



Clinical trial results:

An Open-label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects with Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301)

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2017-003344-21 |
| Trial protocol | DE ES BE AT DK GB NL PT IT |
| Global end of trial date | |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 |
| This version publication date | 07 July 2021 |
| First version publication date | 07 July 2021 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | 7465-CL-0301 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03474107 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. |
| Sponsor organisation address | 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Interim |
| Date of interim/final analysis | 15 July 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 15 July 2020 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to compare the overall survival (OS) of participants with locally advanced or metastatic urothelial cancer treated with enfortumab vedotin (EV) to the OS of participants treated with chemotherapy.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 27 June 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 3 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 2 |
| Country: Number of subjects enrolled | Australia: 13 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 28 |
| Country: Number of subjects enrolled | Canada: 52 |
| Country: Number of subjects enrolled | Denmark: 13 |
| Country: Number of subjects enrolled | France: 54 |
| Country: Number of subjects enrolled | Germany: 13 |
| Country: Number of subjects enrolled | Italy: 19 |
| Country: Number of subjects enrolled | Japan: 86 |
| Country: Number of subjects enrolled | Korea, Republic of: 90 |
| Country: Number of subjects enrolled | Netherlands: 13 |
| Country: Number of subjects enrolled | Portugal: 4 |
| Country: Number of subjects enrolled | Russian Federation: 5 |
| Country: Number of subjects enrolled | Spain: 55 |
| Country: Number of subjects enrolled | Switzerland: 3 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Taiwan: 18 |
| Country: Number of subjects enrolled | United Kingdom: 45 |
| Country: Number of subjects enrolled | United States: 87 |
| Worldwide total number of subjects | 608 |
| EEA total number of subjects | 207 |

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) | 219 |
| From 65 to 84 years | 384 |
| 85 years and over | 5 |

Subject disposition

Recruitment

Recruitment details:

Adult participants with locally advanced or metastatic urothelial cancer (mUC) who had received a platinum-containing chemotherapy and had experienced disease progression or relapse during or following treatment with programmed cell death protein-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors.

Pre-assignment

Screening details:

Participants were stratified by Eastern Cooperative Oncology Group Performance Status (ECOG PS) (0 vs 1), regions of the world Western EU vs US vs Rest of World) and liver metastasis (Yes vs No).

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 | Enfortumab Vedotin 1.25 mg/kg |

Arm description:

Participants received 1.25 milligrams per kilogram (mg/kg) of body weight enfortumab vedotin by intravenous (IV) infusion over approximately 30 minutes on days 1, 8 and 15 of every 28-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020.

| | |
|--|---------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Enfortumab Vedotin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants received 1.25 mg/kg of body weight enfortumab vedotin by intravenous (IV) infusion over approximately 30 minutes on days 1, 8 and 15 of every 28-day cycle.

| | |
|------------------|--------------|
| Arm title | Chemotherapy |
|------------------|--------------|

Arm description:

Participants received either 75 milligram per square meter (mg/m²) docetaxel by IV infusion over approximately 1 hour or 320 mg/m² vinflunine by IV infusion over approximately 20 minutes or 175 mg/m² paclitaxel by IV infusion over approximately 3 hours on day 1 of every 21-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020.

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

Dosage and administration details:

Participants received either 75 mg/m² docetaxel by IV infusion over approximately 1 hour on day 1 of

every 21-day cycle.

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

Dosage and administration details:

Participants received 320 mg/m² vinflunine by IV infusion over approximately 20 minutes on day 1 of every 21-day cycle.

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

Dosage and administration details:

Participants received 175 mg/m² paclitaxel by IV infusion over approximately 3 hours on day 1 of every 21-day cycle.

| Number of subjects in period 1 | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy |
|---------------------------------------|----------------------------------|--------------|
| Started | 301 | 307 |
| Treated | 296 | 291 |
| Completed | 56 | 22 |
| Not completed | 245 | 285 |
| Adverse event, serious fatal | 2 | 2 |
| Consent withdrawn by subject | 15 | 27 |
| Physician decision | 7 | 22 |
| Adverse event, non-fatal | 42 | 46 |
| Progressive Disease | 177 | 180 |
| Miscellaneous | 1 | 6 |
| Lost to follow-up | - | 1 |
| Protocol deviation | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Enfortumab Vedotin 1.25 mg/kg |
|-----------------------|-------------------------------|

Reporting group description:

Participants received 1.25 milligrams per kilogram (mg/kg) of body weight enfortumab vedotin by intravenous (IV) infusion over approximately 30 minutes on days 1, 8 and 15 of every 28-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020.

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

Reporting group description:

Participants received either 75 milligram per square meter (mg/m²) docetaxel by IV infusion over approximately 1 hour or 320 mg/m² vinflunine by IV infusion over approximately 20 minutes or 175 mg/m² paclitaxel by IV infusion over approximately 3 hours on day 1 of every 21-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020.

| Reporting group values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | Total |
|---|----------------------------------|--------------|-------|
| Number of subjects | 301 | 307 | 608 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 108 | 111 | 219 |
| From 65-84 years | 192 | 192 | 384 |
| 85 years and over | 1 | 4 | 5 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 66.52 | 66.81 | |
| standard deviation | ± 9.11 | ± 9.93 | - |
| Sex: Female, Male Units: subjects | | | |
| Female | 63 | 75 | 138 |
| Male | 238 | 232 | 470 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 97 | 103 | 200 |
| Native Hawaiian or Other Pacific Islander | 0 | 1 | 1 |
| Black or African American | 2 | 2 | 4 |
| White | 159 | 155 | 314 |
| More than one race | 0 | 0 | 0 |

| | | | |
|--|-----|-----|-----|
| Unknown or Not Reported | 43 | 46 | 89 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 29 | 24 | 53 |
| Not Hispanic or Latino | 230 | 238 | 468 |
| Unknown or Not Reported | 42 | 45 | 87 |
| ECOG PS | | | |
| ECOG PS was measured on 6 point scale 0-Fully active, able to carry on all pre-disease performance without restriction 1-Restricted in physically strenuous activity but ambulatory & able to carry out work of a light or sedentary nature 2-Ambulatory & capable of all self-care but unable to carry out any work activities.Up & about more than 50% of waking hours 3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours 4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair 5-Dead Participants were categorized based on ECOG PS 0 or 1 | | | |
| Units: Subjects | | | |
| ECOG PS=0 | 120 | 124 | 244 |
| ECOG PS=1 | 181 | 183 | 364 |
| Liver Metastasis | | | |
| Participants were categorized based on liver metastasis (yes or no). | | | |
| Units: Subjects | | | |
| Liver Metastasis=No | 208 | 212 | 420 |
| Liver Metastasis=Yes | 93 | 95 | 188 |
| Region | | | |
| Participants were categorized based on region western europe, US and rest of the world. | | | |
| Units: Subjects | | | |
| Western Europe | 126 | 129 | 255 |
| United States | 43 | 44 | 87 |
| Rest of the World | 132 | 134 | 266 |

End points

End points reporting groups

| | |
|--|-------------------------------|
| Reporting group title | Enfortumab Vedotin 1.25 mg/kg |
| Reporting group description: Participants received 1.25 milligrams per kilogram (mg/kg) of body weight enfortumab vedotin by intravenous (IV) infusion over approximately 30 minutes on days 1, 8 and 15 of every 28-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020. | |
| Reporting group title | Chemotherapy |
| Reporting group description: Participants received either 75 milligram per square meter (mg/m ²) docetaxel by IV infusion over approximately 1 hour or 320 mg/m ² vinflunine by IV infusion over approximately 20 minutes or 175 mg/m ² paclitaxel by IV infusion over approximately 3 hours on day 1 of every 21-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first. In this arm 'completed' refers to participants still on treatment as of data cut-off date 15-Jul-2020. | |

Primary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: OS was defined as the time from the date of randomization until the documented date of death from any cause. OS was analyzed using Kaplan-Meier estimates. Participants who were still alive at the time of data cutoff date were to be censored at the last known alive date or at the data cutoff date, whichever was earlier. The full analysis set (FAS) consisted of all participants who were randomized. | |
| End point type | Primary |
| End point timeframe: From randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months) | |

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|----------------------------------|-------------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 301 | 307 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 12.88 (10.58 to 15.21) | 8.97 (8.05 to 10.74) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Enfortumab Vedotin 1.25 mg/kg v Chemotherapy |

| | |
|---|--------------------------|
| Number of subjects included in analysis | 608 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.00142 ^[1] |
| Method | Stratified Log rank |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.702 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.556 |
| upper limit | 0.886 |

Notes:

[1] - Stratification factors were ECOG PS, geographic region and liver metastasis. P-value was based on log-rank test. P-value of overall survival is \leq the predetermined 1-sided significance level of 0.00679 based on the number of observed deaths.

Secondary: Progression Free Survival on Study Therapy (PFS1) as Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

| | |
|-----------------|---|
| End point title | Progression Free Survival on Study Therapy (PFS1) as Per Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) |
|-----------------|---|

End point description:

PFS: time from date of randomization until date of documented radiological disease progression (PD) per investigator based on RECIST V1.1, or until death due to any cause, whichever occurred first. PD: \geq 20% increase in sum of diameters of target lesions taking as reference the smallest sum, and sum must also demonstrate an absolute increase of \geq 5 mm. Appearance of 1 or more new lesions is also considered progression. A participant who neither progressed nor died was censored at date of last radiological assessment (RA)/ date of randomization if no post-baseline RA was available. Participants who received any further anticancer therapy (ACT) for disease before radiological progression was censored at date of last RA before ACT started and participants who had PD/death after \geq 2 missed RAs were censored at last RA prior to 2 or more missed RAs. Kaplan-Meier estimates was used. Median time of follow-up for PFS was based on data cut-off & is same as median follow-up time for OS. FAS.

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

End point timeframe:

From randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months)

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|----------------------------------|-------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 301 | 307 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.55 (5.32 to 5.82) | 3.71 (3.52 to 3.94) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Enfortumab Vedotin 1.25 mg/kg v Chemotherapy |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 608 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.00001 [2] |
| Method | Stratified Log Rank |
| Parameter estimate | Stratified Hazard Ratio |
| Point estimate | 0.615 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.505 |
| upper limit | 0.748 |

Notes:

[2] - Stratification factors were ECOG PS, geographic region and liver metastasis. P-value was based on log-rank test. P value of PFS is ≤ the predetermined 1-sided significance level of 0.02189 based on the number of observed PFS events.

Secondary: Overall Response Rate (ORR) as Per RECIST V1.1

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|-----------------|--|
| End point title | Overall Response Rate (ORR) as Per RECIST V1.1 |
|-----------------|--|

End point description:

ORR was defined as the percentage of participants with complete response (CR) or partial response (PR) based on the RECIST v1.1. CR was defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement. PR was defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters. ORR was analysed using exact method based on binomial distribution (Clopper-Pearson). Median time of follow up for ORR was based on data cut-off and is same as median follow-up time for OS. Response Evaluable Set (RES): The RES was defined as all participants in the FAS who had measurable disease (per RECIST v1.1) per investigator at baseline.

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

End point timeframe:

From randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months)

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|-----------------------------------|-------------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 | 296 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 40.6 (34.90 to 46.54) | 17.9 (13.71 to 22.76) | | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Enfortumab Vedotin 1.25 mg/kg v Chemotherapy |

| | |
|---|------------------------------------|
| Number of subjects included in analysis | 584 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[3] |
| Method | Stratified Cochran-Mantel-Haenszel |

Notes:

[3] - Stratification factors were ECOG PS, Region and Liver Metastasis.

Secondary: Disease Control Rate (DCR) as Per RECIST V1.1

| | |
|-----------------|---|
| End point title | Disease Control Rate (DCR) as Per RECIST V1.1 |
|-----------------|---|

End point description:

DCR was defined as the percentage of participants with a CR, PR or a stable disease (SD) based on RECIST v1.1. CR was defined as disappearance of all target and nontarget lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm from baseline measurement. PR was defined as at least a 30% decrease in the sum of diameters (longest for nonnodal lesions, short axis for nodal lesions) of target lesions taking as reference to the baseline sum of diameters. SD was defined as neither sufficient decrease to qualify for PR nor sufficient increase to qualify for progressive disease taking as reference the smallest sum of diameters while on study drug. Progressive disease is defined in PFS1 endpoint. DCR was analysed using exact method based on binomial distribution (Clopper-Pearson). Median time of follow up for DCR was based on data cut-off and is same as median follow-up time for OS. RES Population.

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

End point timeframe:

From randomization until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months)

| | | | | |
|-----------------------------------|-------------------------------|-----------------------|--|--|
| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 288 | 296 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 71.9 (66.30 to 76.99) | 53.4 (47.52 to 59.17) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Enfortumab Vedotin 1.25 mg/kg v Chemotherapy |
| Number of subjects included in analysis | 584 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[4] |
| Method | Stratified Cochran-Mantel-Haenszel |

Notes:

[4] - Stratification factors were ECOG PS, Region and Liver Metastasis.

Secondary: Duration of Response (DOR) as Per RECIST V1.1

| | |
|-----------------|---|
| End point title | Duration of Response (DOR) as Per RECIST V1.1 |
|-----------------|---|

End point description:

DOR: time from the date of the first CR/PR (whichever is first recorded) that was subsequently confirmed as assessed by investigator to the date of documented PD or death due to any cause whichever occurred first. If a participant has neither progressed nor died, the participant was censored at the date of last RA or at the date of first CR/PR if no subsequent post-baseline RA was available. Participants who received any further ACT for the disease before radiological progression were censored at the date of the last RA before the ACT started. In addition, participants who had PD/death after ≥ 2 missed RAs were censored at the last RA prior to the 2 or more missed RAs. Kaplan-Meier estimates was used. Median time of follow up for DOR was based on data cut-off and is same as median follow-up time for OS. RES population with available data. CR/PR and PD were defined in ORR and PFS1 endpoints, respectively.

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

End point timeframe:

From date of first objective response until the analysis cut-off date of 15-Jul-2020 (median OS follow-up was 11.10 months)

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|----------------------------------|-------------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 53 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.39 (5.59 to 9.46) | 8.11 (5.65 to 9.56) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Global Health Status (QL2 Score)

| | |
|-----------------|--|
| End point title | Change From Baseline to Week 12 in European Organisation for Research and Treatment of Cancer [EORTC] Quality of Life Questionnaire Global Health Status (QL2 Score) |
|-----------------|--|

End point description:

EORTC QLQ-C30 is a generic questionnaire consisting of 30 items. The instrument yields functional scales (physical, role, emotional, cognitive, social), symptom scales/items (fatigue, Nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea), global health status, and financial impact score. Most items are scored 1 ("not at all") to 4 ("very much") except for the items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The recall period for each question is "during the past week". All raw domain scores are linearly transformed to a 0-100 scale with higher scores on symptoms indicate a worse health state. Higher scores on the global health status and functioning scales indicate better health status/function. FAS population with available data.

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

End point timeframe:

Baseline and week 12

| | | | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 127 | 102 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -2.30 (± 18.02) | -5.72 (± 16.04) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 12 in EuroQOL 5-dimension 5-level Questionnaire [EQ-5D-5L] Visual Analog Scale (VAS)

| | |
|--|---|
| End point title | Change From Baseline to Week 12 in EuroQOL 5-dimension 5-level Questionnaire [EQ-5D-5L] Visual Analog Scale (VAS) |
| End point description: | |
| EQ-5D-5L is a health status instrument for self-reported assessment of 5 domains of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each domain is rated by selecting 1 of 5 standardized categorizations ranging from no problem to extreme problem. The final question is a visual analogue scale (VAS) to rank health status from 0 (best health imaginable) to 100 (worst health imaginable). FAS population with available data. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline and week 12 | |

| | | | | |
|--------------------------------------|-------------------------------|-----------------|--|--|
| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 124 | 102 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -1.8 (± 16.6) | -5.3 (± 14.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events

| | |
|---|---|
| End point title | Number of Participants With Treatment Emergent Adverse Events |
| End point description: | |
| An AE is any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A TEAE is defined as an AE observed or worsened after starting administration of the study drug. The safety analysis set (SAF) consisted of all participants who received any amount of study drug, and was used for safety analyses. | |

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From first dose up to 30 days after last dose (Median (range) time on study drug was 4.99 (0.5, 19.4) months in enfortumab vedotin and 3.45 (0.2, 15.0) months in chemotherapy group) | |

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 291 | | |
| Units: participants | 290 | 288 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With ECOG Performance Status

| | |
|---|---|
| End point title | Number of Participants With ECOG Performance Status |
| End point description: | |
| ECOG performance status was measured on an 6 point scale. 0-Fully active, able to carry on all pre-disease performance without restriction. 1-Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work. 2-Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. 3-Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. 4-Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. 5-Dead. Number of participants with ECOG PS was reported. Safety population. | |
| End point type | Secondary |
| End point timeframe: | |
| From first dose up to 30 days after last dose (Median (range) time on study drug was 4.99 (0.5, 19.4) months in enfortumab vedotin and 3.45 (0.2, 15.0) months in chemotherapy group) | |

| End point values | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | | |
|-----------------------------|-------------------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 296 | 291 | | |
| Units: participants | | | | |
| ECOG PS = 0 | 34 | 57 | | |
| ECOG PS = 1 | 110 | 118 | | |
| ECOG PS = >1 | 40 | 44 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after last dose (Median (range) time on study drug was 4.99 (0.5, 19.4) months in enfortumab vedotin and 3.45 (0.2, 15.0) months in chemotherapy group)

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

Dictionary used

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

| | |
|--------------------|-------|
| Dictionary version | v23.0 |
|--------------------|-------|

Reporting groups

| | |
|-----------------------|-------------------------------|
| Reporting group title | Enfortumab Vedotin 1.25 mg/kg |
|-----------------------|-------------------------------|

Reporting group description:

Participants received 1.25 mg/kg of body weight enfortumab vedotin by IV infusion over approximately 30 minutes on days 1, 8 and 15 of every 28-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first.

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

Reporting group description:

Participants received either 75 mg/m² docetaxel by IV infusion over approximately 1 hour or 320 mg/m² vinflunine by IV infusion over approximately 20 minutes or 175 mg/m² paclitaxel by IV infusion over approximately 3 hours on day 1 of every 21-day cycle. Participants received study treatment until radiological disease progression as determined per investigator assessment or other discontinuation criteria were met or upon study termination, or study completion, whichever occurred first.

| Serious adverse events | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | |
|---|----------------------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 138 / 296 (46.62%) | 128 / 291 (43.99%) | |
| number of deaths (all causes) | 130 | 161 | |
| number of deaths resulting from adverse events | 7 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Adenocarcinoma gastric | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bladder transitional cell carcinoma | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant neoplasm progression | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 12 / 296 (4.05%) | 7 / 291 (2.41%) | |
| occurrences causally related to treatment / all | 0 / 15 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 10 | 0 / 6 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Aortic aneurysm | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Iliac artery occlusion | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular compression | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vein disorder | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chills | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Extravasation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 5 / 291 (1.72%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malaise | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 2 / 3 | 0 / 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 6 / 296 (2.03%) | 9 / 291 (3.09%) | |
| occurrences causally related to treatment / all | 2 / 6 | 4 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspiration | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cough | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 4 / 296 (1.35%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngospasm | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Organising pneumonia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Delirium | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Product issues | | | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| C-reactive protein increased | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Hepatic enzyme increased subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased subjects affected / exposed | 2 / 296 (0.68%) | 5 / 291 (1.72%) | |
| occurrences causally related to treatment / all | 3 / 3 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Platelet count decreased subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radius fracture subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reactive gastropathy subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Toxicity to various agents | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 296 (1.69%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiogenic shock | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palpitations | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ventricular hypokinesia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Brain oedema | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cerebral haematoma | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dementia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Frontotemporal dementia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 6 / 291 (2.06%) | |
| occurrences causally related to treatment / all | 2 / 4 | 3 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 16 / 291 (5.50%) | |
| occurrences causally related to treatment / all | 2 / 4 | 16 / 16 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 8 / 291 (2.75%) | |
| occurrences causally related to treatment / all | 4 / 4 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness neurosensory | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |

| | | | |
|---|-----------------|-----------------|--|
| Blepharitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cataract | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 6 / 291 (2.06%) | |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain lower | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic fistula | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 296 (0.68%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 7 / 296 (2.36%) | 4 / 291 (1.37%) | |
| occurrences causally related to treatment / all | 8 / 8 | 6 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Duodenal obstruction | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fistula of small intestine | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhagic ascites | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (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 | 1 / 296 (0.34%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 296 (0.68%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 5 / 296 (1.69%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 3 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholangitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic function abnormal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 296 (0.68%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 4 / 4 | 2 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Liver disorder | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Drug eruption | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 5 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash vesicular | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Toxic skin eruption | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 19 / 296 (6.42%) | 7 / 291 (2.41%) | |
| occurrences causally related to treatment / all | 6 / 31 | 1 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Azotaemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Calculus bladder | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Choluria | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis noninfective | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 5 / 296 (1.69%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 6 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 296 (1.01%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract obstruction | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal insufficiency | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate antidiuretic hormone secretion | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Lumbar spinal stenosis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (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 | | | |
| Abscess bacterial | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 2 / 3 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related sepsis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia pyelonephritis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 3 / 296 (1.01%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infected skin ulcer | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infective spondylitis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pelvic abscess | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pleural infection | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pneumonia | | | |
| subjects affected / exposed | 12 / 296 (4.05%) | 7 / 291 (2.41%) | |
| occurrences causally related to treatment / all | 4 / 14 | 2 / 9 | |
| deaths causally related to treatment / all | 1 / 2 | 0 / 1 | |
| Pneumonia klebsiella | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia legionella | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia viral | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyelonephritis acute | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 296 (1.69%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Septic shock | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Streptococcal urinary tract infection | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 7 / 296 (2.36%) | 6 / 291 (2.06%) | |
| occurrences causally related to treatment / all | 3 / 7 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 9 / 296 (3.04%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 2 / 10 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection enterococcal | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 296 (0.68%) | 6 / 291 (2.06%) | |
| occurrences causally related to treatment / all | 0 / 2 | 5 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 296 (1.69%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 296 (0.68%) | 4 / 291 (1.37%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 4 / 296 (1.35%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 4 / 291 (1.37%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 2 / 291 (0.69%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 296 (0.68%) | 3 / 291 (1.03%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 296 (0.00%) | 1 / 291 (0.34%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 296 (0.34%) | 0 / 291 (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 | Enfortumab Vedotin 1.25 mg/kg | Chemotherapy | |
|---|----------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 284 / 296 (95.95%) | 266 / 291 (91.41%) | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 43 / 296 (14.53%) | 39 / 291 (13.40%) | |
| occurrences (all) | 85 | 85 | |
| Chills | | | |
| subjects affected / exposed | 16 / 296 (5.41%) | 5 / 291 (1.72%) | |
| occurrences (all) | 18 | 5 | |
| Fatigue | | | |

| | | | |
|--|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 107 / 296 (36.15%) 197 | 77 / 291 (26.46%) 121 | |
| Malaise subjects affected / exposed occurrences (all) | 12 / 296 (4.05%) 13 | 19 / 291 (6.53%) 24 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 25 / 296 (8.45%) 32 | 39 / 291 (13.40%) 46 | |
| Pyrexia subjects affected / exposed occurrences (all) | 60 / 296 (20.27%) 99 | 33 / 291 (11.34%) 47 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 24 / 296 (8.11%) 25 | 17 / 291 (5.84%) 17 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 25 / 296 (8.45%) 31 | 26 / 291 (8.93%) 36 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 31 / 296 (10.47%) 32 | 23 / 291 (7.90%) 25 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 27 / 296 (9.12%) 45 | 4 / 291 (1.37%) 5 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 36 / 296 (12.16%) 56 | 5 / 291 (1.72%) 7 | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 26 / 296 (8.78%) 38 | 6 / 291 (2.06%) 6 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 12 / 296 (4.05%) 35 | 17 / 291 (5.84%) 50 | |
| Neutrophil count decreased | | | |

| | | | |
|--|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 32 / 296 (10.81%) 70 | 52 / 291 (17.87%) 159 | |
| Weight decreased subjects affected / exposed occurrences (all) | 47 / 296 (15.88%) 73 | 20 / 291 (6.87%) 20 | |
| White blood cell count decreased subjects affected / exposed occurrences (all) | 16 / 296 (5.41%) 45 | 32 / 291 (11.00%) 97 | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 15 / 296 (5.07%) 19 | 8 / 291 (2.75%) 8 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 26 / 296 (8.78%) 34 | 16 / 291 (5.50%) 18 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 74 / 296 (25.00%) 99 | 23 / 291 (7.90%) 28 | |
| Headache subjects affected / exposed occurrences (all) | 9 / 296 (3.04%) 10 | 17 / 291 (5.84%) 22 | |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 20 / 296 (6.76%) 45 | 16 / 291 (5.50%) 20 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 15 / 296 (5.07%) 23 | 8 / 291 (2.75%) 10 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 102 / 296 (34.46%) 301 | 66 / 291 (22.68%) 99 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 57 / 296 (19.26%) 98 | 83 / 291 (28.52%) 136 | |
| Neutropenia | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 16 / 296 (5.41%) 30 | 20 / 291 (6.87%) 37 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 19 / 296 (6.42%) | 3 / 291 (1.03%) | |
| occurrences (all) | 24 | 3 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 30 / 296 (10.14%) | 12 / 291 (4.12%) | |
| occurrences (all) | 37 | 15 | |
| Vision blurred | | | |
| subjects affected / exposed | 16 / 296 (5.41%) | 5 / 291 (1.72%) | |
| occurrences (all) | 20 | 5 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 37 / 296 (12.50%) | 24 / 291 (8.25%) | |
| occurrences (all) | 52 | 33 | |
| Constipation | | | |
| subjects affected / exposed | 81 / 296 (27.36%) | 72 / 291 (24.74%) | |
| occurrences (all) | 116 | 105 | |
| Diarrhoea | | | |
| subjects affected / exposed | 98 / 296 (33.11%) | 64 / 291 (21.99%) | |
| occurrences (all) | 171 | 89 | |
| Dry mouth | | | |
| subjects affected / exposed | 24 / 296 (8.11%) | 7 / 291 (2.41%) | |
| occurrences (all) | 26 | 7 | |
| Dyspepsia | | | |
| subjects affected / exposed | 19 / 296 (6.42%) | 9 / 291 (3.09%) | |
| occurrences (all) | 22 | 10 | |
| Nausea | | | |
| subjects affected / exposed | 89 / 296 (30.07%) | 73 / 291 (25.09%) | |
| occurrences (all) | 119 | 92 | |
| Stomatitis | | | |
| subjects affected / exposed | 27 / 296 (9.12%) | 19 / 291 (6.53%) | |
| occurrences (all) | 35 | 27 | |
| Vomiting | | | |

| | | | |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 38 / 296 (12.84%) 50 | 44 / 291 (15.12%) 57 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 139 / 296 (46.96%) | 110 / 291 (37.80%) | |
| occurrences (all) | 163 | 121 | |
| Drug eruption | | | |
| subjects affected / exposed | 26 / 296 (8.78%) | 4 / 291 (1.37%) | |
| occurrences (all) | 40 | 4 | |
| Dry skin | | | |
| subjects affected / exposed | 50 / 296 (16.89%) | 11 / 291 (3.78%) | |
| occurrences (all) | 57 | 11 | |
| Pruritus | | | |
| subjects affected / exposed | 102 / 296 (34.46%) | 20 / 291 (6.87%) | |
| occurrences (all) | 153 | 20 | |
| Rash | | | |
| subjects affected / exposed | 49 / 296 (16.55%) | 16 / 291 (5.50%) | |
| occurrences (all) | 77 | 16 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 49 / 296 (16.55%) | 6 / 291 (2.06%) | |
| occurrences (all) | 99 | 6 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 19 / 296 (6.42%) | 1 / 291 (0.34%) | |
| occurrences (all) | 20 | 2 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 31 / 296 (10.47%) | 22 / 291 (7.56%) | |
| occurrences (all) | 41 | 28 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 19 / 296 (6.42%) | 36 / 291 (12.37%) | |
| occurrences (all) | 23 | 44 | |
| Back pain | | | |
| subjects affected / exposed | 25 / 296 (8.45%) | 23 / 291 (7.90%) | |
| occurrences (all) | 28 | 25 | |
| Muscular weakness | | | |

| | | | |
|---|---------------------------|--------------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 296 (5.07%) 23 | 7 / 291 (2.41%) 8 | |
| Myalgia subjects affected / exposed occurrences (all) | 15 / 296 (5.07%) 23 | 31 / 291 (10.65%) 40 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 16 / 296 (5.41%) 20 | 13 / 291 (4.47%) 19 | |
| Infections and infestations | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 18 / 296 (6.08%) 23 | 2 / 291 (0.69%) 2 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 15 / 296 (5.07%) 18 | 9 / 291 (3.09%) 9 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 21 / 296 (7.09%) 22 | 12 / 291 (4.12%) 15 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 119 / 296 (40.20%) 157 | 78 / 291 (26.80%) 104 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 28 / 296 (9.46%) 64 | 5 / 291 (1.72%) 7 | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 19 / 296 (6.42%) 22 | 10 / 291 (3.44%) 22 | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 18 / 296 (6.08%) 28 | 8 / 291 (2.75%) 9 | |
| Hyponatraemia subjects affected / exposed occurrences (all) | 19 / 296 (6.42%) 36 | 10 / 291 (3.44%) 13 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 22 August 2018 | <ul style="list-style-type: none">• Safety laboratory (hematology, biochemistry and pregnancy test in women of childbearing potential), and concomitant medication assessments were added at the follow-up visit so that pertinent laboratory data were captured at the follow-up visit to ensure follow-up of AEs until 30 days after last dose of study treatment.• A hemoglobin A1c (HbA1c) test was added at the end-of-treatment visit to monitor subjects' safety because hyperglycemia has been identified as an event of interest.• An assessment for ATA was added at the follow-up visit (Arm A only) along with other safety laboratory tests. This was in response to health authority request to ensure the follow-up of subjects' safety.• A monthly urine pregnancy test until 6 months after the last dose of study treatment was added. This was in response to health authority request, given the genotoxicities MMAE had on pregnant rats (Study 8204-397) and to align with the guidance released by the ICH Clinical Trial Facilitation Group "Recommendations Related to Contraception and Pregnancy Testing in Clinical Trials".• The safety and efficacy data were updated in the introduction section per the updated Investigator's Brochure (IB) and to support a continuing positive benefit-risk assessment.• A summary of key safety information was included to support a continuing positive benefit-risk-assessment. |
| 22 August 2018 | <ul style="list-style-type: none">• The benefit-risk assessment was updated based on the current IB (with data cut-off date 02 Oct 2017) for subjects with locally advanced or mUC who previously received CPI therapy. Reference to the benefit-risk assessment responsibilities of the IDMC was included.• Concomitant medication restrictions or requirements were updated for comparator drugs (docetaxel, vinflunine and paclitaxel) per product labels, with a clarification that strong inhibitors or inducers of cytochrome P450 (CYP) 3A4 should be avoided rather than prohibited for subjects receiving docetaxel and vinflunine during the study and that caution (rather than prohibition) should be exercised when paclitaxel was administered with strong inhibitors or inducers of CYP3A4 and CYP2C8.• The exclusion criteria were updated:<ul style="list-style-type: none">o Exclusion criterion 3 was modified to exclude subjects with ongoing immunotherapy-related myocarditis (myocarditis was an immunotherapy-related AE that was also to be excluded) and to clarify that subjects with \leq Grade 2 immunotherapy-related hypothyroidism or panhypopituitarism may have been enrolled when well-maintained/controlled on a stable dose of hormone replacement therapy (if indicated); however, subjects with ongoing \geq Grade 3 immunotherapy-related hypothyroidism or panhypopituitarism were explicitly excluded.o Exclusion criterion 14 was updated to exclude subjects with known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary (CHO) cells because enfortumab vedotin is produced in CHO cells.o Exclusion criterion 15 was changed from subject has known severe hypersensitivity to subject has known hypersensitivity (not only those with severe hypersensitivity) to docetaxel, paclitaxel and vinflunine or to any of the other excipients. This was to reflect the respective contradictions to docetaxel, paclitaxel and vinflunine as per product labels. |

| | |
|----------------|---|
| 22 August 2018 | <p>o Exclusion criterion 16, which excluded subjects who required ongoing medication that strongly inhibits or induces CYP3A4, was deleted to reflect product labels for comparator drugs and the current IB for enfortumab vedotin. o Exclusion criterion 17 was updated to clarify that subjects with superficial punctate keratitis were allowed into the study if, in the opinion of the investigator, the disorder was being adequately treated. • Detailed information including the use of premedications for the management of enfortumab vedotin infusion-related reactions (IRRs) was added because IRRs are a potential risk of enfortumab vedotin. • The criteria detailing when imaging assessments every 56 days (\pm 7 days) were to end in the post-treatment follow-up period were revised to be consistent with on treatment follow-up for PFS1. All efforts were to be made to keep following subjects for disease progression irrespective of the number of visits missed. To evaluate the impact on missing visits, additional sensitivity analysis on PFS1 was to be conducted. • General guidelines on the dose, mode of administration and dose modifications for comparators were provided and the criteria for withholding comparator drug treatment were updated as per product labels in [Appendix 13.1.1, Protocol, Table B and Tables 6, 7, 8 and 9] and in the dose modification section: o In general, treatment with docetaxel, paclitaxel, or vinflunine was to be withheld for drug-related Grade 4 hematologic toxicities and for nonhematologic toxicities \geq Grade 3. Subsequent doses were to be modified. o For docetaxel-, paclitaxel-, or vinflunine-associated hematologic toxicities \geq Grade 3, transfusions or growth factors may have been used as indicated per institutional guidelines. o Dose modification guidelines were provided for Grades 1, 2, 3 or 4 neutropenia, thrombocytopenia, anemia and nonhematological toxicity and other hematological toxicity not described.</p> |
| 22 August 2018 | <p>o Specific dose modifications for docetaxel, paclitaxel or vinflunine were also to be considered according to local product labels or summary of product characteristics (SmPC) and institutional guidelines. • A new analysis set (response evaluable set [RES]) was included and defined; to be used for efficacy analysis on ORR and DCR. Efficacy analysis on OS and PFS was to be conducted on the full analysis set. The pharmacodynamics analysis set was removed. The efficacy variables to be tested (only OS, PFS1, ORR and DCR) were stated formally and the multiplicity adjustment rule was included. • Text was added to indicate that additional sensitivity analyses was to be performed for PFS1 for subjects censored when missing 2 consecutive tumor visits. This was to assess the robustness of the primary analysis of PFS1. • For the subgroup analyses, 1 subgroup (burden of disease at baseline) was removed and existing subgroups (prior platinum, setting of most recent prior chemotherapy, histology, time from completion/discontinuation of most recent platinum-based prior therapy and the primary site of tumor) were clarified. This was to explore study drug efficacy on more appropriate subgroup and clarify the subgroup definition and analysis. • Instruction on the recalculation of subsequent doses of enfortumab vedotin and docetaxel based on a \geq 10% change in body weight from last dose calculation was replaced with a clarification that enfortumab vedotin was to be administered at mg/kg doses based on the subject's actual body weight. Reference was made to local product label or SmPC and institution guidelines for further guidance on comparative drug dosing.</p> |
| 22 August 2018 | <p>• Appendices were updated to be consistent with the prohibited medications in the FDA guidance and to clarify which concomitant medications should be avoided, used with caution or closely monitored: o The condition that subjects must have discontinued treatment with any of the listed medications for at least 2 weeks prior to the first dose of study drug was deleted. o The concomitant medication list was updated to include strong inhibitors/inducers of CYP3A, CYP2C8 and inhibitors of P-glycoprotein (P-gp) that should be avoided, used with caution, or closely monitored. o Reference was made to the FDA website detailing guidance for substrates, inhibitors and guidance. o A summary table of potential drug reactions was provided.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported