Clinical trial results:
Open Label Phase 2 Study of Tisotumab Vedotin for Patients with Platinum-Resistant Ovarian Cancer with a Safety Run-in of a Dose-Dense Regimen

Summary

EudraCT number	2019-001219-22
Trial protocol	ES IE DK IT
Global end of trial date	08 February 2022

Results information

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

Trial information

Trial identification

Sponsor protocol code	SGNTV-002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03657043
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	02 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 February 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

• (Safety run-in) Evaluate safety and tolerability of a dose-dense regimen of tisotumab vedotin • (Part A and B) Evaluate antitumor activity of tisotumab vedotin

Protection of trial subjects:

This study was conducted in accordance with applicable regulations/guidelines set forth by the Food and Drug Administration (FDA) in 21 CFR Parts 11, 50, 54, 56, and 312; the European Union (EU) Directive 2001/20/EC and 2005/28/EC; and with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents are retained in accordance with ICH GCP.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 March 2019
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	United States: 57
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Denmark: 1
Worldwide total number of subjects	98
EEA total number of subjects	41

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)	59
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 98 participants were enrolled into the Safety Run-In and Part B Expansion cohorts, of which 94 received study drug. No participants were enrolled into Part A. The date of first participant enrollment was 21-Mar-2019. The date of last participant completion was 08-Feb-2022.

Pre-assignment

Screening details:

Participants were screened for eligibility prior to enrollment.

Period 1

Period 1 title	All Enrolled
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In 0.9 mg/kg 3Q4W

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental
Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Arm title	Safety Run-In 1.2 mg/kg 3Q4W

Arm description:

Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental
Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 1.2 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Arm title	Part B Expansion

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental

Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Number of subjects in period 1	Safety Run-In 0.9 mg/kg 3Q4W	Safety Run-In 1.2 mg/kg 3Q4W	Part B Expansion
Started	8	8	82
Completed	7	8	79
Not completed	1	0	3
Consent withdrawn by subject	-	-	1
Adverse event, non-fatal	-	-	2
Met exclusion criteria after enrollment	1	-	-

Period 2

Period 2 title	All Treated
Is this the baseline period?	Yes[1]
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Safety Run-In 0.9 mg/kg 3Q4W

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental
Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Arm title	Safety Run-In 1.2 mg/kg 3Q4W

Arm description:

Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental

Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 1.2 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Arm title	Part B Expansion

Arm description:

Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle

Arm type	Experimental
Investigational medicinal product name	Tisotumab vedotin
Investigational medicinal product code	
Other name	TIVDAK
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tisotumab vedotin 0.9 mg/kg as an intravenous (IV) infusion on Days 1, 8, and 15 of every 4-week treatment cycle.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics are based on the All Treated population.

Number of subjects in period 2[2]	Safety Run-In 0.9 mg/kg 3Q4W	Safety Run-In 1.2 mg/kg 3Q4W	Part B Expansion
Started	7	8	79
Completed	0	0	0
Not completed	7	8	79
Consent withdrawn by subject	1	1	3
Study Closure by Sponsor	-	2	17
Death	6	5	53
Withdrawal - declined follow-up	-	-	1
Lost to follow-up	-	-	4
Withdrawal - subsequent treatment	-	-	1

Notes:

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

Justification: Out of 98 enrolled participants, 94 were treated and displayed here. Baseline characteristics are based on participants who received any amount of study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Safety Run-In 0.9 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Safety Run-In 1.2 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Part B Expansion
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	

Reporting group values	Safety Run-In 0.9 mg/kg 3Q4W	Safety Run-In 1.2 mg/kg 3Q4W	Part B Expansion
Number of subjects	7	8	79
Age categorical Units: Participants			
<=18 years	0	0	0
Between 18 and 64 years	3	3	51
>=65 years	4	5	28
Age Continuous Units: Years			
median	69.0	67.5	60.0
full range (min-max)	50.0 to 87.0	51.0 to 74.0	38.0 to 81.0
Sex/Gender, Customized Units: Participants			
Female	7	8	79
Intersex	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino/a, or of Spanish Origin	0	1	9
Not of Hispanic or Latino/a, or of Spanish Origin	6	7	69
Unknown	1	0	1
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	6
White	6	6	69
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Eastern Cooperative Oncology Group (ECOG) Performance Score			
Measure Description: 0=Normal activity; 1=Symtoms but ambulatory; 2=In bed <50% of the time; 3= In bed > 50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			

Grade 0	4	5	48
Grade 1	3	3	31

Reporting group values	Total		
Number of subjects	94		
Age categorical Units: Participants			
<=18 years	0		
Between 18 and 64 years	57		
>=65 years	37		
Age Continuous Units: Years			
median			
full range (min-max)	-		
Sex/Gender, Customized Units: Participants			
Female	94		
Intersex	0		
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino/a, or of Spanish Origin	10		
Not of Hispanic or Latino/a, or of Spanish Origin	82		
Unknown	2		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	4		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	7		
White	81		
More than one race	0		
Unknown or Not Reported	2		
Eastern Cooperative Oncology Group (ECOG) Performance Score			
Measure Description: 0=Normal activity; 1=Symtoms but ambulatory; 2=In bed <50% of the time; 3= In bed > 50% of the time; 4=100% bedridden; 5=Dead			
Units: Subjects			
Grade 0	57		
Grade 1	37		

End points

End points reporting groups

Reporting group title	Safety Run-In 0.9 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Safety Run-In 1.2 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Part B Expansion
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Safety Run-In 0.9 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Safety Run-In 1.2 mg/kg 3Q4W
Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	Part B Expansion
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Subject analysis set title	Part B Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The Full Analysis Set includes all participants who received any amount of study drug.	
Subject analysis set title	Part B Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety Analysis Set includes all participants who received any amount of study drug.	
Subject analysis set title	Part B PK Analysis Set
Subject analysis set type	Per protocol
Subject analysis set description: PK Analysis Set includes enrolled participants who received any amount of study drug and at least one PK parameter can be estimated.	
Subject analysis set title	Part B CA-125 Evaluable Set
Subject analysis set type	Per protocol
Subject analysis set description: The CA-125 evaluable analysis set includes participants who have an elevated baseline CA-125 value of ≥2 x ULN (upper limit of normal) within 2 weeks prior to the first dose of study drug.	
Subject analysis set title	Part B Full Analysis Set - Subjects with Confirmed CR or PR
Subject analysis set type	Per protocol
Subject analysis set description: Subset of the Full Analysis Set includes all participants who received any amount of study drug and had a confirmed CR or PR.	

Primary: Number of Participants with Dose-Limiting Toxicities (DLTs) (Safety Run-In Only)

End point title	Number of Participants with Dose-Limiting Toxicities (DLTs) (Safety Run-In Only)[1]

End point description:

Incidence of dose-limiting toxicity (DLT) was evaluated in participants enrolled in the Safety Run-In, who were followed for protocol-defined DLT events up to 28 days after the first dose of tisotumab

vedotin.

End point type	Primary

End point timeframe:

Up to 0.9 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: The planned analysis was to evaluate the incidence of DLTs, which was observed to occur in 1/8 participants, as reported here.

End point values	Safety Run-In 0.9 mg/kg 3Q4W	Safety Run-In 1.2 mg/kg 3Q4W		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	8		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Primary: Confirmed Objective Response rate (ORR) (Part B)

End point title	Confirmed Objective Response rate (ORR) (Part B)[2]

End point description:

Proportion of participants who achieve a confirmed complete response (CR) or partial response (PR) according to RECIST v1.1 as assessed by the investigator

End point type	Primary

End point timeframe:

Up to 9.7 months

Notes:

[2] - 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: The ORR for Part B with 95% confidence interval provided for the end point is the statistical analysis.

End point values	Part B Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Percentage of Participants				
number (confidence interval 95%)	9.0 (3.6 to 17.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) (Part B)

End point title	Number of Participants with Adverse Events (AEs) (Part B)

End point description:

An AE is any untoward medical occurrence in a patient or clinical investigational participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Treatment emergent AEs (TEAEs) are defined as events that are new or worsened on or after receiving the first dose of study treatment and up through 30 days after the last dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 23.0 months

End point values	Part B Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Participants				
Any TEAE	79			
Treatment-related TEAE	67			
Treatment-related Grade 3-4 TEAE	14			
Treatment-related Grade 5 TEAE	0			
Max severity of TEAE - Grade 1	7			
Max severity of TEAE - Grade 2	35			
Max severity of TEAE - Grade 3	32			
Max severity of TEAE - Grade 4	3			
Max severity of TEAE - Grade 5	2			
Any treatment-emergent serious AE (SAE)	28			
Treatment-related SAE	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Confirmed and unconfirmed ORR (Part B)

End point title	Confirmed and unconfirmed ORR (Part B)

End point description:

Proportion of participants who achieve a CR or PR according to RECIST v1.1 as assessed by the investigator

End point type	Secondary

End point timeframe:

Up to 9.7 months

End point values	Part B Expansion	Part B Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	79	79		
Units: Percentage of Participants				
number (confidence interval 95%)	18.0 (10.0 to 27.9)	18.0 (10.0 to 27.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cancer Antigen 125 (CA-125) response rate according to Gynecologic Cancer Intergroup (GCIG) criteria (Part B)

End point title	Cancer Antigen 125 (CA-125) response rate according to Gynecologic Cancer Intergroup (GCIG) criteria (Part B)

End point description:

Proportion of participants who have at least a 50% reduction in CA-125 value from baseline

End point type	Secondary

End point timeframe:

Up to 10.1 months

End point values	Part B CA-125 Evaluable Set			
Subject group type	Subject analysis set			
Number of subjects analysed	51			
Units: Percentage of Participants				
number (confidence interval 95%)	12.0 (4.4 to 23.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) (Part B)

End point title	Duration of response (DOR) (Part B)

End point description:

Time from the first documentation of objective response (CR or PR that is subsequently confirmed) to the first documentation of PD or death due to any cause, whichever comes first

End point type	Secondary

End point timeframe:

Up to 8.3 months

End point values	Part B Full Analysis Set - Subjects with Confirmed CR or PR			
Subject group type	Subject analysis set			
Number of subjects analysed	7[3]			
Units: Months				
median (confidence interval 95%)	4.21 (3.02 to 999)			

Notes:

[3] - 999 = Not Available

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response according to the Gynecological Cancer Intergroup (GCIG) combined RECIST and CA-125 criteria (Part B)

End point title	Overall response according to the Gynecological Cancer Intergroup (GCIG) combined RECIST and CA-125 criteria (Part B)

End point description:

Proportion of participants whose best response is a CR or PR according to the GCIG combined RECIST and CA-125 criteria

End point type	Secondary

End point timeframe:

Up to 10.1 months

End point values	Part B Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Percentage of Participants				
number (confidence interval 95%)	11.0 (5.3 to 20.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Disease control rate (DCR) (Part B)

End point title	Disease control rate (DCR) (Part B)

End point description:

Proportion of participants who achieved a confirmed Complete Response(CR) or Partial Response (PR) per RECIST v1.1 as assessed by the investigator, or meet the Stable Disease (SD) criteria at least once after start of study treatment at a minimum interval of 12 weeks.

End point type	Secondary

End point timeframe:

Up to 3.0 months

End point values	Part B Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Percentage of Participants				
number (confidence interval 95%)	54.4 (42.8 to 65.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) (Part B)

End point title	Time to response (TTR) (Part B)

End point description:

Time from the start of study treatment to the first documentation of objective response (CR or PR that is subsequently confirmed)

End point type	Secondary

End point timeframe:

Up to 23.0 months

End point values	Part B Full Analysis Set - Subjects with Confirmed CR or PR			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Months				
median (full range (min-max))	1.4 (1.0 to 3.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS) (Part B)

End point title	Progression-free survival (PFS) (Part B)

End point description:

Time from the start of study treatment to the first documentation of PD or death due to any cause, whichever comes first

End point type	Secondary

End point timeframe:

Up to 9.7 months

End point values	Part B Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	2.73 (1.64 to 2.99)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) (Part B)

End point title	Overall survival (OS) (Part B)

End point description:

Time from the start of study treatment to date of death due to any cause

End point type	Secondary

End point timeframe:

Up to 23.0 months

End point values	Part B Full Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	79			
Units: Months				
median (confidence interval 95%)	10.68 (7.75 to 12.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) parameter: Antibody-Drug Conjugate (ADC) Maximum concentration (Cmax) (Part B)

End point title	Pharmacokinetic (PK) parameter: Antibody-Drug Conjugate (ADC) Maximum concentration (Cmax) (Part B)

End point description:

ADC Cmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	20.582 (± 26.963)			
Cycle 1, Dose 3	21.817 (± 26.823)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: ADC Time of Cmax (Tmax) (Part B)

End point title	PK parameter: ADC Time of Cmax (Tmax) (Part B)

End point description:

ADC Tmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: Days				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	0.041 (± 53.112)			
Cycle 1, Dose 3	0.041 (± 78.407)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: ADC Area Under Concentration-Time Curve (AUC) (Part B)

End point title	PK parameter: ADC Area Under Concentration-Time Curve (AUC) (Part B)

End point description:

ADC AUC was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: µg/mL*day				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1 - AUC 7 Days-ADC	25.198 (± 25.335)			
Cycle 1, Dose 3 - AUC 7 Days-ADC	30.159 (± 32.261)			
Cycle 1, Dose 3 - AUC 14 Days-ADC	31.716 (± 31.632)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Free Monomethyl Auristatin E (MMAE) Cmax (Part B)

End point title	PK parameter: Free Monomethyl Auristatin E (MMAE) Cmax (Part B)

End point description:

MMAE Cmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	1.778 (± 66.636)			
Cycle 1, Dose 3	2.552 (± 52.442)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE Tmax (Part B)

End point title	PK parameter: MMAE Tmax (Part B)

End point description:

MMAE Tmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: Days				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	2.061 (± 26.838)			
Cycle 1, Dose 3	2.101 (± 28.820)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE AUC (Part B)

End point title	PK parameter: MMAE AUC (Part B)

End point description:

MMAE AUC was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: ng/mL*day				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1 - AUC Last-MMAE	8.709 (± 63.747)			
Cycle 1, Dose 3 - AUC Last-MMAE	16.578 (± 52.121)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: MMAE Trough Concentration (Ctrough) (Part B)

End point title	PK parameter: MMAE Trough Concentration (Ctrough) (Part B)

End point description:

MMAE Ctrough was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 3	0.230 (± 82.638)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: Total Antibody (TAb) Cmax (Part B)

End point title	PK parameter: Total Antibody (TAb) Cmax (Part B)

End point description:

TAb Cmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	18.418 (± 28.631)			
Cycle 1, Dose 3	19.955 (± 28.405)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: TAb Tmax (Part B)

End point title	PK parameter: TAb Tmax (Part B)

End point description:

TAb Tmax was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: Days				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1	0.041 (± 67.072)			
Cycle 1, Dose 3	0.043 (± 67.795)			

Statistical analyses

No statistical analyses for this end point

Secondary: PK parameter: TAb Area Under Concentration-Time Curve (AUC) (Part B)

End point title	PK parameter: TAb Area Under Concentration-Time Curve (AUC) (Part B)

End point description:

TAb AUC was derived from the PK blood samples collected.

End point type	Secondary

End point timeframe:

Samples for PK endpoints were collected at Cycle 1 Day 1 (predose, end of infusion, 1 hr, and 5 hr), Day 3, Day 8 (predose), Day 15 (predose, end of infusion, 1 hr, and 5 hr), Day 17, Day 22, and Cycle 2 Day 1 (predose). Approximately 4 weeks per cycle.

End point values	Part B PK Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	77			
Units: µg/mL*day				
geometric mean (geometric coefficient of variation)				
Cycle 1, Dose 1 - AUC 7 Days-TAb	35.535 (± 24.950)			
Cycle 1, Dose 3 - AUC 7 Days-TAb	39.371 (± 29.218)			
Cycle 1, Dose 3 - AUC 14 Days-TAb	42.240 (± 29.206)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence of antitherapeutic antibodies (ATA) (Part B)

End point title	Incidence of antitherapeutic antibodies (ATA) (Part B)

End point description:

The proportion of participants who develop ATA at any time during the study. A positive baseline ATA result is considered positive post-baseline if the post-baseline ATA titer result is at least four times higher than the baseline result.

End point type	Secondary

End point timeframe:

Up to 6.9 months

End point values	Part B Safety Analysis Set			
Subject group type	Subject analysis set			
Number of subjects analysed	71[4]			
Units: Participants				
number (not applicable)				
Baseline Negative - Negative post-baseline	65			
Baseline Negative - Positive post-baseline	3			
Baseline Positive - Negative post-baseline	3			
Baseline Positive - Positive post-baseline	0			

Notes:

[4] - Participants in the Safety Analysis Set with a baseline and at least one post-baseline ATA sample.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Non-serious AEs were followed up to 10.5 months. Serious AEs and All-Cause Mortality were followed up to 31.6 months.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups	
Reporting group title	PartBExpansion
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	SafetyRun-In(1.2mg/kg3Q4W)
Reporting group description: Tisotumab Vedotin 1.2 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	
Reporting group title	SafetyRun-In(0.9mg/kg3Q4W)
Reporting group description: Tisotumab Vedotin 0.9 mg/kg by IV infusion on Days 1, 8, and 15 of every 4-week cycle	

Serious adverse events	PartBExpansion	SafetyRun-In(1.2mg/kg3Q4W)	SafetyRun-In(0.9mg/kg3Q4W)
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 79 (35.44%)	4 / 8 (50.00%)	2 / 7 (28.57%)
number of deaths (all causes)	53	5	6
number of deaths resulting from adverse events	2	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Fatigue			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Performance status decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Psychiatric disorders			
Confusional state			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina pectoris			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Peripheral sensory neuropathy			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 79 (3.80%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative dictionary used:			

MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	3 / 79 (3.80%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatomegaly			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	PartBExpansion	SafetyRun-In(1.2mg/kg3Q4W)	SafetyRun-In(0.9mg/kg3Q4W)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 79 (97.47%)	8 / 8 (100.00%)	7 / 7 (100.00%)
Vascular disorders			
Hot flush			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	1 / 79 (1.27%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
General disorders and administration site conditions			
Asthenia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	19 / 79 (24.05%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	23	0	0
Fatigue			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	25 / 79 (31.65%)	4 / 8 (50.00%)	2 / 7 (28.57%)
occurrences (all)	27	4	2
Malaise			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Oedema peripheral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	4	0	1
Pyrexia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	5	1	0
Reproductive system and breast disorders			
Vaginal haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
Vulvovaginal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 79 (7.59%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	7	0	1
Dysphonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	0	1	1
Dyspnoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	9 / 79 (11.39%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Epistaxis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	36 / 79 (45.57%)	3 / 8 (37.50%)	4 / 7 (57.14%)
occurrences (all)	46	4	4
Hiccups			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	9 / 79 (11.39%)	3 / 8 (37.50%)	1 / 7 (14.29%)
occurrences (all)	9	3	1
Pharyngeal inflammation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Upper-airway cough syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	2	0	2
Productive cough			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 79 (3.80%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	3	0	1
Insomnia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 79 (3.80%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	3	1	1
Investigations			
Alanine aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Aspartate aminotransferase increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 79 (7.59%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
International normalised ratio increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Weight decreased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	5	1	1
Injury, poisoning and procedural complications			
Corneal abrasion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	2
Incision site impaired healing			

alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Cognitive disorder			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dizziness			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	4	1	1
Headache			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Paraesthesia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	2	1	0
Peripheral sensory neuropathy			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	18 / 79 (22.78%)	2 / 8 (25.00%)	3 / 7 (42.86%)
occurrences (all)	20	3	3
Restless legs syndrome			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	2 / 7 (28.57%)
occurrences (all)	1	0	2
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	23 / 79 (29.11%)	0 / 8 (0.00%)	4 / 7 (57.14%)
occurrences (all)	33	0	6
Eye disorders			

Blepharitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 79 (8.86%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	9	0	1
Cataract nuclear			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	2	0
Conjunctival haemorrhage			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Conjunctival ulcer			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis allergic			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dacryostenosis acquired			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry eye			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	12 / 79 (15.19%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	14	1	0
Ectropion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Entropion			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Eye discharge			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	8	0	0
Eye pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Keratitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Lacrimation increased			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 79 (8.86%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	8	0	0
Punctate keratitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	2 / 8 (25.00%)	0 / 7 (0.00%)
occurrences (all)	2	2	0
Symblepharon			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	4	1	0
Vision blurred			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	9 / 79 (11.39%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	10	0	1
Gastrointestinal disorders			
Abdominal distension			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	8 / 79 (10.13%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	9	1	0
Abdominal pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	22 / 79 (27.85%)	3 / 8 (37.50%)	0 / 7 (0.00%)
occurrences (all)	27	3	0
Abdominal pain upper			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 79 (7.59%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	7	1	2
Constipation			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	17 / 79 (21.52%)	3 / 8 (37.50%)	2 / 7 (28.57%)
occurrences (all)	20	4	2
Diarrhoea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	18 / 79 (22.78%)	2 / 8 (25.00%)	4 / 7 (57.14%)
occurrences (all)	25	2	4
Gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	3 / 79 (3.80%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	3	1	1
Nausea			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	30 / 79 (37.97%)	2 / 8 (25.00%)	2 / 7 (28.57%)
occurrences (all)	37	2	2
Stomatitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Vomiting			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	15 / 79 (18.99%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	19	1	2

Hepatobiliary disorders			
Hypertransaminasaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 79 (7.59%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	16	1	0
Skin and subcutaneous tissue disorders			
Alopecia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	10 / 79 (12.66%)	2 / 8 (25.00%)	1 / 7 (14.29%)
occurrences (all)	10	2	1
Dermatitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Dry skin			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pruritus			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Rash erythematous			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urticaria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Rash maculo-papular			

alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Dysuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Haematuria			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	6	0	0
Endocrine disorders			
Inappropriate antidiuretic hormone secretion			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 79 (8.86%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Back pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	7 / 79 (8.86%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Limb discomfort			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0

Muscle spasms			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	2 / 79 (2.53%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	2	0	1
Musculoskeletal chest pain			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Myalgia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	8 / 79 (10.13%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0
Pain in extremity			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	5	0	1
Infections and infestations			
Acute sinusitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Conjunctivitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	25 / 79 (31.65%)	1 / 8 (12.50%)	2 / 7 (28.57%)
occurrences (all)	33	1	3
Conjunctivitis viral			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	1	0	1
Device related infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Gingivitis			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Pneumonia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	1 / 79 (1.27%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Pustule			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Sinusitis			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	2 / 8 (25.00%)	2 / 7 (28.57%)
occurrences (all)	6	2	2
Tooth infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	0 / 79 (0.00%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Urinary tract infection			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	5	0	1
Metabolism and nutrition disorders			
Decreased appetite			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	25 / 79 (31.65%)	1 / 8 (12.50%)	1 / 7 (14.29%)
occurrences (all)	29	1	1
Hyperglycaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	4 / 79 (5.06%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	4	0	0
Dehydration			
alternative dictionary used: MedDRA 25.0			

subjects affected / exposed	8 / 79 (10.13%)	1 / 8 (12.50%)	0 / 7 (0.00%)
occurrences (all)	8	1	0
Hypoalbuminaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	6 / 79 (7.59%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	7	0	0
Hyperuricaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Hypocalcaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	5 / 79 (6.33%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	5	0	0
Hypokalaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	14 / 79 (17.72%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	17	0	2
Hypomagnesaemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	10 / 79 (12.66%)	0 / 8 (0.00%)	1 / 7 (14.29%)
occurrences (all)	13	0	1
Hyponatraemia			
alternative dictionary used: MedDRA 25.0			
subjects affected / exposed	8 / 79 (10.13%)	0 / 8 (0.00%)	0 / 7 (0.00%)
occurrences (all)	9	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 October 2018	Removed required on-treatment ophthalmological exam. Updated exclusion criteria from "peripheral neuropathy > Grade 1" to "peripheral neuropathy ≥ Grade 2." Changes to required ocular premedication and preventive eye therapy. Additional administrative changes and clarifications.
02 May 2019	Revised bevacizumab exposure criteria for safety run-in participants. Revise eGFR inclusion criteria. Remove 3 month PFS and 12 month OS timepoints. Additional corrections, administrative changes, and clarifications.
17 October 2019	Part B cohort added and number of planned participants updated to reflect added participants in Part B. 1.2 mg/kg dose escalation added to safety run-in. Additional corrections, administrative changes, and clarifications.
24 August 2020	Changed Part B to enroll approximately 80 participants. Updated exclusion criteria to permit anticoagulation and antiplatelet therapies. Updated inclusion criteria for prior treatments. Addition of interim analysis. Additional administrative changes and clarifications.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported