



Clinical trial results:

Randomized three arm phase III trial on induction treatment with a fluoropyrimidine-, oxaliplatin- and bevacizumab-based chemotherapy for 24 weeks followed by maintenance treatment with a fluoropyrimidine and bevacizumab vs. bevacizumab alone vs. no maintenance treatment and reinduction in case of progression for first-line treatment of patients with metastatic colorectal cancer

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2008-007974-39 |
| Trial protocol | DE |
| Global end of trial date | 14 August 2015 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 21 November 2021 |
| First version publication date | 21 November 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | AIO-KRK-0207 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00973609 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AIO-Studien-gGmbH |
| Sponsor organisation address | Kuno-Fischer-Str. 8, Berlin, Germany, 14057 |
| Public contact | info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de |
| Scientific contact | info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, info@aio-studien-ggmbh.de |

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 | 01 December 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 August 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Investigating the efficacy of maintenance and reinduction treatment or no treatment and watchful waiting in subjects with inoperable or irresectable and non-progressive metastatic colorectal cancer after first line induction treatment for 24 weeks with a fluoropyrimidine-, oxaliplatin- and bevacizumab-based chemotherapy. The maintenance treatment with capecitabine or 5-FU/folinic acid and bevacizumab will be compared with a maintenance treatment with bevacizumab alone or no maintenance treatment. Reinduction treatment will be done in case of progression.

Primary end-point:

Time to failure of maintenance and reinduction treatment strategy measured from randomization.

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) 'Guideline for Good Clinical Practice E6(R1)', CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 17 September 2009 |
| 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 | Germany: 825 |
| Worldwide total number of subjects | 825 |
| EEA total number of subjects | 825 |

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) | 385 |
| From 65 to 84 years | 440 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

837 subjects were recruited between Sept 17, 2009 and Feb 21, 2013, from 106 German institutions (55 hospitals and 51 private practices).

Pre-assignment

Screening details:

Of 852 screened patients, 837 received induction treatment. 12 of these patients were not eligible for analysis due to major protocol violations.

Period 1

| | |
|------------------------------|---------------------|
| Period 1 title | Induction treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|-------------------|
| Arm title | Induction overall |
|-----------|-------------------|

Arm description:

For induction treatment, the investigator had to choose between a capecitabine based or a 5-fluorouracil / FA based chemotherapy regimen for each subject. Allowed regimens were CAPOX, XELOX, FOLFOX6, FOLFOX4, modified FOLFOX7, modified FOLFOX4, and simplified FOLFOX4.

A change of the regimen was allowed if necessary.

| | |
|--|---|
| Arm type | Standard-of-care induction treatment |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

7.5 mg/kg every 3 weeks, or 5 mg/kg every 2 weeks

| | |
|--|---|
| Investigational medicinal product name | Fluoropyrimidine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Concentrate for solution for infusion |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Capecitabine oral at 1000 mg/m² twice daily or 5-FU infusion as stipulated by the regimen chosen by the investigator.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosage was 70 mg/m², 85 mg/m², 100 mg/m², or 130 mg/m², depending on the treatment regimen chosen by the investigator.

| | |
|---------------------------------------|-------------------|
| Number of subjects in period 1 | Induction overall |
| Started | 825 |
| Completed | 825 |

| | |
|--|---|
| Period 2 | |
| Period 2 title | Maintenance treatment |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |
| Arms | |
| Are arms mutually exclusive? | Yes |
| Arm title | Arm 1 (SoC) |
| Arm description: | |
| Maintenance treatment according to standard-of-care (SoC) with fluoropyrimidine plus bevacizumab until progression or unacceptable toxicity, i.e. any of the permitted induction treatments minus oxaliplatin. | |
| Arm type | Active comparator |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 7.5 mg/kg every 3 weeks, or 5 mg/kg every 2 weeks | |
| Investigational medicinal product name | Fluoropyrimidine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |
| Dosage and administration details: | |
| Dosage and administration as given during induction treatment | |
| Arm title | Arm 2 (beva maintenance) |
| Arm description: | |
| Maintenance treatment with bevacizumab until progression or unacceptable toxicity | |
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 7.5 mg/kg IV infusion, if tolerated over 30 minutes day 1, 22; start of next cycle on day 43 | |
| Arm title | Arm 3 (no maintenance treatment) |

| | |
|---|-----------------|
| Arm description: | |
| No maintenance treatment until progression | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 was non-randomized induction treatment according to standard of care. This period is of little scientific interest compared to the experimental treatment phase and therefore was not chosen as baseline period for the purpose of this reporting.

| Number of subjects in period 2 ^[2] [3] | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenace treatment) |
|--|-------------|-----------------------------|---------------------------------------|
| | Started | 158 | 156 |
| Completed | 158 | 156 | 158 |

Notes:

[2] - 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: Period 2 is the experimental phase of the study, and only patients who proceeded to period 2 contributed to the primary endpoint. It was chosen as baseline period for this reason.

[3] - 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: As per study protocol, only a subset of patients who received induction treatment proceeded to the phase of randomized, experimental maintenance treatment. Main reasons for not proceeding to maintenance treatment were disease progression during induction treatment, unacceptable toxicity and other adverse events preventing further treatment.

Period 3

| | |
|------------------------------|------------------------|
| Period 3 title | Re-induction treatment |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

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

Arm description:

Re-induction treatment according to SoC after disease progression during standard-of-care maintenance

| | |
|--|---|
| Arm type | Re-induction of standard-of-care |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

7.5 mg/kg every 3 weeks, or 5 mg/kg every 2 weeks, depending on the treatment regimen chosen by the investigator.

| | |
|--|------------------|
| Investigational medicinal product name | Fluoropyrimidine |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|---|
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |
| Dosage and administration details: Capecitabine oral at 1000 mg/m ² twice daily or 5-FU infusion as stipulated by the regimen chosen by the investigator. | |
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Dosage was 70 mg/m ² , 85 mg/m ² , 100 mg/m ² , or 130 mg/m ² , depending on the treatment regimen chosen by the investigator. | |
| Arm title | Arm 2 |
| Arm description: Re-induction treatment according to SoC after disease progression during bevacizumab maintenance treatment | |
| Arm type | Re-induction of standard-of-care |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 7.5 mg/kg every 3 weeks, or 5 mg/kg every 2 weeks, depending on the treatment regimen chosen by the investigator. | |
| Investigational medicinal product name | Fluoropyrimidine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet, Concentrate for solution for infusion |
| Routes of administration | Intravenous use, Oral use |
| Dosage and administration details: Capecitabine oral at 1000 mg/m ² twice daily or 5-FU infusion as stipulated by the regimen chosen by the investigator. | |
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: Dosage was 70 mg/m ² , 85 mg/m ² , 100 mg/m ² , or 130 mg/m ² , depending on the treatment regimen chosen by the investigator. | |
| Arm title | Arm 3 |
| Arm description: Re-induction treatment according to SoC after disease progression without maintenance treatment | |
| Arm type | Re-induction of standard-of-care |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: 7.5 mg/kg every 3 weeks, or 5 mg/kg every 2 weeks, depending on the treatment regimen chosen by | |

the investigator.

| | |
|--|---|
| Investigational medicinal product name | Fluoropyrimidine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion, Tablet |
| Routes of administration | Intravenous use, Oral use |

Dosage and administration details:

Capecitabine oral at 1000 mg/m² twice daily or 5-FU infusion as stipulated by the regimen chosen by the investigator.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Dosage was 70 mg/m², 85 mg/m², 100 mg/m², or 130 mg/m², depending on the treatment regimen chosen by the investigator.

| Number of subjects in period 3^[4] | Arm 1 (SoC) | Arm 2 | Arm 3 |
|---|-------------|-------|-------|
| Started | 33 | 67 | 75 |
| Completed | 33 | 67 | 75 |

Notes:

[4] - 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: As per study protocol, only a subset of patients proceeded to re-induction. Reasons for treatment discontinuation during maintenance treatment were death, unacceptable toxicity, patient's wish, and decisions to make use of alternative treatment options.

Baseline characteristics

Reporting groups

| | |
|------------------------------|--|
| Reporting group title | Arm 1 (SoC) |
| Reporting group description: | Maintenance treatment according to standard-of-care (SoC) with fluoropyrimidine plus bevacizumab until progression or unacceptable toxicity, i.e. any of the permitted induction treatments minus oxaliplatin. |
| Reporting group title | Arm 2 (beva maintenance) |
| Reporting group description: | Maintenance treatment with bevacizumab until progression or unacceptable toxicity |
| Reporting group title | Arm 3 (no maintenance treatment) |
| Reporting group description: | No maintenance treatment until progression |

| Reporting group values | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenance treatment) |
|---|----------------|--------------------------|----------------------------------|
| Number of subjects | 158 | 156 | 158 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| median full range (min-max) | 64 25 to 82 | 65 32 to 82 | 66 32 to 82 |
| Gender categorical Units: Subjects | | | |
| Female Male | 52 106 | 50 106 | 59 99 |
| ECOG performance score Units: Subjects | | | |
| ECOG 0-1 ECOG 2 | 151 7 | 150 6 | 151 7 |

| Reporting group values | Total | | |
|------------------------------------|-------|--|--|
| Number of subjects | 472 | | |
| 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) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age continuous Units: years median full range (min-max) | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 161 | | |
| Male | 311 | | |
| ECOG performance score Units: Subjects | | | |
| ECOG 0-1 | 452 | | |
| ECOG 2 | 20 | | |

End points

End points reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Induction overall |
|-----------------------|-------------------|

Reporting group description:

For induction treatment, the investigator had to choose between a capecitabine based or a 5-fluorouracil / FA based chemotherapy regimen for each subject. Allowed regimens were CAPOX, XELOX, FOLFOX6, FOLFOX4, modified FOLFOX7, modified FOLFOX4, and simplified FOLFOX4.

A change of the regimen was allowed if necessary.

| | |
|-----------------------|-------------|
| Reporting group title | Arm 1 (SoC) |
|-----------------------|-------------|

Reporting group description:

Maintenance treatment according to standard-of-care (SoC) with fluoropyrimidine plus bevacizumab until progression or unacceptable toxicity, i.e. any of the permitted induction treatments minus oxaliplatin.

| | |
|-----------------------|--------------------------|
| Reporting group title | Arm 2 (beva maintenance) |
|-----------------------|--------------------------|

Reporting group description:

Maintenance treatment with bevacizumab until progression or unacceptable toxicity

| | |
|-----------------------|----------------------------------|
| Reporting group title | Arm 3 (no maintenance treatment) |
|-----------------------|----------------------------------|

Reporting group description:

No maintenance treatment until progression

| | |
|-----------------------|-------------|
| Reporting group title | Arm 1 (SoC) |
|-----------------------|-------------|

Reporting group description:

Re-induction treatment according to SoC after disease progression during standard-of-care maintenance

| | |
|-----------------------|-------|
| Reporting group title | Arm 2 |
|-----------------------|-------|

Reporting group description:

Re-induction treatment according to SoC after disease progression during bevacizumab maintenance treatment

| | |
|-----------------------|-------|
| Reporting group title | Arm 3 |
|-----------------------|-------|

Reporting group description:

Re-induction treatment according to SoC after disease progression without maintenance treatment

Primary: Time to failure of strategy (TFS)

| | |
|-----------------|-----------------------------------|
| End point title | Time to failure of strategy (TFS) |
|-----------------|-----------------------------------|

End point description:

Time to failure of strategy from randomization (TFS from randomization): time from randomization to the first of the following events: death; patient requires the addition of a new therapeutic agent (i.e. an agent not included in the original strategy; end point measured at the first of either the time of disease progression or the time of initiation of a new agent); patient experiences disease progression while being treated with all agents that are components of the initial treatment strategy (except for agents which cannot be used because of persistent toxicity or contraindications); or patient experiences disease progression during a partial or complete treatment holiday from initial treatment strategy and receives no further therapy within 1 month. Subjects who did not have an event as stated above while on study were censored at the last evaluable radiographic assessment date.

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

End point timeframe:

TFS was measured in months between randomization and initiation of second-line treatment. Median follow-up from randomization was 17.0 months.

| End point values | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenance treatment) | |
|----------------------------------|------------------|--------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 147 | 153 | 154 | |
| Units: Months | | | | |
| number (confidence interval 95%) | 6.9 (6.1 to 8.5) | 6.1 (5.3 to 7.4) | 6.4 (4.8 to 7.6) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | SoC vs. beva maintenance |
| Comparison groups | Arm 1 (SoC) v Arm 2 (beva maintenance) |
| Number of subjects included in analysis | 300 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.08 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.85 |
| upper limit | 1.37 |

| | |
|---|--|
| Statistical analysis title | SoC vs. no maintenance |
| Comparison groups | Arm 3 (no maintenance treatment) v Arm 1 (SoC) |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.26 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.99 |
| upper limit | 1.6 |

Secondary: Progression-free survival 1

| | |
|------------------------|--|
| End point title | Progression-free survival 1 |
| End point description: | Progression-free survival time of induction treatment (PFS1): time from randomization to date of first observed progression or death (whichever comes first) over the entire trial. Subjects who have not progressed while on study and have not died while on study were censored at the last evaluable radiographic assessment date. |
| End point type | Secondary |

End point timeframe:

Time from randomization to date of first observed progression or death. Median follow-up from randomization was 17.0 months.

| End point values | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenance treatment) | |
|----------------------------------|------------------|--------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 147 | 153 | 154 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 6.3 (5.8 to 7.6) | 4.6 (4.0 to 5.3) | 3.5 (2.9 to 4.1) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Comparison of Arm 2 to standard Arm 1 |
| Comparison groups | Arm 1 (SoC) v Arm 2 (beva maintenance) |
| Number of subjects included in analysis | 300 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.34 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.06 |
| upper limit | 1.7 |

| | |
|---|--|
| Statistical analysis title | Copy of Comparison of Arm 3 to standard Arm 1 |
| Comparison groups | Arm 1 (SoC) v Arm 3 (no maintenance treatment) |
| Number of subjects included in analysis | 301 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 2.09 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 1.64 |
| upper limit | 2.67 |

Secondary: Overall survival

| | |
|-----------------|------------------|
| End point title | Overall survival |
|-----------------|------------------|

End point description:

Overall survival time (OS): time from randomization to the date of death. Subjects who were known to be alive or for whom a date of death was unknown, were censored on the later date of the last study assessment or last known telephone contact.

End point type Secondary

End point timeframe:

Time from randomization to the date of death. Median follow-up from randomization was 17.0 months.

| End point values | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenance treatment) | |
|----------------------------------|---------------------|--------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 157 | 156 | 158 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 20.2 (18.4 to 24.3) | 21.9 (18.7 to 26.4) | 23.1 (19.6 to 25.7) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival 2

End point title Progression-free survival 2

End point description:

PFS2: Time from enrolment to first progression event for all randomized patients. All other definitions as for PFS1.

End point type Secondary

End point timeframe:

Time from enrolment to first progression event for all randomized patients. Median follow-up from randomization was 17.0 months.

| End point values | Arm 1 (SoC) | Arm 2 (beva maintenance) | Arm 3 (no maintenance treatment) | |
|----------------------------------|---------------------|--------------------------|----------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 147 | 153 | 154 | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.7 (10.8 to 13.2) | 10.0 (9.4 to 10.6) | 9 (8.4 to 9.6) | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from informed consent until 28 days after the last administration of treatment.

Adverse events for individual treatment phases are from the first cycle of the respective step until the the corresponding safety update visit.

Adverse event reporting additional description:

The results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|-----------|
| Dictionary name | NCI CTCAE |
|-----------------|-----------|

| | |
|--------------------|---|
| Dictionary version | 3 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Arm 1 Maintenance |
|-----------------------|-------------------|

Reporting group description:

Fluoropyrimidine plus bevacizumab until progression or unacceptable toxicity

The results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------------|-------------------|
| Reporting group title | Arm 3 Maintenance |
|-----------------------|-------------------|

Reporting group description:

No treatment until progression

The results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------------|-------------------|
| Reporting group title | Arm 2 Maintenance |
|-----------------------|-------------------|

Reporting group description:

Bevacizumab until progression or unacceptable toxicity

The results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------------|------------------|
| Reporting group title | Induction period |
|-----------------------|------------------|

Reporting group description:

The database structure does not allow to analyze overall mortality in individual treatment step periods. Thus, these results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------------|--------------------|
| Reporting group title | Arm 1 Re-Induction |
|-----------------------|--------------------|

Reporting group description: -

| | |
|-----------------------|--------------------|
| Reporting group title | Arm 2 Re-Induction |
|-----------------------|--------------------|

Reporting group description:

The results for 'total number of deaths - all causes' refer to the overall death event number in all patients reaching the respective treatment phase, irrespective of the time point of death.

| | |
|-----------------------|--------------------|
| Reporting group title | Arm 3 Re-Induction |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Arm 1 Maintenance | Arm 3 Maintenance | Arm 2 Maintenance |
|--|-------------------|-------------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 158 (19.62%) | 20 / 158 (12.66%) | 37 / 156 (23.72%) |
| number of deaths (all causes) | 115 | 104 | 120 |
| number of deaths resulting from adverse events | 8 | 5 | 6 |
| Vascular disorders | | | |
| Hemorrhage/Bleeding - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Phlebitis (including superficial thrombosis) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Phlebolympathic cording | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic synd | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Acute vascular leak syndrome | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Flushing | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hypertension | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 2 / 156 (1.28%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Peripheral arterial ischemia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Thrombosis/thrombus/embolism | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Extremity-lower (gait/walking) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - General - Tumor pain | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Other | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight loss | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Death not associated with CTCAE term - Disease progression NOS | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Death not associated with CTCAE term - Multi-organ failure | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Constitutional Symptoms - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 6 / 156 (3.85%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 4 |
| Death not associated with CTCAE term | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Death not associated with CTCAE term - Death NOS | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Death not associated with CTCAE term - Sudden death | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 1 |
| Edema: limb | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Fatigue (asthenia, lethargy, malaise) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 2 / 156 (1.28%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fever (in the absence of neutropenia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Syndromes - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Thrombosis/embolism (vascular access-related) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ulceration | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Immune system disorders | | | |
| Allergic reaction/hypersensitivity (including drug fever) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Allergy/Immunology - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm, wheezing | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, pulmonary/upper respiratory - Nose | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pleural effusion (non-malignant) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Aspiration | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Dyspnea (shortness of breath) | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Lung (pneumonia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pneumonitis/pulmonary infiltrates | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 3 / 158 (1.90%) | 1 / 158 (0.63%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary/Upper Respiratory - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mood alteration - Anxiety | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Investigations | | | |
| Metabolic/Laboratory - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemorrhage/bleeding associated with surgery, intra-operative or postoperative | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Intra-operative injury - Gastrointestinal - Stoma (GI) | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Vessel injury-vein | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Wound complication, non-infectious | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intra-operative Injury - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Cardiac disorders | | | |
| Left ventricular diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Supraventricular and nodal arrhythmia - Atrial tachycardia/Paroxysmal Atrial Tachycardia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Ventricular arrhythmia - Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Cardiac Arrhythmia - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Cardiac General - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Cardiac ischemia/infarction | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Cardiac troponin T (cTnT) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Cardiovascular - Pericardium | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ventricular arrhythmia - Ventricular arrhythmia NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Neuropathy: cranial - CN V Motor-jaw muscles; Sensory-facial | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Neuropathy: cranial - CN VII Motor-face; Sensory-taste | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Seizure | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Speech impairment (e.g., dysphasia or aphasia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Tremor | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy: cranial - CN II Vision | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| CNS cerebrovascular ischemia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Neurology - Other | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Neuropathy: sensory | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Neurology - Head/headache | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Syncope (fainting) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Blood and lymphatic system disorders | | | |
| Lymphatics - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| 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/Bone Marrow - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Coagulation - Other | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia (fever of unknown origin, ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemoglobin | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Blood | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Leukocytes (total WBC) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Neutrophils/granulocytes (ANC/AGC) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 158 (0.63%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Platelets | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula, GI - Anus | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Flatulence | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, GI | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, GI - Colon | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, GI - Esophagus | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, GI - Stoma | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucositis/stomatitis (functional/symptomatic) - Stomach | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Necrosis, GI - Gallbladder | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Obstruction, GI - Ileum | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Pain - Gastrointestinal - Anus | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Gastrointestinal - Stomach | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prolapse of stoma, GI | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Stricture/stenosis (including anastomotic), GI - Duodenum | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Stricture/stenosis (including anastomotic), GI - Ileum | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ascites (non-malignant) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction, GI | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Pain - Gastrointestinal - Peritoneum | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia (difficulty swallowing) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Enteritis (inflammation of the small bowel) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Fistula, GI | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Gastritis (including bile reflux gastritis) | | | |
| subjects affected / exposed | 2 / 158 (1.27%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 158 (0.63%) | 6 / 156 (3.85%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 2 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemorrhage, GI - Rectum | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 2 / 158 (1.27%) | 3 / 156 (1.92%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Peritoneal cavity | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Malabsorption | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mucositis/stomatitis (clinical exam) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mucositis/stomatitis (clinical exam) - Anus | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mucositis/stomatitis (clinical exam) - Oral cavity | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mucositis/stomatitis (functional/symptomatic) - Oral cavity | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Mucositis/stomatitis (functional/symptomatic) - Pharynx | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrosis, GI - Ileum | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Obstruction, GI - Gallbladder | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Perforation, GI - Colon | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perforation, GI - Small bowel NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Stricture/stenosis (including anastomotic), GI - Colon | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Ulcer, GI - Duodenum | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Ulcer, GI - Stomach | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatobiliary/Pancreas - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Hepatobiliary/Pancreas - Gallbladder | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Hepatobiliary/Pancreas - Liver | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Liver dysfunction/failure (clinical) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Bilirubin (hyperbilirubinemia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 2 / 158 (1.27%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| GGT (gamma-Glutamyl transpeptidase) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 4 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash/desquamation | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Dermatology/Skin - Other | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Creatinine | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Fistula, GU | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction, GU - Ureter | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Renal/Genitourinary - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Stricture/stenosis (including anastomotic), GU - Prostate | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stricture/stenosis (including anastomotic), GU - Ureter | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Urinary retention (including neurogenic bladder) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Glomerular filtration rate | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Hemorrhage, GU - Bladder | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Renal/Genitourinary - Bladder | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Renal failure | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 2 / 156 (1.28%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 5 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Endocrine - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain - Musculoskeletal - Bone | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Musculoskeletal - Extremity-limb | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Musculoskeletal - Muscle | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Musculoskeletal/Soft Tissue - Other | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Pain - Musculoskeletal - Back | | | |
| subjects affected / exposed | 3 / 158 (1.90%) | 0 / 158 (0.00%) | 0 / 156 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Abdomen NOS | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Dental-tooth | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Catheter-related | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Lung (pneumonia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection - Other | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Lip/perioral | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Peristomal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Catheter-related | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Foreign body (e.g.,graft, implant | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 1 / 156 (0.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Pulmonary/Upper Respiratory - Bronchus | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Renal/Genitourinary - Urinary tract NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC - | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| Gastrointestinal - Colon | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC - Gastrointestinal - Rectum | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC - General - Blood | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC - General - Catheter-related | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Upper airway NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Blood | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Urinary tract NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Cystitis | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Infection with unknown ANC - Renal/Genitourinary - Urinary tract NOS | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Metabolism and nutrition disorders | | | |
| Acidosis (metabolic or respiratory) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 1 / 158 (0.63%) | 0 / 156 (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 |
| Alcohol intolerance syndrome (antabuse-like syndrome) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Glucose, serum-high (hyperglycemia) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Potassium, serum-high (hyperkalemia) | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Potassium, serum-low (hypokalemia) | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |
| Anorexia | | | |
| subjects affected / exposed | 0 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 / 158 (0.00%) | 0 / 158 (0.00%) | 0 / 156 (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 |

| Serious adverse events | Induction period | Arm 1 Re-Induction | Arm 2 Re-Induction |
|---|--------------------|--------------------|--------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 295 / 825 (35.76%) | 6 / 33 (18.18%) | 18 / 67 (26.87%) |
| number of deaths (all causes) | 596 | 30 | 51 |
| number of deaths resulting from adverse events | | 2 | 3 |
| Vascular disorders | | | |
| Hemorrhage/Bleeding - Other | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Phlebitis (including superficial thrombosis) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Phlebolympathic cording | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic synd | | | |

| | | | |
|--|------------------|----------------|----------------|
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Acute vascular leak syndrome | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Flushing | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hypertension | | | |
| subjects affected / exposed | 7 / 825 (0.85%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 5 / 12 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral arterial ischemia | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis/thrombus/embolism | | | |
| subjects affected / exposed | 27 / 825 (3.27%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 29 / 45 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Extremity-lower (gait/walking) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain | | | |

| | | | |
|--|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - General - Tumor pain | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Other | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight loss | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Death not associated with CTCAE term - Disease progression NOS | | | |
| subjects affected / exposed | 5 / 825 (0.61%) | 1 / 33 (3.03%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 1 |
| Death not associated with CTCAE term - Multi-organ failure | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Constitutional Symptoms - Other | | | |
| subjects affected / exposed | 24 / 825 (2.91%) | 0 / 33 (0.00%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 17 / 37 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 3 |
| Death not associated with CTCAE term | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| Death not associated with CTCAE | | | |

| | | | |
|---|------------------|----------------|----------------|
| term - Death NOS | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Death not associated with CTCAE term - Sudden death | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Edema: limb | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Fatigue (asthenia, lethargy, malaise) | | | |
| subjects affected / exposed | 5 / 825 (0.61%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 7 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fever (in the absence of neutropenia) | | | |
| subjects affected / exposed | 11 / 825 (1.33%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 5 / 15 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syndromes - Other | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis/embolism (vascular access-related) | | | |
| subjects affected / exposed | 6 / 825 (0.73%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 4 / 10 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ulceration | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Immune system disorders | | | |
| Allergic reaction/hypersensitivity (including drug fever) | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Allergy/Immunology - Other | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchospasm, wheezing | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hemorrhage, pulmonary/upper respiratory - Nose | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pleural effusion (non-malignant) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Aspiration | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 1 / 33 (3.03%) | 0 / 67 (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 |
| Dyspnea (shortness of breath) | | | |
| subjects affected / exposed | 9 / 825 (1.09%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 4 / 16 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Lung (pneumonia) | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis/pulmonary infiltrates | | | |
| subjects affected / exposed | 10 / 825 (1.21%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 3 / 12 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| Pulmonary/Upper Respiratory - Other | | | |
| subjects affected / exposed | 8 / 825 (0.97%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 6 / 11 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mood alteration - Anxiety | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 | | | |
| Metabolic/Laboratory - Other | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemorrhage/bleeding associated with surgery, intra-operative or postoperative | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Intra-operative injury - Gastrointestinal - Stoma (GI) | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Vessel injury-vein | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Wound complication, non-infectious | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Intra-operative Injury - Other | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Left ventricular diastolic dysfunction | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 1 / 33 (3.03%) | 0 / 67 (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 |
| Supraventricular and nodal arrhythmia - Atrial tachycardia/Paroxysmal Atrial Tachycardia | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ventricular arrhythmia - Ventricular fibrillation | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac Arrhythmia - Other | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Cardiac General - Other | | | |
| subjects affected / exposed | 7 / 825 (0.85%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 0 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac ischemia/infarction | | | |
| subjects affected / exposed | 6 / 825 (0.73%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 6 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac troponin T (cTnT) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |

| | | | |
|--|-----------------|----------------|----------------|
| Pain - Cardiovascular - Pericardium | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ventricular arrhythmia - Ventricular arrhythmia NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Neuropathy: cranial - CN V Motor-jaw muscles; Sensory-facial | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Neuropathy: cranial - CN VII Motor-face; Sensory-taste | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Speech impairment (e.g., dysphasia or aphasia) | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Tremor | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Neuropathy: cranial - CN II Vision | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| CNS cerebrovascular ischemia | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurology - Other | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neuropathy: sensory | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Neurology - Head/headache | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Syncope (fainting) | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Lymphatics - Other | | | |

| | | | |
|--|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Blood/Bone Marrow - Other | | | |
| subjects affected / exposed | 5 / 825 (0.61%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 4 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Coagulation - Other | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia (fever of unknown origin, ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemoglobin | | | |
| subjects affected / exposed | 4 / 825 (0.48%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Blood | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukocytes (total WBC) | | | |
| subjects affected / exposed | 5 / 825 (0.61%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Neutrophils/granulocytes (ANC/AGC) | | | |
| subjects affected / exposed | 11 / 825 (1.33%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 16 / 17 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Platelets | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 2 / 33 (6.06%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula, GI - Anus | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Flatulence | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hemorrhage, GI | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hemorrhage, GI - Colon | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hemorrhage, GI - Esophagus | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemorrhage, GI - Stoma | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mucositis/stomatitis (functional/symptomatic) - Stomach | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Necrosis, GI - Gallbladder | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Obstruction, GI - Ileum | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 7 / 825 (0.85%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain - Gastrointestinal - Anus | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Gastrointestinal - Stomach | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Prolapse of stoma, GI | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stricture/stenosis (including anastomotic), GI - Duodenum | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Stricture/stenosis (including anastomotic), GI - Ileum | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ascites (non-malignant) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Obstruction, GI | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Gastrointestinal - Peritoneum | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Colitis | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhea | | | |
| subjects affected / exposed | 35 / 825 (4.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 39 / 53 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia (difficulty swallowing) | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis (inflammation of the small bowel) | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fistula, GI | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastritis (including bile reflux gastritis) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 17 / 825 (2.06%) | 1 / 33 (3.03%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 6 / 22 | 0 / 1 | 2 / 2 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Hemorrhage, GI - Rectum | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation) | | | |
| subjects affected / exposed | 17 / 825 (2.06%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 3 / 22 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 5 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Peritoneal cavity | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Malabsorption | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mucositis/stomatitis (clinical exam) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mucositis/stomatitis (clinical exam) - Anus | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mucositis/stomatitis (clinical exam) - Oral cavity | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Mucositis/stomatitis (functional/symptomatic) - Oral cavity | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucositis/stomatitis (functional/symptomatic) - Pharynx | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Nausea | | | |
| subjects affected / exposed | 7 / 825 (0.85%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 4 / 10 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrosis, GI - Ileum | | | |

| | | | |
|--|------------------|----------------|----------------|
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Obstruction, GI - Gallbladder | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Perforation, GI - Colon | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Perforation, GI - Small bowel NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Stricture/stenosis (including anastomotic), GI - Colon | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ulcer, GI - Duodenum | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Ulcer, GI - Stomach | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Vomiting | | | |
| subjects affected / exposed | 14 / 825 (1.70%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 15 / 17 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Hepatobiliary/Pancreas - Other | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Hepatobiliary/Pancreas - Gallbladder | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Hepatobiliary/Pancreas - Liver | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Liver dysfunction/failure (clinical) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Bilirubin (hyperbilirubinemia) | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| GGT (gamma-Glutamyl transpeptidase) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | 8 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Rash/desquamation | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Dermatology/Skin - Other | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 825 (0.24%) | 1 / 33 (3.03%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 4 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Creatinine | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Fistula, GU | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Obstruction, GU - Ureter | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Renal/Genitourinary - Other | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Stricture/stenosis (including anastomotic), GU - Prostate | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Stricture/stenosis (including anastomotic), GU - Ureter | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Urinary retention (including neurogenic bladder) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| Adrenal insufficiency | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Glomerular filtration rate | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Hemorrhage, GU - Bladder | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Renal/Genitourinary - Bladder | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 7 / 825 (0.85%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 4 / 7 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Endocrine - Other | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain - Musculoskeletal - Bone | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Musculoskeletal - Extremity-limb | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Pain - Musculoskeletal - Muscle | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Musculoskeletal/Soft Tissue - Other | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Pain - Musculoskeletal - Back | | | |
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Dental-tooth | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Catheter-related | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Lung (pneumonia) | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 3 / 825 (0.36%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Infection - Other | | | |
| subjects affected / exposed | 13 / 825 (1.58%) | 1 / 33 (3.03%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 8 / 18 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 2 / 67 (2.99%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 6 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Lip/perioral | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Peristomal | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Catheter-related | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Foreign body (e.g.,graft, implant | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Pulmonary/Upper Respiratory - Bronchus | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Renal/Genitourinary - Urinary tract NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with unknown ANC | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with unknown ANC - Gastrointestinal - Colon | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with unknown ANC - Gastrointestinal - Rectum | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with unknown ANC - General - Blood | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with unknown ANC - General - Catheter-related | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Upper airway NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Blood | | | |
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Urinary tract NOS | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with unknown ANC - Renal/Genitourinary - Urinary tract NOS | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Acidosis (metabolic or respiratory) | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 0 / 825 (0.00%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Alcohol intolerance syndrome (antabuse-like syndrome) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Glucose, serum-high (hyperglycemia) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Potassium, serum-high (hyperkalemia) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Potassium, serum-low (hypokalemia) | | | |
| subjects affected / exposed | 1 / 825 (0.12%) | 0 / 33 (0.00%) | 0 / 67 (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 |
| Anorexia | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 0 / 33 (0.00%) | 0 / 67 (0.00%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 8 / 825 (0.97%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences causally related to treatment / all | 6 / 11 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Arm 3 Re-Induction | | |
|---|--------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 74 (21.62%) | | |
| number of deaths (all causes) | 50 | | |
| number of deaths resulting from adverse events | 2 | | |

| | | | | |
|--|----------------|--|--|--|
| Vascular disorders | | | | |
| Hemorrhage/Bleeding - Other | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Phlebitis (including superficial thrombosis) | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Phlebolympathic cording | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic synd | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Acute vascular leak syndrome | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flushing | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypertension | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypotension | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral arterial ischemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis/thrombus/embolism | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Extremity-lower (gait/walking) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - General - Tumor pain | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight loss | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death not associated with CTCAE term - Disease progression NOS | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death not associated with CTCAE term - Multi-organ failure | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Constitutional Symptoms - Other | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Death not associated with CTCAE term | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death not associated with CTCAE term - Death NOS | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Death not associated with CTCAE term - Sudden death | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Edema: limb | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue (asthenia, lethargy, malaise) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Fever (in the absence of neutropenia) | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syndromes - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis/embolism (vascular access-related) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulceration | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune system disorders | | | |
| Allergic reaction/hypersensitivity (including drug fever) | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Allergy/Immunology - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Atelectasis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchospasm, wheezing | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, pulmonary/upper respiratory - Nose | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion (non-malignant) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Aspiration | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyspnea (shortness of breath) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Lung (pneumonia) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonitis/pulmonary infiltrates | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary/Upper Respiratory - | | | |

| | | | |
|---|----------------|--|--|
| Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Confusion | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mood alteration - Anxiety | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Investigations | | | |
| Metabolic/Laboratory - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage/bleeding associated with surgery, intra-operative or postoperative | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intra-operative injury - Gastrointestinal - Stoma (GI) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vessel injury-vein | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Wound complication, non-infectious | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Intra-operative Injury - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Left ventricular diastolic dysfunction | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Supraventricular and nodal arrhythmia - Atrial tachycardia/Paroxysmal Atrial Tachycardia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular arrhythmia - Ventricular fibrillation | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac Arrhythmia - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|--|----------------|--|--|
| Cardiac General - Other | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac ischemia/infarction | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac troponin T (cTnT) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Cardiovascular - Pericardium | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ventricular arrhythmia - Ventricular arrhythmia NOS | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy: cranial - CN V Motor-jaw muscles; Sensory-facial | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy: cranial - CN VII Motor-face; Sensory-taste | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Speech impairment (e.g., dysphasia or aphasia) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tremor | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy: cranial - CN II Vision | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| CNS cerebrovascular ischemia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neurology - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neuropathy: sensory | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Neurology - Head/headache | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope (fainting) | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Blood and lymphatic system disorders | | | |
| Lymphatics - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood/Bone Marrow - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coagulation - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile neutropenia (fever of unknown origin, ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemoglobin | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Blood | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Leukocytes (total WBC) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutrophils/granulocytes (ANC/AGC) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelets | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fistula, GI - Anus | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Flatulence | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, GI | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, GI - Colon | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, GI - Esophagus | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, GI - Stoma | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (functional/symptomatic) - Stomach | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Necrosis, GI - Gallbladder | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction, GI - Ileum | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Gastrointestinal - Anus | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Gastrointestinal - Stomach | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prolapse of stoma, GI | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stricture/stenosis (including anastomotic), GI - Duodenum | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stricture/stenosis (including anastomotic), GI - Ileum | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ascites (non-malignant) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction, GI | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Gastrointestinal - Peritoneum | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Colitis | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysphagia (difficulty swallowing) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Enteritis (inflammation of the small bowel) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fistula, GI | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastritis (including bile reflux gastritis) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemorrhage, GI - Rectum | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation) | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Peritoneal cavity | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malabsorption | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (clinical exam) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (clinical exam) - Anus | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (clinical exam) - Oral cavity | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (functional/symptomatic) - Oral cavity | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mucositis/stomatitis (functional/symptomatic) - Pharynx | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Necrosis, GI - Ileum | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction, GI - Gallbladder | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perforation, GI - Colon | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Perforation, GI - Small bowel NOS | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Stricture/stenosis (including anastomotic), GI - Colon | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulcer, GI - Duodenum | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ulcer, GI - Stomach | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Hepatobiliary/Pancreas - Other | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Hepatobiliary/Pancreas - Gallbladder | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Hepatobiliary/Pancreas - Liver | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Liver dysfunction/failure (clinical) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bilirubin (hyperbilirubinemia) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| GGT (gamma-Glutamyl transpeptidase) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash/desquamation | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dermatology/Skin - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Creatinine | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fistula, GU | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Obstruction, GU - Ureter | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal/Genitourinary - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|----------------|--|--|--|
| Stricture/stenosis (including anastomotic), GU - Prostate | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Stricture/stenosis (including anastomotic), GU - Ureter | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary retention (including neurogenic bladder) | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Adrenal insufficiency | | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 3 | | | |
| Glomerular filtration rate | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hemorrhage, GU - Bladder | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Renal/Genitourinary - Bladder | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Renal failure | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Endocrine - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain - Musculoskeletal - Bone | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Musculoskeletal - Extremity-limb | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Musculoskeletal - Muscle | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal/Soft Tissue - Other | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain - Musculoskeletal - Back | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Abdomen NOS | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Gastrointestinal - Dental-tooth | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Catheter-related | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Lung (pneumonia) | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection - Other | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Lip/perioral | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Dermatology/Skin - Peristomal | | | | |

| | | | | |
|---|----------------|--|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Gastrointestinal - Abdomen NOS | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Catheter-related | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - General - Foreign body (e.g.,graft, implant | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Pulmonary/Upper Respiratory - Bronchus | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with normal ANC or Grade 1 or 2 neutrophils - Renal/Genitourinary - Urinary tract NOS | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC - | | | | |

| | | | | |
|---|----------------|--|--|--|
| Gastrointestinal - Colon | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC - Gastrointestinal - Rectum | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC - General - Blood | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC - General - Catheter-related | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with unknown ANC - Pulmonary/Upper Respiratory - Upper airway NOS | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - General - Blood | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) - Urinary tract NOS | | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cystitis | | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection with unknown ANC - Renal/Genitourinary - Urinary tract NOS | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infection with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Acidosis (metabolic or respiratory) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Alcohol intolerance syndrome (antabuse-like syndrome) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glucose, serum-high (hyperglycemia) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Potassium, serum-high (hyperkalemia) | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Potassium, serum-low (hypokalemia) | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anorexia | | | |
| subjects affected / exposed | 0 / 74 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 74 (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 | Arm 1 Maintenance | Arm 3 Maintenance | Arm 2 Maintenance |
|--|--------------------|--------------------|--------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 149 / 158 (94.30%) | 138 / 158 (87.34%) | 147 / 156 (94.23%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 20 / 158 (12.66%) | 16 / 158 (10.13%) | 26 / 156 (16.67%) |
| occurrences (all) | 108 | 51 | 122 |
| Nervous system disorders | | | |
| Neurology - Other | | | |
| subjects affected / exposed | 12 / 158 (7.59%) | 5 / 158 (3.16%) | 9 / 156 (5.77%) |
| occurrences (all) | 46 | 14 | 34 |
| Neuropathy: sensory | | | |
| subjects affected / exposed | 112 / 158 (70.89%) | 112 / 158 (70.89%) | 113 / 156 (72.44%) |
| occurrences (all) | 577 | 387 | 560 |
| Pain - Neurology - Head/headache | | | |
| subjects affected / exposed | 5 / 158 (3.16%) | 0 / 158 (0.00%) | 3 / 156 (1.92%) |
| occurrences (all) | 16 | 0 | 14 |
| Blood and lymphatic system disorders | | | |
| Bilirubin (hyperbilirubinemia) | | | |
| subjects affected / exposed | 4 / 158 (2.53%) | 0 / 158 (0.00%) | 2 / 156 (1.28%) |
| occurrences (all) | 17 | 0 | 5 |
| Blood/Bone Marrow - Other | | | |

| | | | |
|--|--------------------------|-------------------------|-------------------------|
| subjects affected / exposed occurrences (all) | 6 / 158 (3.80%) 19 | 2 / 158 (1.27%) 6 | 1 / 156 (0.64%) 1 |
| Hemoglobin subjects affected / exposed occurrences (all) | 8 / 158 (5.06%) 29 | 11 / 158 (6.96%) 21 | 14 / 156 (8.97%) 41 |
| Leukocytes (total WBC) subjects affected / exposed occurrences (all) | 12 / 158 (7.59%) 28 | 5 / 158 (3.16%) 7 | 13 / 156 (8.33%) 23 |
| Neutrophils/granulocytes (ANC/AGC) subjects affected / exposed occurrences (all) | 6 / 158 (3.80%) 8 | 2 / 158 (1.27%) 2 | 8 / 156 (5.13%) 15 |
| Platelets subjects affected / exposed occurrences (all) | 16 / 158 (10.13%) 63 | 7 / 158 (4.43%) 17 | 23 / 156 (14.74%) 70 |
| General disorders and administration site conditions | | | |
| Constitutional Symptoms - Other subjects affected / exposed occurrences (all) | 9 / 158 (5.70%) 14 | 7 / 158 (4.43%) 15 | 6 / 156 (3.85%) 11 |
| Fatigue (asthenia, lethargy, malaise) subjects affected / exposed occurrences (all) | 43 / 158 (27.22%) 157 | 31 / 158 (19.62%) 84 | 27 / 156 (17.31%) 90 |
| Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L) subjects affected / exposed occurrences (all) | 4 / 158 (2.53%) 4 | 0 / 158 (0.00%) 0 | 4 / 156 (2.56%) 4 |
| Pain - Other subjects affected / exposed occurrences (all) | 7 / 158 (4.43%) 32 | 5 / 158 (3.16%) 9 | 10 / 156 (6.41%) 22 |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 12 / 158 (7.59%) 33 | 5 / 158 (3.16%) 9 | 13 / 156 (8.33%) 30 |
| Diarrhea subjects affected / exposed occurrences (all) | 26 / 158 (16.46%) 82 | 12 / 158 (7.59%) 24 | 20 / 156 (12.82%) 55 |
| Gastrointestinal - Other | | | |

| | | | |
|--|-------------------|------------------|------------------|
| subjects affected / exposed | 6 / 158 (3.80%) | 4 / 158 (2.53%) | 15 / 156 (9.62%) |
| occurrences (all) | 27 | 16 | 48 |
| Mucositis/stomatitis (clinical exam) | | | |
| subjects affected / exposed | 5 / 158 (3.16%) | 3 / 158 (1.90%) | 6 / 156 (3.85%) |
| occurrences (all) | 16 | 3 | 16 |
| Mucositis/stomatitis (clinical exam) - Oral cavity | | | |
| subjects affected / exposed | 10 / 158 (6.33%) | 3 / 158 (1.90%) | 7 / 156 (4.49%) |
| occurrences (all) | 38 | 3 | 28 |
| Nausea | | | |
| subjects affected / exposed | 20 / 158 (12.66%) | 13 / 158 (8.23%) | 15 / 156 (9.62%) |
| occurrences (all) | 60 | 21 | 43 |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 7 / 158 (4.43%) | 12 / 158 (7.59%) | 4 / 156 (2.56%) |
| occurrences (all) | 13 | 25 | 6 |
| Taste alteration (dysgeusia) | | | |
| subjects affected / exposed | 10 / 158 (6.33%) | 5 / 158 (3.16%) | 4 / 156 (2.56%) |
| occurrences (all) | 31 | 9 | 8 |
| Vomiting | | | |
| subjects affected / exposed | 7 / 158 (4.43%) | 3 / 158 (1.90%) | 4 / 156 (2.56%) |
| occurrences (all) | 13 | 3 | 4 |
| Hepatobiliary disorders | | | |
| AST, SGOT(serum glutamic oxaloacetic transaminase) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 3 / 158 (1.90%) | 10 / 156 (6.41%) |
| occurrences (all) | 2 | 5 | 30 |
| GGT (gamma-Glutamyl transpeptidase) | | | |
| subjects affected / exposed | 1 / 158 (0.63%) | 1 / 158 (0.63%) | 4 / 156 (2.56%) |
| occurrences (all) | 7 | 3 | 14 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 6 / 158 (3.80%) | 1 / 158 (0.63%) | 3 / 156 (1.92%) |
| occurrences (all) | 13 | 2 | 14 |
| Dyspnea (shortness of breath) | | | |
| subjects affected / exposed | 8 / 158 (5.06%) | 6 / 158 (3.80%) | 6 / 156 (3.85%) |
| occurrences (all) | 21 | 17 | 20 |

| | | | |
|--|-------------------------|------------------------|-------------------------|
| Hemorrhage, pulmonary/upper respiratory - Nose subjects affected / exposed occurrences (all) | 8 / 158 (5.06%) 25 | 7 / 158 (4.43%) 14 | 8 / 156 (5.13%) 24 |
| Skin and subcutaneous tissue disorders Dermatology/Skin - Other subjects affected / exposed occurrences (all) | 13 / 158 (8.23%) 31 | 8 / 158 (5.06%) 30 | 5 / 156 (3.21%) 8 |
| Hair loss/alopecia (scalp or body) subjects affected / exposed occurrences (all) | 13 / 158 (8.23%) 45 | 12 / 158 (7.59%) 25 | 16 / 156 (10.26%) 47 |
| Rash: hand-foot skin reaction subjects affected / exposed occurrences (all) | 18 / 158 (11.39%) 74 | 9 / 158 (5.70%) 18 | 9 / 156 (5.77%) 41 |
| Musculoskeletal and connective tissue disorders Musculoskeletal/Soft Tissue - Other subjects affected / exposed occurrences (all) | 4 / 158 (2.53%) 8 | 3 / 158 (1.90%) 16 | 5 / 156 (3.21%) 12 |
| Pain - Musculoskeletal - Back subjects affected / exposed occurrences (all) | 6 / 158 (3.80%) 25 | 3 / 158 (1.90%) 5 | 4 / 156 (2.56%) 14 |
| Pain - Musculoskeletal - Bone subjects affected / exposed occurrences (all) | 1 / 158 (0.63%) 5 | 3 / 158 (1.90%) 6 | 7 / 156 (4.49%) 13 |
| Pain - Musculoskeletal - Extremity- limb subjects affected / exposed occurrences (all) | 2 / 158 (1.27%) 7 | 2 / 158 (1.27%) 5 | 7 / 156 (4.49%) 26 |
| Infections and infestations Infection - Other subjects affected / exposed occurrences (all) | 6 / 158 (3.80%) 22 | 2 / 158 (1.27%) 2 | 2 / 156 (1.28%) 2 |
| Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) | 7 / 158 (4.43%) 21 | 7 / 158 (4.43%) 11 | 7 / 156 (4.49%) 15 |
| Metabolic/Laboratory - Other | | | |

| | | | |
|---|-----------------------|-----------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 3 / 158 (1.90%) 10 | 3 / 158 (1.90%) 9 | 7 / 156 (4.49%) 20 |
| Weight loss subjects affected / exposed occurrences (all) | 8 / 158 (5.06%) 29 | 6 / 158 (3.80%) 12 | 7 / 156 (4.49%) 19 |

| Non-serious adverse events | Induction period | Arm 1 Re-Induction | Arm 2 Re-Induction |
|--|----------------------------|------------------------|-------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 825 / 825 (100.00%) | 25 / 33 (75.76%) | 61 / 67 (91.04%) |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 137 / 825 (16.61%) 403 | 3 / 33 (9.09%) 10 | 10 / 67 (14.93%) 40 |
| Nervous system disorders Neurology - Other subjects affected / exposed occurrences (all) | 46 / 825 (5.58%) 126 | 4 / 33 (12.12%) 15 | 2 / 67 (2.99%) 6 |
| Neuropathy: sensory subjects affected / exposed occurrences (all) | 524 / 825 (63.52%) 2107 | 13 / 33 (39.39%) 64 | 47 / 67 (70.15%) 210 |
| Pain - Neurology - Head/headache subjects affected / exposed occurrences (all) | 40 / 825 (4.85%) 67 | 2 / 33 (6.06%) 2 | 0 / 67 (0.00%) 0 |
| Blood and lymphatic system disorders Bilirubin (hyperbilirubinemia) subjects affected / exposed occurrences (all) | 12 / 825 (1.45%) 27 | 1 / 33 (3.03%) 1 | 5 / 67 (7.46%) 10 |
| Blood/Bone Marrow - Other subjects affected / exposed occurrences (all) | 21 / 825 (2.55%) 53 | 2 / 33 (6.06%) 4 | 0 / 67 (0.00%) 0 |
| Hemoglobin subjects affected / exposed occurrences (all) | 83 / 825 (10.06%) 229 | 1 / 33 (3.03%) 3 | 10 / 67 (14.93%) 40 |
| Leukocytes (total WBC) subjects affected / exposed occurrences (all) | 133 / 825 (16.12%) 323 | 1 / 33 (3.03%) 1 | 8 / 67 (11.94%) 21 |
| Neutrophils/granulocytes (ANC/AGC) | | | |

| | | | |
|--|---------------------------|-----------------------|------------------------|
| subjects affected / exposed occurrences (all) | 116 / 825 (14.06%) 262 | 3 / 33 (9.09%) 5 | 3 / 67 (4.48%) 5 |
| Platelets subjects affected / exposed occurrences (all) | 122 / 825 (14.79%) 317 | 4 / 33 (12.12%) 14 | 14 / 67 (20.90%) 53 |
| General disorders and administration site conditions | | | |
| Constitutional Symptoms - Other subjects affected / exposed occurrences (all) | 92 / 825 (11.15%) 217 | 1 / 33 (3.03%) 7 | 5 / 67 (7.46%) 16 |
| Fatigue (asthenia, lethargy, malaise) subjects affected / exposed occurrences (all) | 288 / 825 (34.91%) 965 | 7 / 33 (21.21%) 19 | 15 / 67 (22.39%) 54 |
| Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L) subjects affected / exposed occurrences (all) | 49 / 825 (5.94%) 67 | 1 / 33 (3.03%) 2 | 4 / 67 (5.97%) 5 |
| Pain - Other subjects affected / exposed occurrences (all) | 51 / 825 (6.18%) 103 | 1 / 33 (3.03%) 7 | 3 / 67 (4.48%) 8 |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 101 / 825 (12.24%) 221 | 3 / 33 (9.09%) 9 | 1 / 67 (1.49%) 1 |
| Diarrhea subjects affected / exposed occurrences (all) | 259 / 825 (31.39%) 605 | 5 / 33 (15.15%) 18 | 7 / 67 (10.45%) 15 |
| Gastrointestinal - Other subjects affected / exposed occurrences (all) | 92 / 825 (11.15%) 204 | 3 / 33 (9.09%) 17 | 3 / 67 (4.48%) 14 |
| Mucositis/stomatitis (clinical exam) subjects affected / exposed occurrences (all) | 40 / 825 (4.85%) 125 | 1 / 33 (3.03%) 2 | 4 / 67 (5.97%) 13 |
| Mucositis/stomatitis (clinical exam) - Oral cavity subjects affected / exposed occurrences (all) | 94 / 825 (11.39%) 209 | 0 / 33 (0.00%) 0 | 6 / 67 (8.96%) 7 |

| | | | |
|--|--------------------|-----------------|----------------|
| Nausea | | | |
| subjects affected / exposed | 268 / 825 (32.48%) | 7 / 33 (21.21%) | 5 / 67 (7.46%) |
| occurrences (all) | 718 | 27 | 16 |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 53 / 825 (6.42%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 95 | 0 | 2 |
| Taste alteration (dysgeusia) | | | |
| subjects affected / exposed | 44 / 825 (5.33%) | 0 / 33 (0.00%) | 1 / 67 (1.49%) |
| occurrences (all) | 138 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 130 / 825 (15.76%) | 1 / 33 (3.03%) | 5 / 67 (7.46%) |
| occurrences (all) | 219 | 1 | 8 |
| Hepatobiliary disorders | | | |
| AST, SGOT(serum glutamic oxaloacetic transaminase) | | | |
| subjects affected / exposed | 17 / 825 (2.06%) | 0 / 33 (0.00%) | 5 / 67 (7.46%) |
| occurrences (all) | 41 | 0 | 15 |
| GGT (gamma-Glutamyl transpeptidase) | | | |
| subjects affected / exposed | 2 / 825 (0.24%) | 1 / 33 (3.03%) | 4 / 67 (5.97%) |
| occurrences (all) | 7 | 1 | 16 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 41 / 825 (4.97%) | 1 / 33 (3.03%) | 4 / 67 (5.97%) |
| occurrences (all) | 61 | 1 | 12 |
| Dyspnea (shortness of breath) | | | |
| subjects affected / exposed | 59 / 825 (7.15%) | 4 / 33 (12.12%) | 2 / 67 (2.99%) |
| occurrences (all) | 145 | 6 | 14 |
| Hemorrhage, pulmonary/upper respiratory - Nose | | | |
| subjects affected / exposed | 72 / 825 (8.73%) | 1 / 33 (3.03%) | 3 / 67 (4.48%) |
| occurrences (all) | 176 | 3 | 9 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatology/Skin - Other | | | |
| subjects affected / exposed | 61 / 825 (7.39%) | 3 / 33 (9.09%) | 3 / 67 (4.48%) |
| occurrences (all) | 140 | 9 | 13 |
| Hair loss/alopecia (scalp or body) | | | |

| | | | |
|---|--------------------------|-----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 86 / 825 (10.42%) 299 | 0 / 33 (0.00%) 0 | 3 / 67 (4.48%) 11 |
| Rash: hand-foot skin reaction subjects affected / exposed occurrences (all) | 57 / 825 (6.91%) 159 | 5 / 33 (15.15%) 30 | 4 / 67 (5.97%) 17 |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal/Soft Tissue - Other subjects affected / exposed occurrences (all) | 24 / 825 (2.91%) 37 | 0 / 33 (0.00%) 0 | 4 / 67 (5.97%) 10 |
| Pain - Musculoskeletal - Back subjects affected / exposed occurrences (all) | 26 / 825 (3.15%) 61 | 3 / 33 (9.09%) 9 | 3 / 67 (4.48%) 19 |
| Pain - Musculoskeletal - Bone subjects affected / exposed occurrences (all) | 25 / 825 (3.03%) 52 | 2 / 33 (6.06%) 7 | 2 / 67 (2.99%) 3 |
| Pain - Musculoskeletal - Extremity- limb subjects affected / exposed occurrences (all) | 23 / 825 (2.79%) 44 | 1 / 33 (3.03%) 1 | 5 / 67 (7.46%) 14 |
| Infections and infestations | | | |
| Infection - Other subjects affected / exposed occurrences (all) | 53 / 825 (6.42%) 90 | 1 / 33 (3.03%) 4 | 0 / 67 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Anorexia subjects affected / exposed occurrences (all) | 79 / 825 (9.58%) 182 | 0 / 33 (0.00%) 0 | 4 / 67 (5.97%) 8 |
| Metabolic/Laboratory - Other subjects affected / exposed occurrences (all) | 21 / 825 (2.55%) 82 | 0 / 33 (0.00%) 0 | 4 / 67 (5.97%) 16 |
| Weight loss subjects affected / exposed occurrences (all) | 70 / 825 (8.48%) 190 | 1 / 33 (3.03%) 3 | 3 / 67 (4.48%) 15 |

| | | | |
|--|--------------------|--|--|
| Non-serious adverse events | Arm 3 Re-Induction | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 69 / 74 (93.24%) | | |

| | | | |
|--|--|--|--|
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 10 / 74 (13.51%) 47 | | |
| Nervous system disorders Neurology - Other subjects affected / exposed occurrences (all) Neuropathy: sensory subjects affected / exposed occurrences (all) Pain - Neurology - Head/headache subjects affected / exposed occurrences (all) | 3 / 74 (4.05%) 11 57 / 74 (77.03%) 284 1 / 74 (1.35%) 3 | | |
| Blood and lymphatic system disorders Bilirubin (hyperbilirubinemia) subjects affected / exposed occurrences (all) Blood/Bone Marrow - Other subjects affected / exposed occurrences (all) Hemoglobin subjects affected / exposed occurrences (all) Leukocytes (total WBC) subjects affected / exposed occurrences (all) Neutrophils/granulocytes (ANC/AGC) subjects affected / exposed occurrences (all) Platelets subjects affected / exposed occurrences (all) | 0 / 74 (0.00%) 0 1 / 74 (1.35%) 2 6 / 74 (8.11%) 22 7 / 74 (9.46%) 18 3 / 74 (4.05%) 5 6 / 74 (8.11%) 8 | | |
| General disorders and administration site conditions Constitutional Symptoms - Other | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 6 / 74 (8.11%) | | |
| occurrences (all) | 15 | | |
| Fatigue (asthenia, lethargy, malaise) | | | |
| subjects affected / exposed | 21 / 74 (28.38%) | | |
| occurrences (all) | 83 | | |
| Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L) | | | |
| subjects affected / exposed | 1 / 74 (1.35%) | | |
| occurrences (all) | 1 | | |
| Pain - Other | | | |
| subjects affected / exposed | 7 / 74 (9.46%) | | |
| occurrences (all) | 9 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | | |
| occurrences (all) | 7 | | |
| Diarrhea | | | |
| subjects affected / exposed | 13 / 74 (17.57%) | | |
| occurrences (all) | 24 | | |
| Gastrointestinal - Other | | | |
| subjects affected / exposed | 2 / 74 (2.70%) | | |
| occurrences (all) | 3 | | |
| Mucositis/stomatitis (clinical exam) | | | |
| subjects affected / exposed | 3 / 74 (4.05%) | | |
| occurrences (all) | 7 | | |
| Mucositis/stomatitis (clinical exam) - Oral cavity | | | |
| subjects affected / exposed | 5 / 74 (6.76%) | | |
| occurrences (all) | 14 | | |
| Nausea | | | |
| subjects affected / exposed | 14 / 74 (18.92%) | | |
| occurrences (all) | 29 | | |
| Pain - Gastrointestinal - Abdomen NOS | | | |
| subjects affected / exposed | 9 / 74 (12.16%) | | |
| occurrences (all) | 21 | | |
| Taste alteration (dysgeusia) | | | |

| | | | |
|---|-----------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | | |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 6 | | |
| Hepatobiliary disorders AST, SGOT (serum glutamic oxaloacetic transaminase) subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | | |
| GGT (gamma-Glutamyl transpeptidase) subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 2 | | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | | |
| Dyspnea (shortness of breath) subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 15 | | |
| Hemorrhage, pulmonary/upper respiratory - Nose subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 28 | | |
| Skin and subcutaneous tissue disorders Dermatology/Skin - Other subjects affected / exposed occurrences (all) | 6 / 74 (8.11%) 18 | | |
| Hair loss/alopecia (scalp or body) subjects affected / exposed occurrences (all) | 7 / 74 (9.46%) 25 | | |
| Rash: hand-foot skin reaction subjects affected / exposed occurrences (all) | 8 / 74 (10.81%) 27 | | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|----------------------|--|--|
| Musculoskeletal/Soft Tissue - Other subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 10 | | |
| Pain - Musculoskeletal - Back subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 1 | | |
| Pain - Musculoskeletal - Bone subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 8 | | |
| Pain - Musculoskeletal - Extremity- limb subjects affected / exposed occurrences (all) | 1 / 74 (1.35%) 3 | | |
| Infections and infestations Infection - Other subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 2 | | |
| Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all) | 5 / 74 (6.76%) 13 | | |
| Metabolic/Laboratory - Other subjects affected / exposed occurrences (all) | 2 / 74 (2.70%) 3 | | |
| Weight loss subjects affected / exposed occurrences (all) | 4 / 74 (5.41%) 20 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 13 April 2010 | Correction of several errors and further specification of technical details, mainly on samples for translational studies. |
| 29 June 2012 | Adjustment of the sample size to be recruited front-line into the study, as the proportion of patients qualifying for randomization after induction therapy was smaller than initially expected. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26361971>

<http://www.ncbi.nlm.nih.gov/pubmed/30036739>

<http://www.ncbi.nlm.nih.gov/pubmed/27753609>