



Clinical trial results:

Open-label, multi-center, randomized, phase II study evaluating the addition of bevacizumab to chemotherapy in childhood and adolescent patients presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma

Summary

| | |
|--------------------------|---|
| EudraCT number | 2007-005017-19 |
| Trial protocol | GB FR NL IT BE ES PL DE CZ Outside EU/EEA |
| Global end of trial date | 30 April 2019 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 |
| This version publication date | 26 October 2019 |
| First version publication date | 07 August 2016 |
| Version creation reason | <ul style="list-style-type: none">New data added to full data set Final Results Disclosure |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | BO20924 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00643565 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000056-PIP01-07 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 April 2019 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 30 April 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

An open-label, multi-center, randomized, Phase 2 study designed to evaluate the benefit of the addition of bevacizumab to chemotherapy in participants presenting with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 29 July 2008 |
| 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 | Netherlands: 7 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Spain: 11 |
| Country: Number of subjects enrolled | United Kingdom: 35 |
| Country: Number of subjects enrolled | Belgium: 8 |
| Country: Number of subjects enrolled | France: 59 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | Italy: 20 |
| Country: Number of subjects enrolled | Brazil: 2 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Chile: 1 |
| Country: Number of subjects enrolled | Switzerland: 2 |
| Worldwide total number of subjects | 154 |
| EEA total number of subjects | 146 |

Notes:

Subjects enrolled per age group

| | |
|--|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 | 0 |

| | |
|--|----|
| wk | |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 6 |
| Children (2-11 years) | 77 |
| Adolescents (12-17 years) | 71 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with metastatic rhabdomyosarcoma and non-rhabdomyosarcoma soft tissue sarcoma underwent screening assessments. An eligibility screening form was completed documenting the investigator's assessment of each screened participant with regard to inclusion and exclusion criteria. A screening failure log was maintained by the investigator.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Chemotherapy |

Arm description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

| | |
|--|---------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Ifosfamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received ifosfamide at 3 grams per square meter (g/m^2) on Day 1 and Day 2 of each cycle for the first 9 cycles only.

| | |
|--|---------------------------------|
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received vincristine at 1.5 milligrams per square meter (mg/m^2) (maximum single dose of 2 mg) every week for first 7 weeks and then on Day 1 of each cycle up to Cycle 9.

| | |
|--|---------------------------------|
| Investigational medicinal product name | Actinomycin D |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received actinomycin D at 1.5 mg/m^2 (maximum single dose of 2 mg) on Day 1 of each cycle for the first 9 cycles only.

| | |
|---|---------------------------------------|
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received doxorubicin at 30 mg/m ² on Day 1 and Day 2 from Cycles 1 to 4 only. | |
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received vinorelbine at 25 mg/m ² on Days 1, 8, and 15 of each cycle for 12 cycles of maintenance therapy phase. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Participants received cyclophosphamide at 25 mg/m ² every day for the entire duration of the cycle (i.e. 28 days). | |
| Arm title | Bevacizumab + Chemotherapy |
| Arm description: | |
| Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles. | |
| Arm type | Experimental |
| Investigational medicinal product name | Bevacizumab |
| Investigational medicinal product code | RO4876646 |
| Other name | Avastin |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received IV infusion of bevacizumab at 7.5 mg/kg every 3 weeks in 3-week cycles for 9 cycles during induction treatment phase and at 5 mg/kg every 2 weeks in 4-weeks cycles for a total of 12 weeks. | |
| Investigational medicinal product name | Ifosfamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received ifosfamide at 3 g/m ² on Day 1 and Day 2 of each cycle for the first 9 cycles only. | |
| Investigational medicinal product name | Vincristine |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|---------------------------------|
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received vincristine at 1.5 mg/m ² (maximum single dose of 2 mg) every week for first 7 weeks and then on Day 1 of each cycle up to Cycle 9. | |
| Investigational medicinal product name | Actinomycin D |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received actinomycin D at 1.5 mg/m ² (maximum single dose of 2 mg) on Day 1 of each cycle for the first 9 cycles only. | |
| Investigational medicinal product name | Doxorubicin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received doxorubicin at 30 mg/m ² on Day 1 and Day 2 from Cycles 1 to 4 only. | |
| Investigational medicinal product name | Vinorelbine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for injection/infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| Participants received vinorelbine at 25 mg/m ² on Days 1, 8, and 15 of each cycle for 12 cycles of maintenance therapy phase. | |
| Investigational medicinal product name | Cyclophosphamide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| Participants received cyclophosphamide at 25 mg/m ² every day for the entire duration of the cycle (i.e. 28 days). | |

| Number of subjects in period 1 | Chemotherapy | Bevacizumab + Chemotherapy |
|---------------------------------------|--------------|----------------------------|
| Started | 80 | 74 |
| Completed | 7 | 7 |
| Not completed | 73 | 67 |
| Consent withdrawn by subject | 4 | 1 |
| Adverse event, non-fatal | 5 | 8 |
| Death | 12 | 11 |
| Refused Treat/Did Not Cooperate | - | 1 |
| Did Not Cooperate | - | 1 |
| Unknown | 7 | 8 |

| | | |
|------------------------|----|----|
| Progression Of Disease | 18 | 14 |
| Administrative/Other | 22 | 16 |
| Lost to follow-up | - | 6 |
| Recurrence Of Disease | 2 | 1 |
| Protocol deviation | 3 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Chemotherapy |
|-----------------------|----------------------------|

Reporting group description:

Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

| Reporting group values | Chemotherapy | Bevacizumab + Chemotherapy | Total |
|--|--------------|----------------------------|-------|
| Number of subjects | 80 | 74 | 154 |
| Age categorical Units: Subjects | | | |
| Infants and toddlers (28 days-23 months) | 3 | 3 | 6 |
| Children (2-11 years) | 39 | 38 | 77 |
| Adolescents (12-17 years) | 38 | 33 | 71 |
| Age continuous Units: years | | | |
| arithmetic mean | 10.5 | 10.3 | |
| standard deviation | ± 4.8 | ± 4.9 | - |
| Gender categorical Units: Subjects | | | |
| Female | 40 | 29 | 69 |
| Male | 40 | 45 | 85 |

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy i.e. with ifosfamide [I], vincristine [V], actinomycin D [A] and doxorubicin [Do] followed by 5 cycles of IVA-containing chemotherapy [i.e. without doxorubicin]) administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Chemotherapy |
|-----------------------|----------------------------|

Reporting group description:

Participants received continuous intravenous (IV) infusion of bevacizumab (7.5 milligrams per kilogram [mg/kg] every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4 cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

Primary: Percentage of Participants Who Experienced Event-Free Survival (EFS) Events as Per Independent Review Committee (IRC) Assessment

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Experienced Event-Free Survival (EFS) Events as Per Independent Review Committee (IRC) Assessment ^[1] |
|-----------------|---|

End point description:

EFS events included tumor progression (IRC assessed), no evidence of response after 3 cycles of induction (derived from IRC assessment), second primary cancer, or death due to any cause. Data for participants who had not experienced an event by the time of clinical cut-off were censored at the date of the last disease assessment prior to the clinical cut-off date. Data for participants who did not have any post-baseline disease assessments were censored at the time of randomization. Tumor progression was defined using Response Evaluation Criteria in Solid Tumors version 1.0 (RECIST v1.0) as at least a 20 percent (%) increase in the disease measurement, taking as reference the smallest disease measurement recorded since the start of treatment, or appearance of one or more new lesions, or evidence of clinical progression and unequivocal progression of existing non-target lesions. Intent-to-treat (ITT) population included all participants randomized to the treatment group in the study

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

End point timeframe:

Screening up to approximately 6.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years)

Notes:

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

Justification: No statistical analysis was planned for this endpoint.

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|-----------------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 74 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 52.5 | 68.9 | | |

Statistical analyses

No statistical analyses for this end point

Primary: EFS Duration as Per IRC Assessment

| | |
|---|------------------------------------|
| End point title | EFS Duration as Per IRC Assessment |
| End point description: | |
| EFS was defined as the time between randomization and occurrence of EFS event (described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC"). Median EFS was estimated using Kaplan-Meier estimates and 95% confidence intervals (CI) for median was computed using the method of Brookmeyer and Crowley. ITT population. | |
| End point type | Primary |
| End point timeframe: | |
| Screening up to approximately 6.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years) | |

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|----------------------------------|------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 74 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 14.85 (10.84 to 35.88) | 20.63 (15.15 to 24.87) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | EFS Duration as Per IRC Assessment |
| Comparison groups | Chemotherapy v Bevacizumab + Chemotherapy |
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7189 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.41 |

Notes:

[2] - The HR was calculated based on a stratified Cox proportional hazards model, with stratification factors of age and histology/disease risk.

Secondary: Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria

| | |
|-----------------|--|
| End point title | Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria |
|-----------------|--|

End point description:

Objective response prior to first local therapy (surgery and/or radiotherapy) was defined as complete response (CR) or partial response (PR) determined on two consecutive occasions greater than equal to (\geq) 4 weeks apart. Tumor response were assessed as per IRC using RECIST 1.0. CR was defined as disappearance of all target and non-target lesions. If immunocytology was available, no disease was to be detected by that methodology. PR was defined as at least a 30% decrease in the disease measurement, taking as reference the disease measurement done to confirm measurable disease at study entry. ITT population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening up to end approximately 6.75 years

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|-----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 74 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 36 (25.23 to 47.91) | 54 (40.94 to 66.61) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Experienced EFS Events Among Participants Who Had Objective Response

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Experienced EFS Events Among Participants Who Had Objective Response |
|-----------------|---|

End point description:

EFS events was described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC" and in endpoint "Percentage of Participants with Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria". ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome measure.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Screening up to end approximately 6.75 years

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|-----------------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 34 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 40.7 | 76.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|---|----------------------|
| End point title | Duration of Response |
| End point description: | |
| Duration of Response was defined as the time between first objective response and the occurrence of an EFS event (described in endpoint "Percentage of Participants Who Experienced EFS Events as Per IRC"). Objective response is defined in Outcome Measure "Percentage of Participants With Objective Response Prior to First Local Therapy Assessed by RECIST v1.0 Criteria". Median duration of response was estimated using Kaplan-Meier estimates and 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT population. Here, number of participants analyzed = participants who were evaluable for this outcome measure. Here, "99.9" and "999.9" was used as median and upper limit of 95% CI, respectively, as data was not estimable because of higher number (more than 50%) of censored participants in this arm group. | |
| End point type | Secondary |
| End point timeframe: | |
| Screening up to end approximately 6.75 years | |

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|----------------------------------|-----------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 34 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99.9 (10.18 to 999.9) | 17.48 (12.29 to 25.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died

| | |
|------------------------|-------------------------------------|
| End point title | Percentage of Participants Who Died |
| End point description: | |
| ITT population. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Screening up to approximately 10.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years. | |

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|-----------------------------------|-----------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 74 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 50 | 51.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival Duration

| | |
|--|---------------------------|
| End point title | Overall Survival Duration |
| End point description: | |
| Overall survival was defined as the time between randomization and death due to any cause. Participants without an event were censored at the last time they were known to be alive. Median overall survival was estimated using Kaplan-Meier estimates and 95% CI for median was computed using the method of Brookmeyer and Crowley. ITT population. Here number of participants analyzed = participants available for the analysis of this outcome measure. Here, "999" was used as upper limit of 95% CI, which was not estimable because of higher number (more than 50%) of censored participants in this arm group. | |
| End point type | Secondary |
| End point timeframe: | |
| Screening up to approximately 10.75 years (assessed at screening, Cycles 4, 7 of induction phase, Cycles 1, 4, 7, 10 of maintenance, then every 3 months for 1.5 years and thereafter every 6 months for 2.5 years) | |

| End point values | Chemotherapy | Bevacizumab + Chemotherapy | | |
|----------------------------------|----------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 74 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 24.02 (17.97 to 999) | 32.79 (25.33 to 999) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Chemotherapy, Bevacizumab + Chemotherapy |
| Comparison groups | Chemotherapy v Bevacizumab + Chemotherapy |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 154 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3211 ^[3] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.25 |

Notes:

[3] - The HR was calculated based on a stratified Cox proportional hazards model, with stratification factors of age and histology/disease risk.

Secondary: Area Under the Curve at Steady State (AUCss) of Bevacizumab

| | |
|-----------------|---|
| End point title | Area Under the Curve at Steady State (AUCss) of |
|-----------------|---|

End point description:

AUC is a measure of the serum concentration of the drug over time. It is used to characterize drug absorption. AUCss is expressed in milligrams times days per milliliter (mg*day/mL). Pharmacokinetic (PK)-evaluable population included all randomized participants for whom at least one blood sample was taken for PK assessment following bevacizumab administration. Only participants who received bevacizumab were to be analyzed for PK assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

| End point values | Bevacizumab + Chemotherapy | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 70 | | | |
| Units: mg*day/mL | | | | |
| arithmetic mean (standard deviation) | 1010 (± 256) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution of Bevacizumab

| | |
|-----------------|--|
| End point title | Volume of Distribution of Bevacizumab ^[5] |
|-----------------|--|

End point description:

Volume of distribution is defined as the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

| | | | | |
|--------------------------------------|----------------------------|--|--|--|
| End point values | Bevacizumab + Chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 70 | | | |
| Units: mL | | | | |
| arithmetic mean (standard deviation) | 2070 (± 891) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life of Bevacizumab

| | |
|-----------------|---|
| End point title | Half-Life of Bevacizumab ^[6] |
|-----------------|---|

End point description:

Half-life is the time measured for the plasma concentration to decrease by one half. PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

| | | | | |
|--------------------------------------|----------------------------|--|--|--|
| End point values | Bevacizumab + Chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 70 | | | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 20.8 (± 8.58) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of Bevacizumab

| | |
|-----------------|--|
| End point title | Clearance (CL) of Bevacizumab ^[7] |
|-----------------|--|

End point description:

CL is a quantitative measure of the rate at which a drug substance is removed from the body. CL is expressed in milliliters per day (mL/day). PK-evaluable population. Only participants who received bevacizumab were to be analyzed for PK assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre- and within 3 hours post-dose on Days 1, 8, and 15 of Cycle 1, Day 1 of Cycle 2-4 of induction phase (1 cycle = 3 weeks)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The PK data were analyzed for bevacizumab, which was not administered to Chemotherapy arm group.

| | | | | |
|--------------------------------------|----------------------------|--|--|--|
| End point values | Bevacizumab + Chemotherapy | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 70 | | | |
| Units: mL/day | | | | |
| arithmetic mean (standard deviation) | 167 (\pm 76.4) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening up to approximately 10.75 years

Adverse event reporting additional description:

The safety-evaluable population included all randomized participants who received any dose of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | Chemotherapy |
|-----------------------|--------------|

Reporting group description:

Participants received 9 cycles of induction chemotherapy (4 cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy administered every 3 weeks as per institutional practice. As per the investigator evaluation, participants had option to undergo local therapy (radiotherapy and/or surgery) during last 3 cycles of IVA (i.e. from Cycle 6 to Cycle 9). During maintenance treatment phase, participants received vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Day 1 and 15 of 4-week cycles for a total of 12 cycles.

| | |
|-----------------------|----------------------------|
| Reporting group title | Bevacizumab + Chemotherapy |
|-----------------------|----------------------------|

Reporting group description:

Participants received continuous IV infusion of bevacizumab (7.5 mg/kg every 3 weeks) on Day 1 of 3-week cycles followed by induction chemotherapy (4 cycles of IVADo-containing chemotherapy followed by 5 cycles of IVA-containing chemotherapy) as per institutional practice for a total of 9 cycles during induction treatment phase. As per the investigator decision, local therapy (radiotherapy and/or surgery) was expected to start after 4 weeks of the last bevacizumab administration in the induction phase and resumed to bevacizumab in maintenance phase at least 4 weeks after the last dose of local therapy. During maintenance treatment phase, participants received IV infusion of bevacizumab (5 mg/kg every 2 weeks) followed by vinorelbine- and cyclophosphamide-containing chemotherapy (as per institutional practice) on Days 1 and 15 of 4-week cycles for a total of 12 cycles.

| Serious adverse events | Chemotherapy | Bevacizumab + Chemotherapy | |
|---|------------------|----------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 68 / 79 (86.08%) | 66 / 71 (92.96%) | |
| number of deaths (all causes) | 40 | 37 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour necrosis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jugular vein thrombosis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Microangiopathy | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venoocclusive disease | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Central venous catheter removal | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Face oedema | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|------------------|------------------|--|
| Mucosal inflammation | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 10 / 71 (14.08%) | |
| occurrences causally related to treatment / all | 14 / 14 | 18 / 18 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 15 / 79 (18.99%) | 14 / 71 (19.72%) | |
| occurrences causally related to treatment / all | 19 / 26 | 3 / 14 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombosis in device | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Erectile dysfunction | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Asthma | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoventilation | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device malfunction | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Candida test positive | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil toxic granulation present | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 5 / 71 (7.04%) | |
| occurrences causally related to treatment / all | 2 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Foot fracture | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural pneumothorax | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Post procedural haematoma subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular procedure complication subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Recall phenomenon subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Torus fracture subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tracheostomy malfunction subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular access complication subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound dehiscence subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Fanconi syndrome subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Cardiac disorders | | | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiotoxicity | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular arrhythmia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Facial nerve disorder | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurotoxicity | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Seizure | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic encephalopathy | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vocal cord paresis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 8 / 8 | 7 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 9 / 79 (11.39%) | 19 / 71 (26.76%) | |
| occurrences causally related to treatment / all | 24 / 24 | 49 / 49 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 47 / 79 (59.49%) | 46 / 71 (64.79%) | |
| occurrences causally related to treatment / all | 134 / 135 | 120 / 120 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 4 / 4 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Eyelid oedema | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal fissure | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anal inflammation | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal inflammation | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal obstruction | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus paralytic | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 71 (4.23%) | |
| occurrences causally related to treatment / all | 5 / 5 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 8 / 71 (11.27%) | |
| occurrences causally related to treatment / all | 7 / 8 | 10 / 10 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin disorder | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder necrosis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proteinuria | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal abscess | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candida sepsis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis bacterial | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 3 / 71 (4.23%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 3 / 71 (4.23%) | |
| occurrences causally related to treatment / all | 4 / 8 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Salmonellosis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Soft tissue infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Varicella | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vulvitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 71 (1.41%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic infection | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 4 / 4 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular Device Infection | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 4 / 71 (5.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Electrolyte imbalance | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 71 (2.82%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 71 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Chemotherapy | Bevacizumab + Chemotherapy | |
|---|------------------|-------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 78 / 79 (98.73%) | 71 / 71 (100.00%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 71 (5.63%) | |
| occurrences (all) | 3 | 5 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 17 / 71 (23.94%) | |
| occurrences (all) | 12 | 23 | |
| Chest pain | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 4 / 71 (5.63%) | |
| occurrences (all) | 7 | 4 | |
| Fatigue | | | |
| subjects affected / exposed | 16 / 79 (20.25%) | 18 / 71 (25.35%) | |
| occurrences (all) | 27 | 26 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 38 / 79 (48.10%) | 42 / 71 (59.15%) | |
| occurrences (all) | 54 | 74 | |
| Pain | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 5 / 71 (7.04%) | |
| occurrences (all) | 11 | 6 | |
| Pyrexia | | | |
| subjects affected / exposed | 33 / 79 (41.77%) | 27 / 71 (38.03%) | |
| occurrences (all) | 73 | 46 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 4 / 71 (5.63%) | |
| occurrences (all) | 1 | 5 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |

| | | | |
|-------------------------------------|------------------|------------------|--|
| subjects affected / exposed | 13 / 79 (16.46%) | 19 / 71 (26.76%) | |
| occurrences (all) | 20 | 29 | |
| Epistaxis | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 23 / 71 (32.39%) | |
| occurrences (all) | 10 | 57 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 9 / 71 (12.68%) | |
| occurrences (all) | 10 | 11 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 4 / 71 (5.63%) | |
| occurrences (all) | 6 | 7 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 9 / 71 (12.68%) | |
| occurrences (all) | 7 | 9 | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 5 / 71 (7.04%) | |
| occurrences (all) | 2 | 5 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 6 / 71 (8.45%) | |
| occurrences (all) | 2 | 7 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 4 / 71 (5.63%) | |
| occurrences (all) | 3 | 5 | |
| Haemoglobin decreased | | | |
| subjects affected / exposed | 13 / 79 (16.46%) | 7 / 71 (9.86%) | |
| occurrences (all) | 27 | 18 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 71 (4.23%) | |
| occurrences (all) | 7 | 15 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 4 / 71 (5.63%) | |
| occurrences (all) | 13 | 13 | |
| Weight decreased | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 27 / 79 (34.18%) 31 | 22 / 71 (30.99%) 26 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 3 | 4 / 71 (5.63%) 6 | |
| Injury, poisoning and procedural complications | | | |
| Procedural pain subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 7 / 71 (9.86%) 8 | |
| Radiation skin injury subjects affected / exposed occurrences (all) | 12 / 79 (15.19%) 12 | 8 / 71 (11.27%) 9 | |
| Radiation Injury subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 4 / 71 (5.63%) 4 | |
| Cardiac disorders | | | |
| Left ventricular dysfunction subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 5 / 71 (7.04%) 5 | |
| Tachycardia subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 1 / 71 (1.41%) 1 | |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 6 / 79 (7.59%) 7 | 7 / 71 (9.86%) 8 | |
| Headache subjects affected / exposed occurrences (all) | 16 / 79 (20.25%) 23 | 32 / 71 (45.07%) 49 | |
| Neuralgia subjects affected / exposed occurrences (all) | 5 / 79 (6.33%) 6 | 2 / 71 (2.82%) 2 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 2 | 9 / 71 (12.68%) 10 | |
| Paraesthesia | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 79 (3.80%) 3 | 6 / 71 (8.45%) 6 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 2 / 79 (2.53%) 3 | 5 / 71 (7.04%) 6 | |
| Polyneuropathy subjects affected / exposed occurrences (all) | 1 / 79 (1.27%) 1 | 4 / 71 (5.63%) 4 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 50 / 79 (63.29%) 141 | 55 / 71 (77.46%) 128 | |
| Febrile neutropenia subjects affected / exposed occurrences (all) | 14 / 79 (17.72%) 23 | 12 / 71 (16.90%) 16 | |
| Leukopenia subjects affected / exposed occurrences (all) | 11 / 79 (13.92%) 30 | 13 / 71 (18.31%) 36 | |
| Neutropenia subjects affected / exposed occurrences (all) | 53 / 79 (67.09%) 244 | 56 / 71 (78.87%) 264 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 37 / 79 (46.84%) 116 | 31 / 71 (43.66%) 101 | |
| Ear and labyrinth disorders | | | |
| Ear pain subjects affected / exposed occurrences (all) | 4 / 79 (5.06%) 4 | 5 / 71 (7.04%) 6 | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 27 / 79 (34.18%) 43 | 31 / 71 (43.66%) 58 | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 8 / 79 (10.13%) 10 | 8 / 71 (11.27%) 12 | |
| Anal fissure | | | |

| | | | |
|--|------------------|------------------|--|
| subjects affected / exposed | 5 / 79 (6.33%) | 13 / 71 (18.31%) | |
| occurrences (all) | 7 | 15 | |
| Anal inflammation | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 6 / 71 (8.45%) | |
| occurrences (all) | 7 | 7 | |
| Constipation | | | |
| subjects affected / exposed | 40 / 79 (50.63%) | 48 / 71 (67.61%) | |
| occurrences (all) | 61 | 95 | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 79 (34.18%) | 30 / 71 (42.25%) | |
| occurrences (all) | 54 | 56 | |
| Dyspepsia | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 4 / 71 (5.63%) | |
| occurrences (all) | 5 | 4 | |
| Mouth ulceration | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 71 (4.23%) | |
| occurrences (all) | 4 | 3 | |
| Nausea | | | |
| subjects affected / exposed | 42 / 79 (53.16%) | 44 / 71 (61.97%) | |
| occurrences (all) | 146 | 145 | |
| Oral pain | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 2 / 71 (2.82%) | |
| occurrences (all) | 6 | 2 | |
| Stomatitis | | | |
| subjects affected / exposed | 23 / 79 (29.11%) | 15 / 71 (21.13%) | |
| occurrences (all) | 29 | 21 | |
| Vomiting | | | |
| subjects affected / exposed | 61 / 79 (77.22%) | 64 / 71 (90.14%) | |
| occurrences (all) | 186 | 202 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 4 / 71 (5.63%) | |
| occurrences (all) | 1 | 4 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 22 / 79 (27.85%) | 17 / 71 (23.94%) | |
| occurrences (all) | 23 | 18 | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 5 / 71 (7.04%) | |
| occurrences (all) | 2 | 6 | |
| Erythema | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 12 / 71 (16.90%) | |
| occurrences (all) | 7 | 13 | |
| Pruritus | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 10 / 71 (14.08%) | |
| occurrences (all) | 7 | 14 | |
| Rash | | | |
| subjects affected / exposed | 10 / 79 (12.66%) | 5 / 71 (7.04%) | |
| occurrences (all) | 13 | 6 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 7 / 71 (9.86%) | |
| occurrences (all) | 3 | 10 | |
| Haematuria | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 8 / 71 (11.27%) | |
| occurrences (all) | 3 | 9 | |
| Proteinuria | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 4 / 71 (5.63%) | |
| occurrences (all) | 6 | 8 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 79 (10.13%) | 10 / 71 (14.08%) | |
| occurrences (all) | 10 | 15 | |
| Back pain | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 15 / 71 (21.13%) | |
| occurrences (all) | 8 | 23 | |
| Bone pain | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 4 / 71 (5.63%) | |
| occurrences (all) | 2 | 6 | |
| Myalgia | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 4 / 79 (5.06%) | 6 / 71 (8.45%) | |
| occurrences (all) | 4 | 9 | |
| Pain in extremity | | | |
| subjects affected / exposed | 16 / 79 (20.25%) | 20 / 71 (28.17%) | |
| occurrences (all) | 22 | 30 | |
| Pain in jaw | | | |
| subjects affected / exposed | 12 / 79 (15.19%) | 5 / 71 (7.04%) | |
| occurrences (all) | 14 | 5 | |
| Infections and infestations | | | |
| Candida infection | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 0 / 71 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 7 / 71 (9.86%) | |
| occurrences (all) | 5 | 7 | |
| Ear infection | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 6 / 71 (8.45%) | |
| occurrences (all) | 4 | 7 | |
| Herpes zoster | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 3 / 71 (4.23%) | |
| occurrences (all) | 4 | 3 | |
| Infection | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 5 / 71 (7.04%) | |
| occurrences (all) | 5 | 5 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 10 / 71 (14.08%) | |
| occurrences (all) | 8 | 15 | |
| Oral candidiasis | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 5 / 71 (7.04%) | |
| occurrences (all) | 11 | 7 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 5 / 71 (7.04%) | |
| occurrences (all) | 0 | 5 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 4 / 71 (5.63%) | |
| occurrences (all) | 0 | 5 | |

| | | | |
|------------------------------------|------------------|------------------|--|
| Rhinitis | | | |
| subjects affected / exposed | 6 / 79 (7.59%) | 12 / 71 (16.90%) | |
| occurrences (all) | 7 | 20 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 79 (8.86%) | 9 / 71 (12.68%) | |
| occurrences (all) | 13 | 13 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 8 / 71 (11.27%) | |
| occurrences (all) | 2 | 8 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 18 / 79 (22.78%) | 21 / 71 (29.58%) | |
| occurrences (all) | 21 | 27 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 18 / 79 (22.78%) | 8 / 71 (11.27%) | |
| occurrences (all) | 20 | 9 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 5 / 79 (6.33%) | 2 / 71 (2.82%) | |
| occurrences (all) | 5 | 2 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 4 / 71 (5.63%) | |
| occurrences (all) | 2 | 4 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 4 / 79 (5.06%) | 5 / 71 (7.04%) | |
| occurrences (all) | 5 | 7 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 05 March 2008 | Amended inclusion criteria as related to assessment of cardiac function and related sections as to cardiac toxicity, documenting the stress-velocity index information on smaller age ranges (less than [$<$] 1 year, versus 1 to 2 years, 2 to 3 years, >3 years). In healthy children less than 3 years of age, the minimal shortening fraction documented was between 35% and 45%, compared to between 28% and 38% for children aged 3 years and older. Adequate cardiac function at screen was redefined as shortening fraction (SF) $\geq 28\%$ for participants of at least 3 years of age, and SF $\geq 35\%$ for participants below 3 years of age. The diagnosis of congestive heart failure was redefined to include a decrease of SF below 28% for participants of at least 3 years of age and below 35% for participants below 3 years of age, or if the SF decreased by an absolute of ≥ 10 percentile points from the previous test. Dose modification guidelines for doxorubicin and bevacizumab in cases of treatment-emergent cardiotoxicity events were rewritten to included the redefinitions above. |
| 22 January 2009 | This amendment was done to describe study design and endpoints, radiological tumor assessment. Statistical analysis plan was amended to add the futility analysis which was performed on 80 participants who completed 6 cycles. Due to new requirements for safety follow-up after randomization that extended study duration by 4 years, and with the requirement that the events of the primary endpoint were to be assessed by magnetic resonance imaging and evaluated by a central independent image reviewing committee, the schedule of assessments and study procedures section were completely revised to provide clear guidance for treating physicians and to allow for a meaningful review of trial efficacy data. Amended the study population criteria. |
| 30 May 2011 | Updated with increased investigational site from 50 to 60. Updated with possibility of omission of the first two doses of bevacizumab (induction therapy Cycles 1 and 2) for participants who presented with a surgical wound, bone fracture, or bleeding related to tumor oozing not satisfactorily healed at randomization or transient clotting diathesis or transient obstructive renal failure that had not resolved at randomization. Updated randomization timeframe from 4 weeks to 3 weeks for participants who underwent a major surgical procedure or open biopsy, or had suffered from a significant traumatic injury or bone fracture prior to study entry. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported