 0 | 0 |
| ALT/AST ELEV>3XULN;TOTAL BILIRUBIN>2XULN IN 30DAYS | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from start of treatment up to 30 days after last treatment dose.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | RT + Nivo |
|-----------------------|-----------|

Reporting group description:

Subjects who were ineligible for cisplatin chemotherapy received nivolumab 240 milligrams (mg) single dose on day 1 then 3 dose of 360 mg every 3 weeks followed by 6 dose of 480 mg every 4 weeks intravenously (IV) plus placebo cetuximab 400 milligrams per square meter (mg/m²) single dose and 250 mg/m² every week for 7 weeks in combination with radiotherapy (RT). The infusion duration of nivolumab was 30 minutes.

| | |
|-----------------------|-----------|
| Reporting group title | RT + Cetu |
|-----------------------|-----------|

Reporting group description:

Subjects who were ineligible for cisplatin chemotherapy received placebo nivolumab 240 mg single dose on day 1 then 3 dose of 360 mg every 3 weeks followed by 6 dose of 480 mg every 4 weeks IV in plus cetuximab 400 mg/m² single dose and 250 mg/m² every week for 7 weeks in combination with RT. The infusion duration of nivolumab was 30 minutes. The infusion of cetuximab began at least 30 minutes after the completion of the nivolumab infusion.

| | |
|-----------------------|-----------------|
| Reporting group title | RT + Cis + Nivo |
|-----------------------|-----------------|

Reporting group description:

Subjects who were ineligible for cisplatin chemotherapy received nivolumab 240 mg single dose on day 1 then 3 dose of 360 mg every 3 weeks followed by 6 dose of 480 mg every 4 weeks IV in combination with 3 dose of cisplatin 100 mg/m² and RT. The infusion duration of nivolumab was 30 minutes. The infusion of cisplatin began at least 30 minutes after the completion of the nivolumab infusion.

| | |
|-----------------------|----------|
| Reporting group title | RT + Cis |
|-----------------------|----------|

Reporting group description:

Subjects who were ineligible for cisplatin chemotherapy received placebo nivolumab 240 mg single dose on day 1 then 3 dose of 360 mg every 3 weeks followed by 6 dose of 480 mg every 4 weeks IV in combination with 3 dose of cisplatin 100 mg/m² and RT. The infusion duration of nivolumab was 30 minutes. The infusion of cisplatin began at least 30 minutes after the completion of the nivolumab infusion.

| Serious adverse events | RT + Nivo | RT + Cetu | RT + Cis + Nivo |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | 5 / 10 (50.00%) | 9 / 27 (33.33%) |
| number of deaths (all causes) | 2 | 1 | 2 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Oropharyngeal squamous cell carcinoma | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (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 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (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 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (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 |
| Pharyngeal necrosis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (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 |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychotic disorder | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (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 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| 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 | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (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 |

| | | | |
|---|----------------|-----------------|----------------|
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (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 |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bacillus bacteraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (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 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (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 |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|--|--|
| Serious adverse events | RT + Cis | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | | |
| number of deaths (all causes) | 1 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Oropharyngeal squamous cell carcinoma | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pharyngeal necrosis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Delirium | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychotic disorder | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 3 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bacillus bacteraemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucosal infection | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypokalaemia | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 24 (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 | RT + Nivo | RT + Cetu | RT + Cis + Nivo |
|---|-------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 12 / 12 (100.00%) | 10 / 10 (100.00%) | 26 / 27 (96.30%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyogenic granuloma | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Lymphoedema | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 0 / 10 (0.00%) 0 | 1 / 27 (3.70%) 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 3 | 0 | 2 |
| Fatigue | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 5 / 10 (50.00%) | 8 / 27 (29.63%) |
| occurrences (all) | 5 | 5 | 12 |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Malaise | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 10 (20.00%) | 7 / 27 (25.93%) |
| occurrences (all) | 2 | 4 | 7 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 2 | 1 | 4 |
| Xerosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 2 | 1 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 4 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-------------------------------|-----------------|-----------------|-----------------|
| Cough | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 3 | 1 | 4 |
| Dysphonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 10 (20.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 2 | 2 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 1 | 0 | 3 |
| Haemoptysis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 0 | 1 |
| Hiccups | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 1 | 1 | 5 |
| Laryngeal inflammation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 3 / 10 (30.00%) | 8 / 27 (29.63%) |
| occurrences (all) | 3 | 3 | 8 |
| Paranasal sinus hyposecretion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pharyngeal inflammation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 1 | 1 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 1 | 1 |
| Delirium | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Depression | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 10 (20.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 2 | 2 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 8 / 27 (29.63%) |
| occurrences (all) | 2 | 1 | 10 |
| Blood electrolytes abnormal | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood thyroid stimulating hormone increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Lipase increased | | | |

| | | | |
|--|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 0 | 0 | 5 |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 9 / 27 (33.33%) |
| occurrences (all) | 0 | 0 | 10 |
| Platelet count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 0 | 0 | 5 |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 2 / 10 (20.00%) | 11 / 27 (40.74%) |
| occurrences (all) | 5 | 2 | 13 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 7 / 27 (25.93%) |
| occurrences (all) | 0 | 0 | 8 |
| C-Reactive protein increased | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Incision site inflammation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 10 (20.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Radiation skin injury | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 5 / 10 (50.00%) | 8 / 27 (29.63%) |
| occurrences (all) | 3 | 5 | 8 |
| Recall phenomenon | | | |

| | | | |
|--------------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Stoma site inflammation | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 10 (20.00%) | 12 / 27 (44.44%) |
| occurrences (all) | 2 | 2 | 12 |
| Headache | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 10 (20.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 2 | 1 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 0 | 0 | 4 |
| Taste disorder | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 0 | 1 | 3 |
| Tremor | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 3 / 10 (30.00%) | 12 / 27 (44.44%) |
| occurrences (all) | 4 | 3 | 14 |
| Leukocytosis | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 1 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 1 | 0 | 3 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 0 | 2 |
| Ear pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Tinnitus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 5 / 27 (18.52%) |
| occurrences (all) | 0 | 0 | 5 |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 10 (20.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Cheilitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |

| | | | |
|----------------------------------|-----------------|-----------------|------------------|
| subjects affected / exposed | 4 / 12 (33.33%) | 2 / 10 (20.00%) | 13 / 27 (48.15%) |
| occurrences (all) | 7 | 3 | 14 |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 3 / 10 (30.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 5 | 3 | 3 |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 3 / 10 (30.00%) | 12 / 27 (44.44%) |
| occurrences (all) | 4 | 3 | 12 |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 1 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 3 / 10 (30.00%) | 11 / 27 (40.74%) |
| occurrences (all) | 6 | 3 | 12 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Glossodynia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lip dry | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 1 / 10 (10.00%) | 17 / 27 (62.96%) |
| occurrences (all) | 5 | 1 | 24 |
| Odynophagia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 7 / 27 (25.93%) |
| occurrences (all) | 0 | 0 | 8 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Oral pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 10 (20.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Saliva altered | | | |

| | | | |
|--|----------------------|----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 10 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Stomatitis subjects affected / exposed occurrences (all) | 4 / 12 (33.33%) 6 | 4 / 10 (40.00%) 4 | 10 / 27 (37.04%) 12 |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 10 (10.00%) 1 | 6 / 27 (22.22%) 8 |
| Hepatobiliary disorders Hepatic function abnormal subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 10 (0.00%) 0 | 2 / 27 (7.41%) 2 |
| Dermatitis subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 | 8 / 27 (29.63%) 8 |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 4 / 10 (40.00%) 4 | 0 / 27 (0.00%) 0 |
| Dermatitis bullous subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 1 / 10 (10.00%) 1 | 1 / 27 (3.70%) 1 |
| Dry skin subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 10 (20.00%) 2 | 1 / 27 (3.70%) 1 |
| Erythema subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 1 / 10 (10.00%) 1 | 0 / 27 (0.00%) 0 |
| Lichen planus subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 10 (0.00%) 0 | 0 / 27 (0.00%) 0 |
| Pruritus | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 3 | 0 | 4 |
| Rash | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 4 / 10 (40.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 5 | 4 | 3 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin exfoliation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 10 (20.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Anuria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dysuria | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Urinary hesitation | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 0 | 1 | 4 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 6 / 27 (22.22%) |
| occurrences (all) | 0 | 0 | 6 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 10 (0.00%) | 3 / 27 (11.11%) |
| occurrences (all) | 0 | 0 | 3 |
| Back pain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 1 | 0 | 3 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 1 / 10 (10.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 4 | 1 | 2 |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Trismus | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infected dermal cyst | | | |

| | | | |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 1 / 10 (10.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 2 | 1 | 3 |
| Paronychia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pyoderma | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 4 / 12 (33.33%) | 2 / 10 (20.00%) | 9 / 27 (33.33%) |
| occurrences (all) | 4 | 2 | 11 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 0 | 1 | 2 |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 2 | 1 | 4 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 0 / 27 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 10 (0.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 2 | 0 | 1 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 5 / 27 (18.52%) |
| occurrences (all) | 1 | 1 | 6 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 10 (30.00%) | 4 / 27 (14.81%) |
| occurrences (all) | 0 | 4 | 5 |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 10 (0.00%) | 2 / 27 (7.41%) |
| occurrences (all) | 2 | 0 | 2 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 1 | 1 | 1 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 10 (10.00%) | 1 / 27 (3.70%) |
| occurrences (all) | 0 | 2 | 1 |

| Non-serious adverse events | RT + Cis | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 24 (100.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyogenic granuloma | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |

| | | | |
|--|-----------------|--|--|
| Hypertension | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphoedema | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Malaise | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 8 / 24 (33.33%) | | |
| occurrences (all) | 8 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 5 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Xerosis | | | |

| | | | |
|--|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | | |
| Dysphonia subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 | | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | | |
| Haemoptysis subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | | |
| Hiccups subjects affected / exposed occurrences (all) | 7 / 24 (29.17%) 7 | | |
| Laryngeal inflammation subjects affected / exposed occurrences (all) | 1 / 24 (4.17%) 1 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 24 (8.33%) 2 | | |
| Paranasal sinus hyposecretion subjects affected / exposed occurrences (all) | 0 / 24 (0.00%) 0 | | |
| Pharyngeal inflammation subjects affected / exposed occurrences (all) | 5 / 24 (20.83%) 5 | | |
| Psychiatric disorders | | | |

| | | | |
|---|-----------------|--|--|
| Agitation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Delirium | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Depression | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Blood electrolytes abnormal | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood magnesium decreased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood thyroid stimulating hormone decreased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood thyroid stimulating hormone increased | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood urea increased | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Lipase increased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 8 / 24 (33.33%) | | |
| occurrences (all) | 13 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Protein total decreased | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 8 | | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 13 | | |
| C-Reactive protein increased | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Injury, poisoning and procedural complications | | | |
| Incision site inflammation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infusion related reaction | | | |

| | | | |
|-----------------------------|------------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Radiation skin injury | | | |
| subjects affected / exposed | 11 / 24 (45.83%) | | |
| occurrences (all) | 11 | | |
| Recall phenomenon | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stoma site inflammation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | | |
| occurrences (all) | 7 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Taste disorder | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

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|--------------------------------------|-----------------|--|--|
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Leukopenia | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | | |
| occurrences (all) | 5 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Neutropenia | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 5 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear pain | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Tinnitus | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vision blurred | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------|------------------|--|--|
| Cheilitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Constipation | | | |
| subjects affected / exposed | 12 / 24 (50.00%) | | |
| occurrences (all) | 13 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Dry mouth | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Dysphagia | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 5 | | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Glossodynia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Lip dry | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nausea | | | |
| subjects affected / exposed | 11 / 24 (45.83%) | | |
| occurrences (all) | 16 | | |
| Odynophagia | | | |
| subjects affected / exposed | 5 / 24 (20.83%) | | |
| occurrences (all) | 5 | | |
| Oesophagitis | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |

| | | | |
|--|-----------------|--|--|
| Oral pain | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Saliva altered | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Stomatitis | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 24 (29.17%) | | |
| occurrences (all) | 7 | | |
| Hepatobiliary disorders | | | |
| Hepatic function abnormal | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Dermatitis | | | |
| subjects affected / exposed | 6 / 24 (25.00%) | | |
| occurrences (all) | 6 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Lichen planus | | | |

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|-----------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Rash papular | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Seborrhoeic dermatitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Anuria | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

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|---|----------------|--|--|
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Trismus | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes simplex | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

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|------------------------------------|------------------|--|--|
| Infected dermal cyst | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mucosal infection | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 4 | | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyoderma | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 10 / 24 (41.67%) | | |
| occurrences (all) | 11 | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Hyperkalaemia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 24 (12.50%) | | |
| occurrences (all) | 3 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 4 / 24 (16.67%) | | |
| occurrences (all) | 4 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 24 (8.33%) | | |
| occurrences (all) | 2 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 24 (4.17%) | | |
| occurrences (all) | 1 | | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 24 (0.00%) | | |
| occurrences (all) | 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 01 November 2017 | Update to questionnaire administration updated to align with dosing cycles. Outcome research assessment and endpoints redefined updated to align with analysis planned. TNM Staging clarified for high and intermediate risk definition. Other minor corrections, clarifications |
| 21 February 2018 | Added exclusion of participants with active interstitial lung disease (ILD) / pneumonitis or with a history of ILD / pneumonitis requiring steroids. Aligned thyroid testing to study visits. Added guidance for premedications for cetuximab if necessary. |
| 16 November 2018 | Enrollment in the study was closed as of 15-Oct-2018. Revised Protocol 03 covers the changes implemented to the protocol post study enrollment closure: study treatment unblinding, removal of placebo treatment, and removal of analysis of efficacy end-points and efficacy follow-up. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported