



Clinical trial results:

A Single-arm, Open-label, Multicenter Study of Enfortumab vedotin (ASG-22CE) for Treatment of Subjects With Locally Advanced or Metastatic Urothelial Cancer who Previously Received Immune Checkpoint Inhibitor (CPI) Therapy.

Summary

EudraCT number	2017-003479-78
Trial protocol	DE ES NL IT
Global end of trial date	28 July 2023

Results information

Result version number	v1 (current)
This version publication date	07 August 2024
First version publication date	07 August 2024

Trial information

Trial identification

Sponsor protocol code	SGN22E-001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03219333
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Seagen Inc
Sponsor organisation address	21823 30th Drive S.E., Bothell, United States, 98021
Public contact	Chief Medical Officer, Seagen Inc., 1 8554732436, medinfo@seagen.com
Scientific contact	Chief Medical Officer, Seagen Inc, 1 8554732436, medinfo@seagen.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 January 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	28 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the antitumor activity of single-agent enfortumab vedotin as measured by confirmed Objective Response Rate (ORR) in participants with locally advanced or metastatic urothelial cancer who have previously received systemic therapy with a CPI and either previously received platinum-containing chemotherapy or are platinum-naïve and cisplatin ineligible.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 178
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 14
Country: Number of subjects enrolled	Korea, Republic of: 13
Worldwide total number of subjects	219
EEA total number of subjects	14

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)	61
From 65 to 84 years	146
85 years and over	12

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Eligible participants with locally advanced or metastatic urothelial cancer who have previously received systemic therapy with a programmed cell death protein-1/programmed death-ligand 1 (PD-1/PD-L1) inhibitor and met inclusion criteria and none of the exclusion criteria were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Enfortumab vedotin - Cohort 1

Arm description:

Participants in Cohort 1 had received prior treatment with platinum-containing chemotherapy. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Enfortumab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.25 mg/kg was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Arm title	Enfortumab vedotin - Cohort 2
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Arm description:

Participants in Cohort 2 had received no platinum-containing chemotherapy were ineligible for treatment with cisplatin at the time of enrollment. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Arm type	Experimental
Investigational medicinal product name	Enfortumab vedotin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

1.25 mg/kg was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Number of subjects in period 1	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2
Started	128	91
Treated	125	89
Completed	0	0
Not completed	128	91
Consent withdrawn by subject	9	4
Death	104	72
Unspecified	2	2
Study closed 2023,major completed 5year follow-up	12	12
Lost to follow-up	1	1

Baseline characteristics

Reporting groups

Reporting group title	Enfortumab vedotin - Cohort 1
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Reporting group description:

Participants in Cohort 1 had received prior treatment with platinum-containing chemotherapy. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Reporting group title	Enfortumab vedotin - Cohort 2
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Reporting group description:

Participants in Cohort 2 had received no platinum-containing chemotherapy were ineligible for treatment with cisplatin at the time of enrollment. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Reporting group values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2	Total
Number of subjects	128	91	219
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)	45	16	61
From 65-84 years	83	63	146
85 years and over	0	12	12
Age Continuous			
Units: Years			
median	69.0	75.0	
full range (min-max)	40 to 84	49 to 91	-
Sex: Female, Male			
Units: Participants			
Female	38	23	61
Male	90	68	158
Race Customised			
Units: Subjects			
Asian	12	20	32
Black or African American	2	0	2
White	108	64	172
Other	1	0	1
Not Reportable	5	7	12
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	1	6
Not Hispanic or Latino	121	85	206
Unknown or Not Reported	2	5	7

Region of Enrollment			
Units: Subjects			
North America	119	59	178
Europe	0	14	14
Asia	9	18	27
Eastern Cooperative Oncology Group (ECOG) Performance Status			
ECOG performance status was used to assess participants disease progression, and ability to carry out daily living activities. 0=Normal activity; 1=Symptoms but ambulatory; 2=In bed <50% of the time; 3=In bed >50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			
ECOG: 0	40	37	77
ECOG: 1	85	41	126
ECOG: 2	0	11	11
Missing	3	2	5

End points

End points reporting groups

Reporting group title	Enfortumab vedotin - Cohort 1
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Reporting group description:

Participants in Cohort 1 had received prior treatment with platinum-containing chemotherapy. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Reporting group title	Enfortumab vedotin - Cohort 2
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Reporting group description:

Participants in Cohort 2 had received no platinum-containing chemotherapy were ineligible for treatment with cisplatin at the time of enrollment. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Primary: Objective Response Rate (ORR) per Blinded Independent Central Review (BICR)

End point title	Objective Response Rate (ORR) per Blinded Independent Central Review (BICR) ^[1]
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End point description:

ORR was defined as the percentage of participants with confirmed complete response (CR) or partial response (PR) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). CR is defined as disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type	Primary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

Notes:

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

Justification: Only descriptive analysis was planned for this endpoint.

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Percentage of Participants				
number (confidence interval 95%)	44 (35.1 to 53.2)	51.7 (40.8 to 62.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) per BICR

End point title	Progression-Free Survival (PFS) per BICR
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End point description:

The time from start of study treatment to first documentation of objective tumor progression (PD per RECIST 1.1), or to death due to any cause, whichever comes first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Months				
median (confidence interval 95%)	5.8 (4.93 to 7.46)	5.8 (5.03 to 8.28)		

Statistical analyses

No statistical analyses for this end point

Secondary: ORR per Investigator Assessment

End point title	ORR per Investigator Assessment
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End point description:

ORR was defined as the percentage of participants with confirmed CR or PR according to RECIST 1.1. CR is defined as disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Percentage of Participants				
number (confidence interval 95%)	39 (30.6 to 48.3)	50.6 (39.8 to 61.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR) per BICR

End point title	Duration of Objective Response (DOR) per BICR
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End point description:

Time from first documentation of objective response (CR or PR that is subsequently confirmed) to first documentation of progressive disease (PD) or death due to any cause, whichever comes first. CR = disappearance of all target lesions, non-target lesions. Any pathological lymph nodes (whether target or non-target) reduction in short axis to <10 mm. PR = $\geq 30\%$ decrease in sum of diameters of target lesions, reference: baseline sum of diameters. PD = at least 20% increase in sum of diameters of target lesions, taking reference smallest sum on study (this includes baseline sum if that is smallest on study). In addition to relative increase of 20%, sum must demonstrate an absolute increase of at least 0.5 cm. Appearance of one or more new lesions = progression. DOR analyzed using Kaplan-Meier methodology. Full analysis set. '99999' = Upper limit of 95% CI not estimated due to insufficient number of participants with events. Here, 'Number of Participants Analyzed' = number of participants evaluable.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	46		
Units: Months				
median (confidence interval 95%)	7.6 (6.34 to 99999)	10.9 (5.78 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR per Investigator Assessment

End point title	DOR per Investigator Assessment
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End point description:

CR is defined as disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression. Full analysis

set. '99999'=Upper limit of 95%CI not estimated due to insufficient number of participants with events. Here, 'Number of Participants Analyzed' signifies number of participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	45		
Units: Months				
median (confidence interval 95%)	7.9 (5.95 to 99999)	10.7 (5.85 to 16.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per Investigator Assessment

End point title	PFS per Investigator Assessment
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End point description:

The time from start of study treatment to first documentation of objective tumor progression (PD per RECIST 1.1), or to death due to any cause, whichever comes first. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The appearance of one or more new lesions is also considered progression. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up time: 10.15 months (range 0.49, 16.46); Cohort 2: median follow up time: 13.4 months (range 0.33 to 29.27)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Months				
median (confidence interval 95%)	5.8 (4.93 to 7.46)	7.2 (5.42 to 7.69)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Laboratory Abnormalities (Hematology)

End point title	Number of Participants with Treatment-Emergent Laboratory Abnormalities (Hematology)
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End point description:

A treatment-emergent laboratory abnormality is a value increases or decrease by 1 toxicity grade after the first study dose. Abnormalities were graded based on National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 - Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. Safety Analysis set. Here 'Number Analyzed' for each laboratory parameter is based on the number of participants who received at least one dose of enfortumab vedotin and have a baseline and post-baseline laboratory value.

End point type	Secondary
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End point timeframe:

The median duration of treatment was 4.60 months for Cohort 1 [range: 0.5, 29.4 months] and 5.98 months for Cohort 2 [range: 0.3, 24.6 months]

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Participants				
Hemoglobin decreased (all grades)n=122,88	52	39		
Hemoglobin decreased (grade 3-4)n=122,88	12	4		
Leukocytes decreased (all grades)n=122,88	33	28		
Leukocytes decreased (grade 3-4)n=122,88	5	4		
Lymphocytes decreased (all grades)n=122,88	55	61		
Lymphocytes decreased (grade 3-4)n=122,88	12	13		
Lymphocytes increased (all grades)n=125,88	0	1		
Lymphocytes increased (grade 3-4)n=125,89	0	0		
Neutrophils decreased (all grades)n=122,88	28	27		
Neutrophils decreased (grade 3-4)n=122,88	7	8		
Platelets decreased (all grades)n=121,88	39	20		
Platelets decreased (grade 3-4)n=125,89	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Laboratory Abnormalities (Serum Chemistry)

End point title	Number of Participants with Treatment-Emergent Laboratory Abnormalities (Serum Chemistry)
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End point description:

A treatment-emergent laboratory abnormality is a value increases or decrease by 1 toxicity grade after the first study dose. Abnormalities were graded based NCI CTCAE version 4.03 - Grade 1: mild; Grade 2: moderate; Grade 3: severe or clinically significant; Grade 4: life-threatening. Safety Analysis set. '99999': Fasting glucose is required for CTCAE grading of hyperglycemia grade 1-2, not grade 3-4. Since fasting glucose was not required for this study, grade 1-2 (glucose-high) could not be determined. Only grade 3-4 was determined. Here 'Number Analyzed' for each laboratory parameter is based on the number of participants who received at least one dose of enfortumab vedotin and have a baseline and post-baseline laboratory value.

End point type	Secondary
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End point timeframe:

The median duration of treatment was 4.60 months for Cohort 1 [full range: 0.5, 29.4 months] and 5.98 months for Cohort 2 [full range: 0.3, 24.6 months]

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Participants				
Alanine aminotransferase increase(all G) n=122,88	34	26		
Alanine aminotransferase increase(G 3-4)n=122,89	1	0		
Albumin decreased (all G)n=122,88	38	16		
Albumin decreased (G 3-4)n=122,88	1	0		
Alkaline phosphatase increased (all G)n=122,88	21	12		
Alkaline phosphatase increased (G 3-4)n=122,88	1	0		
Aspartate aminotransferase increase(all G)n=121,88	79	52		
Aspartate aminotransferase increase(G 3-4)n=121,88	3	2		
Bilirubin increased (all G)n=122,88	13	5		
Bilirubin increased (G 3-4)n=122,89	1	0		
Calcium decreased (all G)n=122,88	15	7		
Calcium decreased (G 3-4)n=125,89	0	0		
Calcium increased (all G)n=122,88	1	7		
Calcium increased (G 3-4)n=125,88	0	3		
Creatinine increased (all G)n=122,88	73	46		
Creatinine increased (G 3-4)n=122,88	2	3		
Glucose decreased (all G)n=122,88	32	26		
Glucose decreased (G 3-4)n=125,89	0	0		
Glucose increased (all G)n=125,89	99999	99999		
Glucose increased (G 3-4)n=125,89	10	11		
Phosphate decreased (all G)n=122,88	42	22		
Phosphate decreased (G 3-4)n=122,88	12	6		
Potassium decreased (all G)n=122,88	25	11		
Potassium decreased (G 3-4)n=122,88	2	1		

Potassium increased (all G)n=122,88	13	17		
Potassium increased (G 3-4)n=125,88	0	5		
Sodium decreased (all G)n=122,88	54	28		
Sodium decreased (G 3-4)n=122,88	10	6		
Sodium increased (all G)n=122,88	2	1		
Sodium increased (G 3-4)n=125,89	0	0		
Urate increased (all G)n=122,88	32	38		
Urate increased (grade 3-4)n=122,88	8	8		
Amylase increased (all grades)n=122,88	20	18		
Amylase increased (grade 3-4)n=122,88	1	3		
Lipase increased (all grades)n=122,88	37	32		
Lipase increased (grade 3-4)n=122,88	12	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of Antitherapeutic Antibody (ATA)

End point title	Incidence of Antitherapeutic Antibody (ATA)
End point description:	
<p>Participants who were tested positive for ATA at any time post-baseline were considered to be transiently positive or persistently positive if ≥ 2 consecutive samples were confirmed as positive. Safety Analysis Set: Participants who received at least one dose of enfortumab vedotin. Here, 'Overall Number of Participants Analyzed' signifies ATA subset (participants with a baseline and at least one post-baseline sample). Here, 'Number Analyzed' signifies participants evaluable for specified rows.</p>	
End point type	Secondary
End point timeframe:	
<p>The median duration of treatment was 4.60 months for Cohort 1 [full range: 0.5, 29.4 months] and 5.98 months for Cohort 2 [full range: 0.3, 24.6 months]</p>	

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	114	81		
Units: Participants				
Baseline Negative Negative post-baseline(n=112,80)	109	76		
Baseline Positive Negative post-baseline(n=112,80)	1	1		
Baseline Negative Transiently P post-basl(n=112,80)	2	3		
Baseline Positive Transiently P post-basl(n=2,1)	1	0		
Baseline Negative Persistently P post-basl(n=2,1)	1	1		
Baseline Positive Persistently P post-basl(n=2,1)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: DCR16 per Investigator Assessment

End point title | DCR16 per Investigator Assessment

End point description:

Percentage of participants with CR, PR, or stable disease (SD) at Week 16 visit. CR = disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR = $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. PD = at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. Appearance of one or more new lesions = considered progression. SD = neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type | Secondary

End point timeframe:

Up to Week 16

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Percentage of Participants				
number (confidence interval 95%)	55 (46.0 to 64.1)	64.0 (53.2 to 73.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate at 16 weeks (DCR16) per BICR

End point title | Disease Control Rate at 16 weeks (DCR16) per BICR

End point description:

Percentage of participants with CR, PR, or stable disease (SD) at Week 16 visit. CR is defined as disappearance of all target lesions and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. PR is defined as a $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type | Secondary

End point timeframe:

Up to Week 16

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Percentage of Participants				
number (confidence interval 95%)	50 (41.3 to 59.5)	58.4 (47.5 to 68.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) at Time of Primary Analysis

End point title Overall Survival (OS) at Time of Primary Analysis

End point description:

OS is defined as the time from first dose of enfortumab vedotin to death from any cause. Full analysis set: included all enrolled participants who received at least one dose of enfortumab vedotin.

End point type Secondary

End point timeframe:

Cohort 1 median follow-up time: 28.4 months [range 0.49, 32.62]; Cohort 2 median follow up time: 13.4 months [range 0.33 to 29.27]

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Months				
median (confidence interval 95%)	12.4 (9.46 to 15.57)	14.7 (10.51 to 18.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) at Time of Primary Analysis

End point title Number of Participants with Adverse Events (AEs) at Time of Primary Analysis

End point description:

AE=untoward medical occurrence associated with use of study intervention, whether or not considered related. Treatment emergent adverse event(TEAE)=newly occurring/worsening AE after first dose, within 30 days after last dose. According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03: Grade(G)3=severe AE,G4=life-threatening, urgent intervention indicated, G5=death related to AE. Participants who discontinued treatment due to treatment related TEAEs captured under TEAEs leading to treatment discontinuation. SAE=event at any dose led to death;life-threatening;required inpatient hospitalization/prolongation of existing hospitalization; persistent/significant disability/incapacity;congenital anomaly/birth defect/ important medical event. Treatment related AEs, SAEs, deaths also included. Treatment relatedness was judged by investigator. Safety Analysis Set: includes all participants who received at least one dose of enfortumab vedotin.

End point type	Secondary
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End point timeframe:

The median duration of treatment was 4.60 months for Cohort 1 [range: 0.5, 29.4 months] and 5.98 months for Cohort 2 [range: 0.3, 24.6 months]

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Participants				
Any treatment-emergent AEs (TEAEs)	125	89		
Treatment-related TEAEs	117	86		
Any grade 3-5 TEAEs	93	62		
Treatment-related grade 3-5 TEAEs	70	49		
Any serious TEAEs	59	35		
Treatment-related serious TEAEs	24	15		
Any TEAEs leading to treatment discontinuation	21	18		
TR TEAEs lead to treatment discontinuation	15	14		
Any TEAEs leading to death	7	8		
Treatment-related TEAEs leading to death	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) Parameter for Enfortumab Vedotin: Maximum Concentration (Cmax) (Serum)

End point title	Pharmacokinetics (PK) Parameter for Enfortumab Vedotin: Maximum Concentration (Cmax) (Serum)
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End point description:

Cmax was derived from the PK blood samples collected. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
End point timeframe:	
Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22	

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Microgram per milliliter (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 (n=120,87)	26.6 (± 28.5)	23.9 (± 24.4)		
Cycle 1, Day 15 (n=93,64)	26.0 (± 28.3)	21.7 (± 29.7)		
Cycle 2, Day 1 (n=105,73)	24.5 (± 31.4)	22.0 (± 24.5)		
Cycle 2, Day 15 (n=95,62)	26.3 (± 25.2)	20.7 (± 27.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Enfortumab Vedotin: Time to Maximum Concentration (Tmax) (Serum)

End point title	PK Parameter for Enfortumab Vedotin: Time to Maximum Concentration (Tmax) (Serum)
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End point description:

Tmax was derived from the PK blood samples collected. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Days				
median (full range (min-max))				
Cycle 1, Day 1 (n=119,87)	0.0278 (0.010 to 0.052)	0.0264 (0.021 to 0.088)		

Cycle 1, Day 15 (n=92,63)	0.0285 (0.014 to 0.054)	0.0264 (0.014 to 0.084)		
Cycle 2, Day 1 (n=104,73)	0.0264 (0.011 to 0.042)	0.0264 (0.015 to 0.074)		
Cycle 2, Day 15 (n=94,62)	0.0285 (0.020 to 0.115)	0.0257 (0.010 to 0.047)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Enfortumab Vedotin: Area Under Concentration-Time Curve (AUC) (Serum)

End point title	PK Parameter for Enfortumab Vedotin: Area Under Concentration-Time Curve (AUC) (Serum)
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End point description:

AUC was derived from the PK blood samples collected. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

AUC0-7 was assessed (in cycles 1 and 2) based on concentration data from Day 1 to Day 8 (pre dose) and AUC0-14 was assessed based on data from D15 (pre dose) to D29 (pre-dose)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Day*microgram per milliliter				
geometric mean (geometric coefficient of variation)				
7-day post-inf AUC(AUC(d0-7))-Cycle 1,D1 n=115,85	34.6 (± 34.0)	33.5 (± 41.4)		
AUC(d0-7) - Cycle 1, Day 15 n=88,63	31.3 (± 43.8)	26.3 (± 46.0)		
AUC(d0-7) - Cycle 2, Day 1 n=104,72	36.4 (± 36.7)	32.0 (± 30.0)		
AUC(d0-7) - Cycle 2, Day 15 n=88,56	35.9 (± 41.2)	27.8 (± 35.8)		
14-day post-inf AUC(AUC(d0-14))Cycle1,D15 n=85,59	34.7 (± 44.7)	30.9 (± 47.5)		
AUC(d0-14) - Cycle 2, Day 15 n=82,60	41.2 (± 40.4)	33.1 (± 36.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Free Monomethyl Auristatin E (MMAE): Cmax (Plasma)

End point title	PK Parameter for Free Monomethyl Auristatin E (MMAE): Cmax (Plasma)
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End point description:

Cmax was derived from the PK blood samples collected. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE or Tab concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Overall Number of Participants Analyzed'=number of participants evaluable for this outcome measure. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	84		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=117,84	3.1 (± 67.0)	2.6 (± 57.8)		
Cycle 1, Day 15 n=93,64	3.9 (± 64.8)	3.5 (± 51.8)		
Cycle 2, Day 1 n=106,72	2.4 (± 57.4)	2.2 (± 60.8)		
Cycle 2, Day 15 n=90,62	3.0 (± 64.8)	2.9 (± 59.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Free MMAE: Tmax (Plasma)

End point title	PK Parameter for Free MMAE: Tmax (Plasma)
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End point description:

Tmax was derived from the PK blood samples collected. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE or Tab concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Overall Number of Participants Analyzed'=number of participants evaluable for this outcome measure. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	84		
Units: Days				
median (full range (min-max))				
Cycle 1, Day 1 n=117,84	1.9 (1 to 5)	1.9 (1 to 4)		
Cycle 1, Day 15 n=93,64	2.0 (1 to 11)	1.9 (1 to 9)		
Cycle 2, Day 1 n=106,72	2.0 (1 to 5)	1.8 (1 to 5)		
Cycle 2, Day 15 n=90,62	1.9 (1 to 9)	1.9 (1 to 10)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Free MMAE: AUC (Plasma)

End point title	PK Parameter for Free MMAE: AUC (Plasma)
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End point description:

AUC was derived from the PK blood samples collected. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, MMAE or Tab concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Overall Number of Participants Analyzed'=number of participants evaluable for this outcome measure. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

AUC0-7 was assessed (in cycles 1 and 2) based on concentration data from Day 1 to Day 8 (pre dose) and AUC0-14 was assessed based on data from D15 (pre dose) to D29 (pre-dose)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	117	84		
Units: Day*nanogram per milliliter				
geometric mean (geometric coefficient of variation)				
7-day post-inf AUC(AUC(d0-7))- Cycle1,Day1 n=115,84	14.1 (± 81.7)	13.0 (± 64.1)		
AUC(d0-7) - Cycle 1, Day 15 n=88,66	19.1 (± 79.1)	18.1 (± 65.0)		
AUC(d0-7) - Cycle 2, Day 1 n=104,72	11.3 (± 58.0)	10.6 (± 65.0)		
AUC(d0-7) - Cycle 2, Day 15 n=88,57	14.9 (± 64.7)	15.3 (± 60.2)		
14-day post-inf AUC(AUC(d0-14))- Cycle1,D15 n=91,62	25.9 (± 74.7)	22.6 (± 76.4)		
AUC(d0-14) - Cycle 2, Day 15 n=84,63	19.1 (± 61.2)	21.3 (± 65.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for Total Antibody (TAb): Cmax (Serum)

End point title | PK Parameter for Total Antibody (TAb): Cmax (Serum)

End point description:

Cmax was derived from the PK blood samples collected. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type | Secondary

End point timeframe:

Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Microgram per milliliter				
geometric mean (geometric coefficient of variation)				
Cycle 1, Day 1 n=120,87	26.6 (± 30.4)	26.4 (± 23.4)		
Cycle 1, Day 15 n=93,64	30.9 (± 22.9)	27.3 (± 25.7)		
Cycle 2, Day 1 n=105,74	26.2 (± 30.5)	26.3 (± 23.8)		
Cycle 2, Day 15 n=95,62	30.2 (± 22.7)	27.1 (± 28.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for TAb: Tmax (Serum)

End point title | PK Parameter for TAb: Tmax (Serum)

End point description:

Tmax was derived from the PK blood samples collected. Time of maximum concentration corresponds to the end of infusion sample time. Day 1 data informed by samples collected on Day 1, Day 3, and Day 8. Day 15 data informed by samples collected on Day 15, Day 17, and Day 22. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type | Secondary

End point timeframe:

Collected during cycle 1 and 2 of treatment (each cycle=28 days) at Day 1 pre-dose and end of infusion, Day 3, Day 8 pre-dose and end of infusion, Day 15 pre-dose and end of infusion, Day 17, and Day 22

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Days				
median (full range (min-max))				
Cycle 1, Day 1 n=119,87	0.0278 (0.010 to 0.052)	0.0264 (0.021 to 0.088)		
Cycle 1, Day 15 n=92,63	0.0285 (0.014 to 0.054)	0.0264 (0.014 to 0.084)		
Cycle 2, Day 1 n=104,74	0.0264 (0.011 to 0.042)	0.0264 (0.015 to 0.074)		
Cycle 2, Day 15 n=94,62	0.0285 (0.020 to 0.115)	0.0257 (0.010 to 0.047)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter for TAB: AUC (Serum)

End point title	PK Parameter for TAB: AUC (Serum)
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End point description:

AUC was derived from the PK blood samples collected. PK analysis set: all participants who received enfortumab vedotin and from whom at least one blood sample was collected and assayed for enfortumab vedotin, monomethyl auristatin E (MMAE) or total antibody (Tab) concentration. Corresponding records of the time of dosing and sample collection must also be available for all enfortumab vedotin. Here, 'Number Analyzed'= participants evaluable at specified timepoints.

End point type	Secondary
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End point timeframe:

AUC0-7 was assessed (in cycles 1 and 2) based on concentration data from Day 1 to Day 8 (pre dose) and AUC0-14 was assessed based on data from D15 (pre dose) to D29 (pre-dose)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	120	87		
Units: Day*microgram per milliliter				
geometric mean (geometric coefficient of variation)				
7-day post-inf AUC(AUC(d0-7)) - Cycle1,D1 n=115,85	63.4 (± 33.6)	66.8 (± 34.3)		
AUC(d0-7) - Cycle 1, Day 15 n=88,63	77.6 (± 35.2)	72.3 (± 37.9)		
AUC(d0-7) - Cycle 2, Day 1 n=104,72	73.2 (± 33.5)	72.9 (± 26.4)		
AUC(d0-7) - Cycle 2, Day 15 n=88,56	87.9 (± 30.6)	81.0 (± 30.9)		

14-day post-inf AUC(AUC(d0-14))- Cycle1,D15 n=93,62	98.1 (± 38.8)	91.1 (± 40.3)		
AUC(d0-14) - Cycle 2, Day 15 n=84,62	113.0 (± 33.8)	109.7 (± 41.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Adverse Events (AEs): Final Analysis

End point title	Number of Subjects With Adverse Events (AEs): Final Analysis
End point description:	
<p>AE=untoward medical occurrence associated with use of study intervention, whether or not considered related. Treatment emergent adverse event(TEAE)=newly occurring/worsening AE after first dose, within 30 days after last dose. According to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03: Grade(G)3=severe AE,G4=life-threatening, urgent intervention indicated, G5=death related to AE. Participants who discontinued treatment due to treatment related TEAEs captured under TEAEs leading to treatment discontinuation. SAE=event at any dose led to death;life-threatening;required inpatient hospitalization/prolongation of existing hospitalization; persistent/significant disability/incapacity;congenital anomaly/birth defect/ important medical event. Treatment related AEs, SAEs, deaths also included. Treatment relatedness was judged by investigator. Safety Analysis Set: includes all participants who received at least one dose of enfortumab vedotin.</p>	
End point type	Secondary
End point timeframe:	
<p>Cohort 1: median treatment duration time: 4.60 months (range 0.5, 43.0); Cohort 2: median treatment duration time: 5.98 months (range 0.3 to 25.8)</p>	

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Participants				
Any treatment-emergent AEs (TEAEs)	125	89		
Treatment-related TEAEs	117	86		
Any grade 3-5 TEAEs	93	62		
Treatment-related grade 3-5 TEAEs	70	49		
Any serious TEAEs	59	35		
Treatment-related serious TEAEs	24	15		
Any TEAEs leading to treatment discontinuation	22	21		
TR TEAEs leading to treatment discontinuation	16	17		
Any TEAEs leading to death	7	8		
Treatment-related TEAEs leading to death	0	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Final Analysis

End point title	Overall Survival (OS): Final Analysis
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End point description:

OS is defined as the time from first dose of enfortumab vedotin to death from any cause. Full analysis set: includes all enrolled participants who received at least one dose of enfortumab vedotin.

End point type	Secondary
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End point timeframe:

Cohort 1: median follow-up: 61.0 months (range 59.63, 62.36); Cohort 2: median follow-up time: 45.8 months (range 44.91 to 48.95)

End point values	Enfortumab vedotin - Cohort 1	Enfortumab vedotin - Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	89		
Units: Months				
median (confidence interval 95%)	12.4 (9.46 to 15.57)	15.6 (11.24 to 20.37)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Cohort 1: maximum up to 43.0 months of treatment; Cohort 2: maximum up to 25.8 months of treatment

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	v26.0

Reporting groups

Reporting group title	Enfortumab vedotin - Cohort 2
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Reporting group description:

Participants in Cohort 2 had received no platinum-containing chemotherapy were ineligible for treatment with cisplatin at the time of enrollment. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Reporting group title	Enfortumab vedotin - Cohort 1
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Reporting group description:

Participants in Cohort 1 had received prior treatment with platinum-containing chemotherapy. Enfortumab vedotin, at a dose of 1.25 mg/kg, was administered to participants as an IV infusion over approximately 30 minutes on Days 1, 8, and 15 of each 28-day cycle.

Serious adverse events	Enfortumab vedotin - Cohort 2	Enfortumab vedotin - Cohort 1	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 89 (39.33%)	59 / 125 (47.20%)	
number of deaths (all causes)	72	104	
number of deaths resulting from adverse events	8	7	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cancer pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
alternative dictionary used:			

MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma metastatic			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 89 (3.37%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Transitional cell carcinoma			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Embolism			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (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			
Chills alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Non-cardiac chest pain alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aspiration alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pulmonary embolism		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic obstructive pulmonary disease		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cough		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspnoea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	4 / 125 (3.20%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoxia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	3 / 125 (2.40%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Interstitial lung disease		
alternative dictionary used: MedDRA 26.0		

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Amylase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (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			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (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 alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urine output decreased alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
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			
Compression fracture alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial thrombosis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	2 / 89 (2.25%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (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			
Spinal cord compression alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral motor neuropathy alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Demyelinating polyneuropathy alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (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			
Neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	5 / 125 (4.00%)	
occurrences causally related to treatment / all	1 / 1	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	1 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Odynophagia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal haemorrhage		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Enterocolitis		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diarrhoea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	3 / 89 (3.37%)	3 / 125 (2.40%)
occurrences causally related to treatment / all	2 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Colitis		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	1 / 89 (1.12%)	2 / 125 (1.60%)
occurrences causally related to treatment / all	0 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal pain		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	1 / 89 (1.12%)	3 / 125 (2.40%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Small intestinal obstruction		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0

Vomiting alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders Bile duct stone alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders Rash vesicular alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 89 (10.11%)	4 / 125 (3.20%)	
occurrences causally related to treatment / all	3 / 10	1 / 4	
deaths causally related to treatment / all	1 / 2	0 / 0	
Urinary tract obstruction			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 89 (3.37%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	1 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Kidney infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint abscess			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	6 / 125 (4.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	0 / 89 (0.00%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia bacterial			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	4 / 89 (4.49%)	4 / 125 (3.20%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Urinary tract infection			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	3 / 89 (3.37%)	6 / 125 (4.80%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary tract infection staphylococcal alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders Metabolic acidosis alternative dictionary used: MedDRA 26.0 subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypomagnesaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed	0 / 89 (0.00%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	1 / 89 (1.12%)	0 / 125 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	2 / 125 (1.60%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	1 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	1 / 125 (0.80%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	3 / 125 (2.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
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 - Cohort 2	Enfortumab vedotin - Cohort 1	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	88 / 89 (98.88%)	123 / 125 (98.40%)	
Vascular disorders			
Hypertension			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 5	7 / 125 (5.60%) 12	
Hypotension alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	4 / 89 (4.49%) 5	9 / 125 (7.20%) 10	
General disorders and administration site conditions			
Asthenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 15	7 / 125 (5.60%) 7	
Chills alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	7 / 89 (7.87%) 8	5 / 125 (4.00%) 9	
Fatigue alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	40 / 89 (44.94%) 41	66 / 125 (52.80%) 71	
Gait disturbance alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 9	7 / 125 (5.60%) 7	
Malaise alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	2 / 89 (2.25%) 3	10 / 125 (8.00%) 10	
Oedema peripheral alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	20 / 89 (22.47%) 22	31 / 125 (24.80%) 45	
Pyrexia alternative dictionary used: MedDRA 26.0			

subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 16	15 / 125 (12.00%) 17	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 9	7 / 125 (5.60%) 8	
Dyspnoea alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	14 / 89 (15.73%) 16	15 / 125 (12.00%) 19	
Dysphonia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	7 / 125 (5.60%) 7	
Cough alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	12 / 89 (13.48%) 15	20 / 125 (16.00%) 25	
Psychiatric disorders			
Anxiety alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 5	4 / 125 (3.20%) 5	
Insomnia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	13 / 89 (14.61%) 13	18 / 125 (14.40%) 18	
Investigations			
Amylase increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	15 / 89 (16.85%) 19	13 / 125 (10.40%) 17	
Aspartate aminotransferase increased alternative dictionary used:			

MedDRA 26.0			
subjects affected / exposed	11 / 89 (12.36%)	19 / 125 (15.20%)	
occurrences (all)	15	27	
Blood alkaline phosphatase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	1 / 89 (1.12%)	7 / 125 (5.60%)	
occurrences (all)	1	7	
Blood creatinine increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	5 / 89 (5.62%)	11 / 125 (8.80%)	
occurrences (all)	10	17	
Lipase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 89 (10.11%)	16 / 125 (12.80%)	
occurrences (all)	15	27	
Lymphocyte count decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	2 / 89 (2.25%)	9 / 125 (7.20%)	
occurrences (all)	5	9	
Weight decreased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	31 / 89 (34.83%)	40 / 125 (32.00%)	
occurrences (all)	33	41	
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 89 (10.11%)	15 / 125 (12.00%)	
occurrences (all)	11	16	
Injury, poisoning and procedural complications			
Fall			
alternative dictionary used: MedDRA 26.0			
subjects affected / exposed	9 / 89 (10.11%)	14 / 125 (11.20%)	
occurrences (all)	12	18	
Infusion related reaction			
alternative dictionary used: MedDRA 26.0			

subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 6	4 / 125 (3.20%) 5	
Cardiac disorders			
Palpitations alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 7	1 / 125 (0.80%) 1	
Tachycardia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	1 / 89 (1.12%) 1	9 / 125 (7.20%) 10	
Nervous system disorders			
Dizziness alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 89 (11.24%) 12	20 / 125 (16.00%) 23	
Dysgeusia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	27 / 89 (30.34%) 28	49 / 125 (39.20%) 53	
Headache alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	5 / 89 (5.62%) 6	6 / 125 (4.80%) 6	
Paraesthesia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	6 / 89 (6.74%) 7	4 / 125 (3.20%) 4	
Peripheral motor neuropathy alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 9	14 / 125 (11.20%) 16	
Peripheral sensory neuropathy alternative dictionary used: MedDRA 26.0			

subjects affected / exposed occurrences (all)	47 / 89 (52.81%) 53	54 / 125 (43.20%) 59	
Blood and lymphatic system disorders			
Anaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	34 / 89 (38.20%) 42	44 / 125 (35.20%) 62	
Neutropenia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	10 / 89 (11.24%) 12	13 / 125 (10.40%) 22	
Eye disorders			
Dry eye alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	17 / 89 (19.10%) 19	30 / 125 (24.00%) 32	
Lacrimation increased alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	12 / 89 (13.48%) 14	21 / 125 (16.80%) 25	
Punctate keratitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3	9 / 125 (7.20%) 9	
Vision blurred alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	9 / 89 (10.11%) 10	20 / 125 (16.00%) 25	
Blepharitis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)	3 / 89 (3.37%) 3	8 / 125 (6.40%) 9	
Gastrointestinal disorders			
Abdominal distension alternative dictionary used: MedDRA 26.0			

subjects affected / exposed	7 / 89 (7.87%)	4 / 125 (3.20%)
occurrences (all)	8	4
Abdominal pain		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	6 / 89 (6.74%)	23 / 125 (18.40%)
occurrences (all)	8	26
Abdominal pain upper		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	5 / 89 (5.62%)	6 / 125 (4.80%)
occurrences (all)	7	6
Constipation		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	19 / 89 (21.35%)	35 / 125 (28.00%)
occurrences (all)	26	41
Diarrhoea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	30 / 89 (33.71%)	52 / 125 (41.60%)
occurrences (all)	52	73
Dry mouth		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	8 / 89 (8.99%)	11 / 125 (8.80%)
occurrences (all)	10	11
Dysphagia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	2 / 89 (2.25%)	7 / 125 (5.60%)
occurrences (all)	3	7
Gastroesophageal reflux disease		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	5 / 89 (5.62%)	9 / 125 (7.20%)
occurrences (all)	5	9
Nausea		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	26 / 89 (29.21%)	56 / 125 (44.80%)
occurrences (all)	35	68

<p>Stomatitis</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>6 / 89 (6.74%)</p> <p>7</p>	<p>10 / 125 (8.00%)</p> <p>11</p>	
<p>Vomiting</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p>	<p>11 / 89 (12.36%)</p> <p>13</p>	<p>24 / 125 (19.20%)</p> <p>36</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Dry skin</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Alopecia</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash maculo-papular</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash macular</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Rash erythematous</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Pruritus</p> <p>alternative dictionary used: MedDRA 26.0</p> <p>subjects affected / exposed occurrences (all)</p> <p>Skin hyperpigmentation</p> <p>alternative dictionary used: MedDRA 26.0</p>	<p>18 / 89 (20.22%)</p> <p>20</p> <p>48 / 89 (53.93%)</p> <p>49</p> <p>28 / 89 (31.46%)</p> <p>40</p> <p>6 / 89 (6.74%)</p> <p>8</p> <p>6 / 89 (6.74%)</p> <p>10</p> <p>31 / 89 (34.83%)</p> <p>37</p>	<p>35 / 125 (28.00%)</p> <p>38</p> <p>64 / 125 (51.20%)</p> <p>67</p> <p>29 / 125 (23.20%)</p> <p>45</p> <p>6 / 125 (4.80%)</p> <p>7</p> <p>15 / 125 (12.00%)</p> <p>16</p> <p>34 / 125 (27.20%)</p> <p>41</p>	

<p>subjects affected / exposed occurrences (all)</p> <p>Skin exfoliation alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p>	<p>4 / 89 (4.49%) 4</p> <p>3 / 89 (3.37%) 4</p>	<p>13 / 125 (10.40%) 14</p> <p>7 / 125 (5.60%) 10</p>	
<p>Renal and urinary disorders</p> <p>Pollakiuria alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Acute kidney injury alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Dysuria alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Haematuria alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p>	<p>5 / 89 (5.62%) 5</p> <p>6 / 89 (6.74%) 6</p> <p>5 / 89 (5.62%) 6</p> <p>10 / 89 (11.24%) 11</p>	<p>4 / 125 (3.20%) 4</p> <p>4 / 125 (3.20%) 4</p> <p>6 / 125 (4.80%) 6</p> <p>10 / 125 (8.00%) 13</p>	
<p>Musculoskeletal and connective tissue disorders</p> <p>Back pain alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Arthralgia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Pain in extremity alternative dictionary used: MedDRA 26.0</p>	<p>4 / 89 (4.49%) 4</p> <p>8 / 89 (8.99%) 10</p>	<p>21 / 125 (16.80%) 22</p> <p>14 / 125 (11.20%) 16</p>	

<p>subjects affected / exposed occurrences (all)</p> <p>Myalgia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Muscular weakness alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p>	<p>10 / 89 (11.24%) 10</p> <p>6 / 89 (6.74%) 6</p> <p>8 / 89 (8.99%) 10</p>	<p>14 / 125 (11.20%) 16</p> <p>9 / 125 (7.20%) 11</p> <p>10 / 125 (8.00%) 12</p>	
<p>Infections and infestations</p> <p>Oral candidiasis alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Urinary tract infection alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p>	<p>5 / 89 (5.62%) 5</p> <p>13 / 89 (14.61%) 17</p>	<p>7 / 125 (5.60%) 7</p> <p>18 / 125 (14.40%) 23</p>	
<p>Metabolism and nutrition disorders</p> <p>Decreased appetite alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Dehydration alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Hypercalcaemia alternative dictionary used: MedDRA 26.0 subjects affected / exposed occurrences (all)</p> <p>Hyperglycaemia alternative dictionary used: MedDRA 26.0</p>	<p>35 / 89 (39.33%) 43</p> <p>10 / 89 (11.24%) 11</p> <p>6 / 89 (6.74%) 6</p>	<p>64 / 125 (51.20%) 81</p> <p>12 / 125 (9.60%) 14</p> <p>2 / 125 (1.60%) 2</p>	

subjects affected / exposed	12 / 89 (13.48%)	17 / 125 (13.60%)
occurrences (all)	13	20
Hyperkalaemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	5 / 89 (5.62%)	2 / 125 (1.60%)
occurrences (all)	8	2
Hyperuricaemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	4 / 89 (4.49%)	8 / 125 (6.40%)
occurrences (all)	4	14
Hypoalbuminaemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	5 / 89 (5.62%)	4 / 125 (3.20%)
occurrences (all)	6	4
Hypokalaemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	6 / 89 (6.74%)	16 / 125 (12.80%)
occurrences (all)	7	20
Hyponatraemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	9 / 89 (10.11%)	15 / 125 (12.00%)
occurrences (all)	12	17
Hypophosphataemia		
alternative dictionary used: MedDRA 26.0		
subjects affected / exposed	5 / 89 (5.62%)	8 / 125 (6.40%)
occurrences (all)	5	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 November 2017	<p>Amendment 1: Added Management of Hyperglycemia section as follows:</p> <p>Investigators should monitor blood glucose levels and are advised to perform additional assessments if any symptoms of hyperglycemia are observed, including a thorough evaluation for infection. In addition, if steroids are used to treat any other condition, blood glucose levels may require additional monitoring. If elevated blood glucose levels are observed, patients should be treated according to local standard of care and referral to endocrinology may be considered.</p> <p>Patients, especially those with a history of or ongoing diabetes mellitus or hyperglycemia, should be advised to immediately notify their physician if their glucose level becomes difficult to control or if they experience symptoms suggestive of hyperglycemia such as frequent urination, increased thirst, blurred vision, fatigue, and headache.</p> <p>Patients who enter the study with an elevated HbA1c ($\geq 6.5\%$) at baseline should be referred to an appropriate provider during Cycle 1 for glucose management. Blood glucose should be checked prior to each dosing and dose should be withheld for blood glucose >250 mg/dL (Grade 3 or higher). Dosing may continue once the patient's blood glucose has improved to \leq Grade 2 and patient is clinically and metabolically stable.</p>
13 February 2018	<p>Amendment 2: Added Cycle 6 (± 1 week) slit lamp examinations for at least the first 60 enrolled patients.</p> <p>Clarified that end of treatment (EOT) slit lamp exams will be performed for all patients who experience a corneal adverse event on study.</p>
13 April 2018	<p>Amendment 3: Added text regarding drug administration setting as follows: The patient should be observed during administration of enfortumab vedotin and for at least 60 minutes following the infusion during the first 3 cycles. All supportive measures consistent with optimal subject care should be given throughout the study according to institutional standards.</p>
16 April 2018	<p>Amendment 4: Revised primary objective as follows:</p> <p>To determine the antitumor activity of singleagent enfortumab vedotin as measured by confirmed objective response rate (ORR) in patients with locally advanced or metastatic urothelial cancer who to have previously received systemic therapy with a CPI and either previously received platinum-containing chemotherapy or are platinum-naïve and cisplatin-ineligible</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported