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	v3 (current)
This version publication date	05 September 2021
First version publication date	07 July 2021
Version creation reason	

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/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.

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/m^2 docetaxel by IV infusion over approximately 1 hour 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/m^2 paclitaxel by IV infusion over approximately 3 hours 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/m^2 vinflunine by IV infusion over approximately 20 minutes 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/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.	

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 ≤ 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: >= 20% increase in sum of diameters of target lesions taking as reference the smallest sum, and sum must also demonstrate an absolute increase of >= 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 >=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

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 with available data.

End point type	Secondary

End point timeframe:

End of treatment (EOT) (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	184	219		
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/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.

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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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	
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 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	
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	
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	
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	
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	
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 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 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 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	
Fatigue			
subjects affected / exposed	107 / 296 (36.15%)	77 / 291 (26.46%)	
occurrences (all)	197	121	
Chills			

subjects affected / exposed	16 / 296 (5.41%)	5 / 291 (1.72%)	
occurrences (all)	18	5	
Malaise			
subjects affected / exposed	12 / 296 (4.05%)	19 / 291 (6.53%)	
occurrences (all)	13	24	
Oedema peripheral			
subjects affected / exposed	25 / 296 (8.45%)	39 / 291 (13.40%)	
occurrences (all)	32	46	
Pyrexia			
subjects affected / exposed	60 / 296 (20.27%)	33 / 291 (11.34%)	
occurrences (all)	99	47	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 296 (8.11%)	17 / 291 (5.84%)	
occurrences (all)	25	17	
Dyspnoea			
subjects affected / exposed	25 / 296 (8.45%)	26 / 291 (8.93%)	
occurrences (all)	31	36	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	31 / 296 (10.47%)	23 / 291 (7.90%)	
occurrences (all)	32	25	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	27 / 296 (9.12%)	4 / 291 (1.37%)	
occurrences (all)	45	5	
Aspartate aminotransferase increased			
subjects affected / exposed	36 / 296 (12.16%)	5 / 291 (1.72%)	
occurrences (all)	56	7	
Blood creatinine increased			
subjects affected / exposed	26 / 296 (8.78%)	6 / 291 (2.06%)	
occurrences (all)	38	6	
Lymphocyte count decreased			
subjects affected / exposed	12 / 296 (4.05%)	17 / 291 (5.84%)	
occurrences (all)	35	50	
Neutrophil count decreased			

subjects affected / exposed	32 / 296 (10.81%)	52 / 291 (17.87%)	
occurrences (all)	70	159	
Weight decreased			
subjects affected / exposed	47 / 296 (15.88%)	20 / 291 (6.87%)	
occurrences (all)	73	20	
White blood cell count decreased			
subjects affected / exposed	16 / 296 (5.41%)	32 / 291 (11.00%)	
occurrences (all)	45	97	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	15 / 296 (5.07%)	8 / 291 (2.75%)	
occurrences (all)	19	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	26 / 296 (8.78%)	16 / 291 (5.50%)	
occurrences (all)	34	18	
Dysgeusia			
subjects affected / exposed	74 / 296 (25.00%)	23 / 291 (7.90%)	
occurrences (all)	99	28	
Headache			
subjects affected / exposed	9 / 296 (3.04%)	17 / 291 (5.84%)	
occurrences (all)	10	22	
Neuropathy peripheral			
subjects affected / exposed	20 / 296 (6.76%)	16 / 291 (5.50%)	
occurrences (all)	45	20	
Paraesthesia			
subjects affected / exposed	15 / 296 (5.07%)	8 / 291 (2.75%)	
occurrences (all)	23	10	
Peripheral sensory neuropathy			
subjects affected / exposed	102 / 296 (34.46%)	66 / 291 (22.68%)	
occurrences (all)	301	99	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	16 / 296 (5.41%)	20 / 291 (6.87%)	
occurrences (all)	30	37	
Anaemia			

subjects affected / exposed	57 / 296 (19.26%)	83 / 291 (28.52%)	
occurrences (all)	98	136	
Eye disorders			
Vision blurred			
subjects affected / exposed	16 / 296 (5.41%)	5 / 291 (1.72%)	
occurrences (all)	20	5	
Lacrimation increased			
subjects affected / exposed	30 / 296 (10.14%)	12 / 291 (4.12%)	
occurrences (all)	37	15	
Dry eye			
subjects affected / exposed	19 / 296 (6.42%)	3 / 291 (1.03%)	
occurrences (all)	24	3	
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	
Vomiting			
subjects affected / exposed	38 / 296 (12.84%)	44 / 291 (15.12%)	
occurrences (all)	50	57	
Stomatitis			

subjects affected / exposed	27 / 296 (9.12%)	19 / 291 (6.53%)	
occurrences (all)	35	27	
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	15 / 296 (5.07%)	7 / 291 (2.41%)	
occurrences (all)	23	8	
Myalgia			
subjects affected / exposed	15 / 296 (5.07%)	31 / 291 (10.65%)	
occurrences (all)	23	40	
Pain in extremity			
subjects affected / exposed	16 / 296 (5.41%)	13 / 291 (4.47%)	
occurrences (all)	20	19	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	18 / 296 (6.08%)	2 / 291 (0.69%)	
occurrences (all)	23	2	
Nasopharyngitis			
subjects affected / exposed	15 / 296 (5.07%)	9 / 291 (3.09%)	
occurrences (all)	18	9	
Urinary tract infection			
subjects affected / exposed	21 / 296 (7.09%)	12 / 291 (4.12%)	
occurrences (all)	22	15	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	119 / 296 (40.20%)	78 / 291 (26.80%)	
occurrences (all)	157	104	
Hyperglycaemia			
subjects affected / exposed	28 / 296 (9.46%)	5 / 291 (1.72%)	
occurrences (all)	64	7	
Hypokalaemia			
subjects affected / exposed	19 / 296 (6.42%)	10 / 291 (3.44%)	
occurrences (all)	22	22	
Hypomagnesaemia			
subjects affected / exposed	18 / 296 (6.08%)	8 / 291 (2.75%)	
occurrences (all)	28	9	
Hyponatraemia			
subjects affected / exposed	19 / 296 (6.42%)	10 / 291 (3.44%)	
occurrences (all)	36	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 August 2018	•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	• 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: 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 ≤ 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 ≥ 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	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 (± 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 ≥ Grade 3. Subsequent doses were to be modified. o For docetaxel-, paclitaxel-, or vinflunine-associated hematologic toxicities ≥ 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.
22 August 2018	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 usedfor ef ficacy 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 forPFS1 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 ≥ 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.
22 August 2018	● 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported