



## Clinical trial results:

### A Single arm, Multicenter, International Trial of Tisotumab Vedotin (HuMax®-TF-ADC) in Previously Treated, Recurrent or Metastatic Cervical Cancer

#### Summary

EudraCT number	2017-003413-25
Trial protocol	CZ DK BE DE IT ES
Global end of trial date	02 August 2022

#### Results information

Result version number	v1 (current)
This version publication date	13 July 2023
First version publication date	13 July 2023

#### Trial information

##### Trial identification

Sponsor protocol code	GCT1015-04
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03438396
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Genmab A/S
Sponsor organisation address	Kalvebod Brygge 43, Copenhagen V, Denmark, 1560
Public contact	Medical Lead, Genmab, +45 7020 2728, regulatory@genmab.com
Scientific contact	Medical Lead, Genmab, +45 7020 2728, regulatory@genmab.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	02 August 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 August 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of the trial is to determine the anti-tumor efficacy in subjects with cervical cancer.

Protection of trial subjects:

All the subjects will sign the informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 June 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czechia: 11
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Denmark: 9
Country: Number of subjects enrolled	Spain: 16
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	101
EEA total number of subjects	86

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)	88
From 65 to 84 years	13
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

This study was conducted in Europe and the US.

### Pre-assignment

Screening details:

102 subjects with recurrent or metastatic cervical cancer were enrolled in the study out of which 101 subjects received study treatment. These subjects were assessed until they experienced IRC-verified disease progression, started new anti-cancer therapy, discontinued the trial, or died.

### Pre-assignment period milestones

Number of subjects started	102 <sup>[1]</sup>
Number of subjects completed	101

### Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not Treated: 1
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Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 102 subjects were enrolled in the study out of which 101 received atleast one dose of treatment

### Period 1

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

### Arms

Arm title	Tisotumab Vedotin 2.0 mg/kg
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Arm description:

Participants received intravenous (IV) tisotumab vedotin 2.0 mg/kg every 3 weeks (Q3W) until radiographic disease progression verified by the Independent Review Committee (IRC), unacceptable adverse events (AEs) requiring drug discontinuation, withdrawal of consent, lost to follow up, or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Tisotumab Vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Once every 3 weeks until progression or toxicity.

<b>Number of subjects in period 1</b>	<b>Tisotumab Vedotin 2.0 mg/kg</b>
Started	101
Treated	101
Completed	0
Not completed	101
Consent withdrawn by subject	5
Death	85
Lost to follow-up	2
Reason not Specified	9

## Baseline characteristics

### Reporting groups

Reporting group title	Tisotumab Vedotin 2.0 mg/kg
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Reporting group description:

Participants received intravenous (IV) tisotumab vedotin 2.0 mg/kg every 3 weeks (Q3W) until radiographic disease progression verified by the Independent Review Committee (IRC), unacceptable adverse events (AEs) requiring drug discontinuation, withdrawal of consent, lost to follow up, or death, whichever occurred first.

Reporting group values	Tisotumab Vedotin 2.0 mg/kg	Total	
Number of subjects	101	101	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gest. age lt 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64years)	88	88	
Elderly (65-84 years)	13	13	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	101	101	
Male	0	0	

## End points

### End points reporting groups

Reporting group title	Tisotumab Vedotin 2.0 mg/kg
Reporting group description: Participants received intravenous (IV) tisotumab vedotin 2.0 mg/kg every 3 weeks (Q3W) until radiographic disease progression verified by the Independent Review Committee (IRC), unacceptable adverse events (AEs) requiring drug discontinuation, withdrawal of consent, lost to follow up, or death, whichever occurred first.	

### Primary: Percentage of Participants With Confirmed Objective Response (OR) as Assessed by the Independent Review Committee (IRC)

End point title	Percentage of Participants With Confirmed Objective Response (OR) as Assessed by the Independent Review Committee (IRC) <sup>[1]</sup>
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#### End point description:

Confirmed OR is defined as best overall response of confirmed complete response (CR) or confirmed partial response (PR) based upon RECIST v1.1, assessed by IRC. CR is disappearance of all target and non-target lesions and no new lesions. Confirmed CR is 2 CRs (CR-CR sequence) that were separated by at least 4 weeks with no evidence of progression in-between. PR is  $\geq 30\%$  decrease in sum of diameters of target lesions (compared to baseline) and no unequivocal progression of existing non-target lesions and no new lesion. Confirmed PR is PR-PR sequence or PR-CR sequence that were separated by at least 4 weeks. Intermediate missing (Not Evaluable [NE]) scan evaluations between response scan and confirmation scan were allowed, eg, PR-NE-PR and PR-NE-NE-PR was considered PR confirmed (a repeat scan not earlier than 4 weeks after initial scan documenting response). 95% CI was calculated using the Clopper-Pearson method. FAS=all participants who received at least 1 dose of drug.

End point type	Primary
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#### End point timeframe:

From Day 1 through IRC verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 20 months)

#### 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: This is a single-arm study and no comparison groups could be selected for the primary endpoint. Thus, only descriptive data is provided.

End point values	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: percentage of subjects				
number (confidence interval 95%)	23.8 (15.9 to 33.3)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Duration of Response (DOR) as Assessed by the IRC

End point title	Duration of Response (DOR) as Assessed by the IRC
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**End point description:**

The DOR is defined as the duration from the first documented response of CR or PR (the start date of response, not the date when response was confirmed) to the date of the first documented progression disease (PD) verified by IRC or death. Based upon RECIST v1.1, the CR is defined as disappearance of all target and non-target lesions and no new lesions; the PR is defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions (compared to baseline) and no unequivocal progression of existing non-target lesions and no new lesion; and the PD is defined as at least 20% increase in the sum of diameters of target lesions (compared to baseline), unequivocal progression of existing non-target lesions, and/or new lesion. The DOR was estimated using Kaplan-Meier method. FAS included all subjects who received at least 1 dose of tisotumab vedotin. The DOR was analyzed for those subjects in FAS who achieved confirmed OR, as assessed by the IRC.

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End point type	Secondary
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**End point timeframe:**

From Day 1 through IRC verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

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<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Months				
median (confidence interval 95%)	8.3 (4.2 to 13.5)			

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Percentage of Subjects With Confirmed OR as Assessed by the Investigator**

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End point title	Percentage of Subjects With Confirmed OR as Assessed by the Investigator
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**End point description:**

Confirmed OR is defined as best overall response of confirmed CR or confirmed PR based upon RECIST v1.1, assessed by investigator. CR is defined as disappearance of all target and non-target lesions and no new lesions. Confirmed CR is defined as 2 CRs (CR-CR sequence) that were separated by at least 4 weeks with no evidence of progression in-between. PR is defined as  $\geq 30\%$  decrease in sum of diameters of target lesions (compared to baseline) and no unequivocal progression of existing non-target lesions and no new lesion. Confirmed PR is defined as PR-PR sequence or PR-CR sequence that were separated by at least 4 weeks. Intermediate missing (NE) scan evaluations between response scan and the confirmation scan were allowed, eg, PR-NE-PR and PR-NE-NE-PR was considered PR confirmed (a repeat scan not earlier than 4 weeks after initial scan documenting response). 95% CI was calculated using the Clopper-Pearson method. FAS=all participants who received at least 1 dose of drug.

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End point type	Secondary
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**End point timeframe:**

From Day 1 through investigator verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

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<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Percentage of subjects				
number (confidence interval 95%)	20.8 (13.4 to 30.0)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: DOR as Assessed by the Investigator

End point title	DOR as Assessed by the Investigator
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End point description:

The DOR is defined as the duration from the first documented response of CR or PR (the start date of response, not the date when response was confirmed) to the date of the first documented PD verified by investigator or death. Based upon RECIST v1.1, the CR is defined as disappearance of all target and non-target lesions and no new lesions; the PR is defined as  $\geq 30\%$  decrease in the sum of diameters of target lesions (compared to baseline) and no unequivocal progression of existing non-target lesions and no new lesion; and the PD is defined as at least 20% increase in the sum of diameters of target lesions (compared to baseline), unequivocal progression of existing non-target lesions, and/or new lesion. The DOR was estimated using Kaplan-Meier method. FAS included all participants who received at least 1 dose of tisotumab vedotin. The DOR was analyzed for those participants in FAS who achieved confirmed OR, as assessed by the investigator.

End point type	Secondary
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End point timeframe:

From Day 1 through investigator verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: Months				
median (confidence interval 95%)	8.2 (3.7 to 18.4)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Response (TTR) as Assessed by the IRC

End point title	Time to Response (TTR) as Assessed by the IRC
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End point description:

The TTR is defined as the duration from the start of study drug to the first documented response of either CR or PR based on RECIST v1.1, assessed by the IRC. A confirmed CR is defined as 2 CRs

(disappearance of all target and non-target lesions and no new lesions) that were separated by at least 4 weeks with no evidence of progression in-between. A confirmed PR is defined as 2 PRs ( $\geq 30\%$  decrease in the sum of diameters of target lesions compared to baseline and no unequivocal progression of existing non-target lesions and no new lesion) or an un-confirmed PR and an un-confirmed CR or achieved PR-NE-PR or PR-NE-NE-PR that were separated by at least 4 weeks with no evidence of progression in-between. FAS included all participants who received at least 1 dose of tisotumab vedotin. The TTR was analyzed for those participants in FAS who achieved confirmed OR, as assessed by the IRC.

End point type	Secondary
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End point timeframe:

From Day 1 through IRC verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Months				
median (confidence interval 95%)	1.4 (1.1 to 5.1)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: TTR as Assessed by the Investigator

End point title	TTR as Assessed by the Investigator
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End point description:

The TTR is defined as the duration from the start of study drug to the first documented response of either CR or PR based on RECIST v1.1, assessed by the investigator. A confirmed CR is defined as 2 CRs (disappearance of all target and non-target lesions and no new lesions) that were separated by at least 4 weeks with no evidence of progression in-between. A confirmed PR is defined as 2 PRs ( $\geq 30\%$  decrease in the sum of diameters of target lesions compared to baseline and no unequivocal progression of existing non-target lesions and no new lesion) or an un-confirmed PR and an un-confirmed CR or achieved PR-NE-PR or PR-NE-NE-PR that were separated by at least 4 weeks with no evidence of progression in-between. FAS included all participants who received at least 1 dose of tisotumab vedotin. The TTR was analyzed for those participants in FAS who achieved confirmed OR, as assessed by the investigator.

End point type	Secondary
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End point timeframe:

From Day 1 through investigator verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Months				
median (confidence interval 95%)	1.4 (1.1 to 4.5)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival (PFS) as Assessed by the IRC

End point title	Progression Free Survival (PFS) as Assessed by the IRC
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End point description:

The PFS is defined as the time from the start of study drug until the first documentation of PD based on RECIST v1.1, as assessed by the IRC or death due to any cause, whichever occurred first. The PD based upon RECIST v1.1 is defined as at least 20% increase in the sum of diameters of target lesions (compared to baseline), unequivocal progression of existing non-target lesions, and/or new lesion. The PFS was estimated using Kaplan-Meier method. FAS included all participants who received at least 1 dose of tisotumab vedotin.

End point type	Secondary
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End point timeframe:

From Day 1 through IRC verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)

End point values	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Months				
median (confidence interval 95%)	4.2 (3.0 to 4.4)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs

End point title	Number of Participants With Abnormal Clinical Laboratory Parameters Reported as TEAEs
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End point description:

Laboratory abnormalities that induced clinical signs or symptoms, required concomitant therapy or required changes during treatment emergent period were reported as TEAEs. Number of participants with abnormal clinical laboratory parameters reported as TEAEs are reported. FAS included all participants who received at least 1 dose of tisotumab vedotin.

End point type	Secondary
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End point timeframe:

From Day 1 through 30 days after the last dose of study drug (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Participants				
Anaemia	34			
Neutropenia	4			
Iron deficiency anaemia	3			
Leukocytosis	1			
Leukopenia	1			
Thrombocytopenia	1			
Thrombocytosis	1			
Hypokalaemia	6			
Hypomagnesaemia	6			
Hypocalcaemia	4			
Hyperglycaemia	3			
Hypercreatininaemia	2			
Hyperuricaemia	2			
Hypercalcaemia	1			
Hypernatraemia	1			
Hypoalbuminaemia	1			
Hyponatraemia	1			
Activated partial thromboplastin time prolonged	3			
Neutrophil count decreased	3			
Blood creatinine increased	2			
C-reactive protein increased	2			
International normalised ratio increased	2			
Lymphocyte count decreased	2			
Alanine aminotransferase increased	1			
Aspartate aminotransferase increased	1			
Blood alkaline phosphatase increased	1			
Blood bicarbonate decreased	1			
Blood creatine phosphokinase increased	2			
Blood potassium decreased	1			
Creatinine renal clearance decreased	1			
Platelet count decreased	2			
Prothrombin time prolonged	1			
White blood cell count decreased	1			
Hyperthyroidism	1			
Hypothyroidism	1			
Hypertransaminaemia	3			
Hyperbilirubinaemia	1			
Haematuria	10			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)
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End point description:

An adverse event (AE) is any untoward medical occurrence in a participant who received study drug without regard to possibility of causal relationship. A SAE is defined as an AE that meets one of the following criteria: fatal or life-threatening; results in persistent or significant disability/incapacity; constitutes a congenital anomaly/birth defect; medically significant (an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above [medical and scientific judgment must be exercised in deciding whether an AE is "medically important"]); required inpatient hospitalization or prolongation of existing hospitalization. A TEAE is defined as an AE occurring or worsening between the first dose of tisotumab vedotin and 30 days after the last dose received. FAS included all participants who received at least 1 dose of tisotumab vedotin.

End point type	Secondary
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End point timeframe:

From Day 1 through 30 days after the last dose of study drug (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Participants				
Any TEAE	101			
Any TESAE	44			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival (OS)

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

The OS is defined as the time from the start of study treatment until death due to any cause. The OS was estimated using Kaplan-Meier method. FAS included all participants who received at least 1 dose of tisotumab vedotin.

End point type	Secondary
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End point timeframe:

From Day 1 until death or withdrawal from the study, whichever occurred first (approximately 49 months)

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Months				
median (confidence interval 95%)	12.3 (9.6 to 14.1)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: PFS as Assessed by the Investigator

End point title	PFS as Assessed by the Investigator
End point description:	
The PFS is defined as the time from the start of study drug until the first documentation of PD based on RECIST v1.1, as assessed by the investigator or death due to any cause, whichever occurred first. The PD based upon RECIST v1.1 is defined as at least 20% increase in the sum of diameters of target lesions (compared to baseline), unequivocal progression of existing non-target lesions, and/or new lesion. The PFS was estimated using Kaplan-Meier method. FAS included all participants who received at least 1 dose of tisotumab vedotin.	
End point type	Secondary
End point timeframe:	
From Day 1 through investigator verified disease progression, initiation of new anticancer therapy, study withdrawal, or death, whichever occurred first (approximately 49 months)	

<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: Months				
median (confidence interval 95%)	4.1 (3.3 to 4.6)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Plasma Concentrations of Tisotumab Vedotin (HuMax-TF), Tisotumab Vedotin Antibody-drug Conjugate (HuMax-TF-ADC), and Free Monomethyl Auristatin E (MMAE)

End point title	Plasma Concentrations of Tisotumab Vedotin (HuMax-TF), Tisotumab Vedotin Antibody-drug Conjugate (HuMax-TF-ADC), and Free Monomethyl Auristatin E (MMAE)
End point description:	
Plasma concentrations of HuMax-TF, HuMax-TF-ADC, and Free MMAE measures on Cycle 1 Day 1 (predose and end of infusion) and Cycle 6 Day 1 (predose and end of infusion) are reported. FAS included all participants who received at least 1 dose of tisotumab vedotin. n indicates number analysed	

is the number of subjects available for analysis.

End point type	Secondary
End point timeframe:	
Predose and end of infusion of Cycle 1 Day 1 (C1D1) and Cycle 6 Day 1 (C6D1)	

End point values	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	101			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
HuMax-TF (C1D1-predose) [n=98]	163.48 (± 60.70)			
HuMax-TF (C1D1-end of infusion) [n=98]	41691.0 (± 68.02)			
HuMax-TF (C6D1-predose) [n=54]	150.0 (± 0.0)			
HuMax-TF (C6D1-end of infusion) [n=54]	37042.0 (± 26.10)			
HuMax-TF-ADC (C1D1-predose) [n=96]	30.0 (± 0.0)			
HuMax-TF-ADC (C1D1-end of infusion) [N=97]	38105 (± 92.62)			
HuMax-TF-ADC (C6D1-predose) [n=53]	30.0 (± 0.0)			
HuMax-TF-ADC (C6D1-end of infusion) [n=53]	38105 (± 92.62)			
MMAE (C1D1-predose) [n=96]	12.50 (± 0.0)			
MMAE (C1D1-end of infusion) [n=97]	171.27 (± 102.05)			
MMAE (C6D1-predose) [n=53]	46.71 (± 146.11)			
MMAE (C6D1-end of infusion) [n=54]	177.46 (± 82.62)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Positive Anti-drug Antibodies (ADA) to Tisotumab Vedotin

End point title	Number of Participants With Positive Anti-drug Antibodies (ADA) to Tisotumab Vedotin
End point description:	
Number of participants with positive ADA titer to tisotumab vedotin at baseline and post-baseline are reported. Baseline is defined as the latest available measurement made before the first dose of tisotumab vedotin. For post-baseline results, a participant was considered ADA positive if either ADA is negative at baseline and at least one post-baseline result is positive or positive at baseline and at least one positive post-baseline result with a titer higher than baseline. Participants in FAS (received at least 1 dose of tisotumab vedotin) and who had ADA results at baseline and post-baseline are analysed for this outcome measure.	
End point type	Secondary

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End point timeframe:

Predose of each treatment cycle (Cycle 1 to 21) and end of treatment visit (approximately 49 months)

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<b>End point values</b>	Tisotumab Vedotin 2.0 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	93			
Units: Participants				
ADA positive at Baseline	2			
ADA positive at post-baseline	5			

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Day 1 through 30 days after the last dose of study drug (approximately 49 months)

Adverse event reporting additional description:

The AEs were evaluated per the safety set.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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### Reporting groups

Reporting group title	Tisotumab Vedotin 2.0 mg/kg
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Reporting group description:

Tisotumab Vedotin 2.0 mg/kg - 1Q3W Dose Administration

Serious adverse events	Tisotumab Vedotin 2.0 mg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 101 (43.56%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder Cancer			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cancer Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Lymphoedema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pyrexia			

subjects affected / exposed	3 / 101 (2.97%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Asthenia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Death			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Infusion Site Extravasation			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Non-Cardiac Chest Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Vaginal Haemorrhage			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pleural Effusion			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary Embolism			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
General Physical Condition Abnormal			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Foot Fracture			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post-Traumatic Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thoracic Vertebral Fracture			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Peripheral Sensorimotor Neuropathy			

subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Peripheral Motor Neuropathy			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ulcerative Keratitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ileus			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		
Rectal Haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Constipation			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Intestinal Obstruction			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Subileus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large Intestinal Obstruction			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary Tract Obstruction			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Acute Kidney Injury			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cystitis Haemorrhagic			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Failure			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fistula Discharge			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic Sepsis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lower Respiratory Tract Infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Septic Shock			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Pneumonia			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory Tract Infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

<b>Non-serious adverse events</b>	Tisotumab Vedotin 2.0 mg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 101 (98.02%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Tumour pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Cancer pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Venous thrombosis limb			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Thrombosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Lymphoedema			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Aortic thrombosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Hot flush			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	6		
Deep vein thrombosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	18 / 101 (17.82%)		
occurrences (all)	18		
Oedema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Peripheral swelling			



subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Pain			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Oedema peripheral			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	9		
Non-cardiac chest pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Nodule			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Mucosal disorder			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Facial pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	15 / 101 (14.85%)		
occurrences (all)	38		
Face oedema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	4		
Fatigue			

subjects affected / exposed	35 / 101 (34.65%)		
occurrences (all)	47		
Chest pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Chest discomfort			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Influenza like illness			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	7		
Gait disturbance			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Infusion site coldness			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Localised oedema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Immune system disorders			
Allergy to metals			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Vulvovaginal pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Vaginal ulceration			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Vaginal fistula			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Vaginal discharge			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	5		
Rectocele			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Vaginal haemorrhage			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	13		
Cystocele			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Metrorrhagia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Genital swelling			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Genital prolapse			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Pulmonary embolism			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Paranasal sinus haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Paranasal sinus discomfort			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Oropharyngeal pain			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Nasal obstruction			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Sinus congestion			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Nasal dryness			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Nasal congestion			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Haemoptysis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Pulmonary oedema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Epistaxis			
subjects affected / exposed	39 / 101 (38.61%)		
occurrences (all)	49		
Dysphonia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	9 / 101 (8.91%)		
occurrences (all)	9		
Sneezing			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed occurrences (all)	5 / 101 (4.95%) 6		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	5		
Insomnia			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	10		
Depression			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Depressed mood			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Investigations			
White blood cell count decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Weight increased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Weight decreased			
subjects affected / exposed	14 / 101 (13.86%)		
occurrences (all)	14		
Prothrombin time prolonged			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Neutrophil count decreased			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Lymphocyte count decreased			

subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
International normalised ratio increased			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Ejection fraction decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Creatinine renal clearance decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
C-reactive protein increased			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Blood potassium decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Blood creatinine increased			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Blood bicarbonate decreased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Alanine aminotransferase increased			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Activated partial thromboplastin time prolonged			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Thermal burn			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	2		
Urinary tract stoma complication			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Spinal compression fracture			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Ligament sprain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Foot fracture			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Conjunctival scar			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Conjunctival abrasion			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Radiation proctitis			

subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Radiation associated haemorrhage subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Procedural pain subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Post procedural haemorrhage subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Cardiac disorders			
Stress cardiomyopathy subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Sinus tachycardia subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Myocardial infarction subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Nervous system disorders			
Sensory loss subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Polyneuropathy subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Peripheral sensorimotor neuropathy subjects affected / exposed occurrences (all)	4 / 101 (3.96%) 4		
Peripheral motor neuropathy subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3		
Paraesthesia			



subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	6		
Neuropathy peripheral			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Neuralgia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
Sciatica			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hypoaesthesia			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	4		
Headache			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	12		
Dysgeusia			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Dizziness			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Burning sensation			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Hyperaesthesia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Peripheral sensory neuropathy			
subjects affected / exposed	19 / 101 (18.81%)		
occurrences (all)	24		
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

Anaemia			
subjects affected / exposed	33 / 101 (32.67%)		
occurrences (all)	39		
Leukopenia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Thrombocytosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Iron deficiency anaemia			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Vertigo			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Eye disorders			
Eye irritation			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Eye discharge			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Amblyopia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Foreign body sensation in eyes			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Corneal bleeding			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Conjunctival haemorrhage			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
Keratitis			
subjects affected / exposed	11 / 101 (10.89%)		
occurrences (all)	15		
Eye inflammation			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Blepharospasm			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Ocular hyperaemia			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Chalazion			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Corneal erosion			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Eye movement disorder			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Conjunctival erosion			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Entropion			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Vision blurred			

subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Corneal scar			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Conjunctival hyperaemia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Dry eye			
subjects affected / exposed	25 / 101 (24.75%)		
occurrences (all)	30		
Punctate keratitis			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Trichiasis			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Retinal exudates			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Noninfective conjunctivitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Keratopathy			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Lacrimation increased			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Ulcerative keratitis			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Meibomianitis			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Asthenopia			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Photophobia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Meibomian gland dysfunction			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Ocular hypertension			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Blepharitis			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	10		
Eye pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Eye pruritus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Gastrointestinal disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Dry mouth			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	8		
Constipation			
subjects affected / exposed	20 / 101 (19.80%)		
occurrences (all)	20		

Dyschezia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Colitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Anal incontinence			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	25 / 101 (24.75%)		
occurrences (all)	29		
Anal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	2		
Abdominal pain upper			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Abdominal pain lower			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	13 / 101 (12.87%)		
occurrences (all)	18		
Abdominal distension			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Duodenogastric reflux			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Haematochezia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

Subileus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	4		
Retching			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Oesophagitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	41 / 101 (40.59%)		
occurrences (all)	51		
Mouth ulceration			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Large intestinal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Small intestinal stenosis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hiatus hernia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Enteritis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Gastritis subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Gingival bleeding subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Flatulence subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Vomiting subjects affected / exposed occurrences (all)	17 / 101 (16.83%) 25		
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Hypertransaminaemia subjects affected / exposed occurrences (all)	3 / 101 (2.97%) 3		
Skin and subcutaneous tissue disorders Rash macular subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Dermatitis acneiform subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Skin hyperpigmentation subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Skin discolouration subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Rash maculo-papular			



subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	14 / 101 (13.86%)		
occurrences (all)	16		
Pain of skin			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	4		
Erythema			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	5		
Eczema			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Dermatitis allergic			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Alopecia			
subjects affected / exposed	39 / 101 (38.61%)		
occurrences (all)	39		
Pruritus			
subjects affected / exposed	14 / 101 (13.86%)		
occurrences (all)	18		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	6		
Urinary tract obstruction			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

Urinary tract disorder subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Urinary incontinence subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Urinary bladder haemorrhage subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Ureteric obstruction subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Renal failure subjects affected / exposed occurrences (all)	2 / 101 (1.98%) 2		
Hydronephrosis subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Haematuria subjects affected / exposed occurrences (all)	9 / 101 (8.91%) 11		
Chromaturia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Bladder outlet obstruction subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 2		
Hyperthyroidism subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1		
Musculoskeletal and connective tissue disorders			

Pain in extremity			
subjects affected / exposed	13 / 101 (12.87%)		
occurrences (all)	13		
Neck pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	17 / 101 (16.83%)		
occurrences (all)	26		
Musculoskeletal pain			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	7		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Muscle spasms			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	4		
Limb discomfort			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Joint stiffness			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hypercreatinaemia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Groin pain			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		

Flank pain			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	5		
Osteoarthritis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Bone pain			
subjects affected / exposed	5 / 101 (4.95%)		
occurrences (all)	6		
Back pain			
subjects affected / exposed	8 / 101 (7.92%)		
occurrences (all)	8		
Arthralgia			
subjects affected / exposed	17 / 101 (16.83%)		
occurrences (all)	25		
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Herpes ophthalmic			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Clostridium difficile colitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	31 / 101 (30.69%)		
occurrences (all)	49		
Corona virus infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Device related infection			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Folliculitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Herpes zoster oticus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	2		
Gastroenteritis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Gingivitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Genital herpes			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	7 / 101 (6.93%)		
occurrences (all)	7		
Parotitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Stenotrophomonas infection			

subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	10 / 101 (9.90%)		
occurrences (all)	12		
Vaginal infection			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Urinary tract infection bacterial			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Abscess limb			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Catheter site infection			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Tooth abscess			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hypomagnesaemia			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		
Hypokalaemia			
subjects affected / exposed	6 / 101 (5.94%)		
occurrences (all)	6		

Hypocalcaemia			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	4 / 101 (3.96%)		
occurrences (all)	5		
Hypernatraemia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hyperglycaemia			
subjects affected / exposed	3 / 101 (2.97%)		
occurrences (all)	3		
Hypercreatininaemia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	3		
Hypercalcaemia			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Diabetes mellitus			
subjects affected / exposed	1 / 101 (0.99%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	2 / 101 (1.98%)		
occurrences (all)	2		
Decreased appetite			
subjects affected / exposed	18 / 101 (17.82%)		
occurrences (all)	19		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 January 2018	Amendment 1 – The protocol was updated to include – A justification for control group was added. • A subgroup analysis was added by region (EU/US) to assess regional consistency of treatment effects. • A third post-treatment observation period was defined. • The assumption of the 25% true objective response rate (ORR) was justified.
08 February 2018	Amendment 2 - The protocol was amended to clarify the statistical power for ORRs in the range 21% to 25%.
11 February 2018	Amendment 3 - The protocol was amended for the following updates - The frequency of survival follow-up was specified. • It was made clear that chemotherapy should not be considered a prior systemic treatment regimen if it was given in an adjuvant or neoadjuvant setting, alone or in conjunction with radiation therapy. • The duration of preservative-free lubricating eye drops' prophylactic use was indicated. • The allowed concurrent anticoagulation therapy guidance has been clarified. • The dosage delay guidelines and dose reduction methodology have been updated. • The mitigation strategy for bleeding events was changed to state that, regardless of the severity, any pulmonary or central nervous system (CNS) haemorrhage would result in a permanent end to therapy. • It was stated that no additional adverse events (AEs) should be recorded after the AE reporting period expires, which is 30 days following the final dose.
31 October 2018	Amendment 4 – The protocol was amended for the following updates - • The window for screening visit 2 was extended by 2 days, allowing for performance of this visit seven days (instead of five) before Cycle 1 (D1). • It was made clear that tisotumab vedotin had to be given over at least 30 minutes and ideally within 60 minutes. • The specifications for measuring body weight in order to calculate dose were clarified. • The tisotumab vedotin program's safety reporting standards were all aligned.
17 June 2019	Based on health authority feedback, the timing of the primary analysis of the trial was changed to ensure that all responders were followed for $\geq 6$ months.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported