Clinical trial results:
A Randomized, Open-Label, Phase 3 Trial of Brentuximab Vedotin (SGN-35) Versus Physician's Choice (Methotrexate or Bexarotene) in Patients With CD30-Positive Cutaneous T-Cell Lymphoma

Summary

EudraCT number	2010-024215-14
Trial protocol	BE GB ES DE AT IT PL
Global end of trial date	06 July 2018

Results information

Result version number	v2 (current)
This version publication date	17 July 2019
First version publication date	07 January 2018
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	C25001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01578499
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda Oncology
Sponsor organisation address	40 Lansdowne Street, Cambridge MA, United States, 02139
Public contact	Medical Director, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.com
Scientific contact	Medical Director, Takeda, +1 877-825-3327, clinicaltrialregistry@tpna.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	06 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2016
Global end of trial reached?	Yes
Global end of trial date	06 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine ORR, lasting at least 4 months (ORR4), with brentuximab vedotin in participants with CD30+ MF or pcALCL compared to that achieved with therapy in the control arm.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Belgium: 6
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 5
Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	United States: 33
Worldwide total number of subjects	131
EEA total number of subjects	68

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)	79
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 34 investigative sites in Australia, Belgium, Brazil, France, Germany, Italy, Poland, Spain, Switzerland, United Kingdom, United States from 11 June 2012 to the Primary Completion data of 06 July 2018.

Pre-assignment

Screening details:

Participants with a diagnosis of cluster of differentiation antigen 30 (CD30)-Positive Cutaneous T-Cell Lymphoma were enrolled equally in 1 of 2 arms: brentuximab vedotin 1.8 mg/kg or physician's choice (Methotrexate or Bexarotene).

Pre-assignment period milestones

Number of subjects started	131
Number of subjects completed	128

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did not Receive Study Drug: 3

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Brentuximab vedotin

Arm description:

Brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).

Arm type	Experimental
Investigational medicinal product name	Brentuximab vedotin
Investigational medicinal product code	
Other name	SGN-35
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received 1.8 milligram per kilogram (mg/kg) intravenous (IV) infusion over approximately 30 minutes on Day 1 of each 21-day cycle.

Arm title	Methotrexate or Bexarotene

Arm description:

Methotrexate 5 to 50 mg, tablets, orally, once weekly (dose adjustment is guided by patient response and toxicity) or Bexarotene 300 mg/m^2, tablets, orally, once daily with meals for up to 48 weeks.

Arm type	Active comparator
Investigational medicinal product name	Bexarotene
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details: Participant received single oral daily dose of 300 mg/m^2/day	
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participant received a single dose of 5 to 50 mg methotrexate orally once weekly.

Number of subjects in period 1[1]	Brentuximab vedotin	Methotrexate or Bexarotene
Started	66	62
Completed	32	19
Not completed	34	43
Died and End of Study Page not Completed	2	-
Death	20	25
Withdrawal by Subject	10	16
Lost to follow-up	-	1
Reason not Specified	-	1

Notes:

[1] - 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: The number of subjects reported to be in the baseline period is based on the Safety Population that included all participants who received at least one dose of study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Brentuximab vedotin
Reporting group description:	
Brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).	
Reporting group title	Methotrexate or Bexarotene
Reporting group description:	
Methotrexate 5 to 50 mg, tablets, orally, once weekly (dose adjustment is guided by patient response and toxicity) or Bexarotene 300 mg/m^2, tablets, orally, once daily with meals for up to 48 weeks.	

Reporting group values	Brentuximab vedotin	Methotrexate or Bexarotene	Total
Number of subjects	66	62	128
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	38	39	77
From 65-84 years	28	23	51
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	59.4	56.6	
standard deviation	± 13.80	± 14.43	-
Gender, Male/Female Units: Subjects			
Female	33	28	61
Male	33	34	67
Region of Enrollment			
Safety population included participants who received at least 1 dose of study drug, analyzed according to the actual treatment received.			
Units: Subjects			
Australia	12	8	20
Belgium	4	2	6
France	4	3	7
Germany	3	2	5
Italy	12	6	18
Poland	2	1	3
Spain	2	3	5
Switzerland	3	3	6
United Kingdom	8	15	23
United States	14	17	31
Brazil	2	2	4

End points

End points reporting groups

Reporting group title	Brentuximab vedotin
Reporting group description:	
Brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).	
Reporting group title	Methotrexate or Bexarotene
Reporting group description:	
Methotrexate 5 to 50 mg, tablets, orally, once weekly (dose adjustment is guided by patient response and toxicity) or Bexarotene 300 mg/m^2, tablets, orally, once daily with meals for up to 48 weeks.	
Subject analysis set title	pcALCL: Brentuximab vedotin
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with pcALCL received brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).	
Subject analysis set title	MF: Brentuximab vedotin 1.8 mg/kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants with MF received brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).	
Subject analysis set title	Brentuximab vedotin
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).	
Subject analysis set title	Methotrexate or Bexarotene
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Methotrexate 5 to 50 mg, tablets, orally, once weekly (dose adjustment is guided by patient response and toxicity) or Bexarotene 300 mg/m^2, tablets, orally, once daily with meals for up to 48 weeks.	

Primary: Percentage of Participants Achieving an Objective Response that Lasts at Least 4 Months (ORR4)

End point title	Percentage of Participants Achieving an Objective Response that Lasts at Least 4 Months (ORR4)
End point description:	
ORR4 was determined by an Independent Review Facility (IRF) based on Global Response Score (GRS) which consisted of a skin assessment by the investigator using the modified severity-weighted assessment tool (mSWAT), nodal and visceral radiographic assessment by an IRF and for the participants with mycosis fungoides (MF) only, detection of circulation Sezary cells. Participants whose first response occurred after the start of subsequent anticancer therapy were excluded. Response Criteria was based on International Society for Cutaneous Lymphomas (ISCL), United States Cutaneous Lymphoma Consortium (USCLC) and Cutaneous Lymphoma Task Force (CLTF) of the European Organisation for Research and Treatment of Cancer (EORTC) Consensus guidelines (Olsen, 2011). The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment.	
End point type	Primary
End point timeframe:	
Each Cycle until disease progression, death End of treatment (Median overall follow-up 38.8 months)	

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: percentage of participants				
number (confidence interval 95%)	54.7 (42.5 to 66.9)	12.5 (4.4 to 20.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Brentuximab vedotin v Methotrexate or Bexarotene
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	42.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	27.5
upper limit	56.8

Notes:

[1] - Based on a two-sided X^2 test with a significance level of 0.05, and a 10% dropout rate, a sample size of approximately 124 participants was calculated to provide 90% power to detect a 30% improvement in ORR4 in the brentuximab vedotin group.
[2] - P-value was stratified by baseline disease diagnosis (pcALCL and MF).

Secondary: Percentage of Participants achieving a CR

End point title	Percentage of Participants achieving a CR

End point description:

Complete Response (CR) was determined by the IRF based on Global Response Score (GRS) which consisted of a skin assessment by the investigator using the modified severity-weighted assessment tool (mSWAT), nodal and visceral radiographic and for the participants with mycosis fungoides (MF) only, detection of circulation Sezary cells. Response Criteria was based on ISCL, USCLC and CLTF of the EORTC Consensus guidelines (Olsen, 2011). The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment.

End point type	Secondary

End point timeframe:

Each Cycle until disease progression, death or data cutoff (Median overall follow-up 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: percentage of participants				
number (confidence interval 95%)	17.2 (7.9 to 26.4)	1.6 (0.0 to 8.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Brentuximab vedotin v Methotrexate or Bexarotene
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Risk difference (RD)
Point estimate	15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	33

Notes:

[3] - P-value was stratified by baseline disease diagnosis (pcALCL and MF).

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was assessed by the IRF and is defined as the time from randomization until disease progression or death due to any cause, whichever occurs first. Disease progression was based on ISCL, USCLC and CLTF of the EORTC Consensus guidelines (Olsen, 2011). The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment.

End point type	Secondary

End point timeframe:

Until disease progression, death or data cutoff (Median PFS follow-up of 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: months				
median (confidence interval 95%)	16.7 (15.4 to 21.6)	3.5 (2.4 to 4.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Brentuximab vedotin v Methotrexate or Bexarotene
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	< 0.001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.378
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.247
upper limit	0.577

Notes:

[4] - Hazard ratio brentuximab vedotin/ comparator (methotrexate or bexarotene) with the 95% CI from a stratified Cox regression model with treatment as the explanatory variable and baseline disease diagnosis (MF or pcALCL) as stratification factor.

Secondary: Maximum Change from Baseline in Symptom Domain Score of the Skindex-29 Questionnaire

End point title	Maximum Change from Baseline in Symptom Domain Score of the Skindex-29 Questionnaire

End point description:

Skindex-29 is a 29-item dermatology-specific health-related quality of life (HRQoL). The Skindex-29 incorporates a 28-day recall period and consists of 3 domains: symptoms, emotions, and functioning. The domain scores and an overall score are expressed on a 100-point scale, from 0 to 100 with higher scores indicating lower levels of health- HRQoL. A negative change (reduction) from Baseline indicates improvement. The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment. Here number of participants analyzed are participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Baseline up to End of Treatment (Week 52)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	54		
Units: score on a scale				
arithmetic mean (standard deviation)	-28.08 (± 26.863)	-8.62 (± 17.013)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

P-value is calculated using the analysis of covariance (ANCOVA) model controlling for baseline symptom domain score, eastern cooperative oncology group (ECOG) performance status score (=0 and ≥1), and disease diagnosis (pcALCL and MF) between the brentuximab vedotin and comparator (methotrexate or bexarotene) arms.

Comparison groups	Brentuximab vedotin v Methotrexate or Bexarotene
Number of subjects included in analysis	112
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Estimate of difference
Point estimate	-19
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.7
upper limit	-11.4

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Duration of response was assessed by the IRF in participants with confirmed response [CR or Partial Response (PR)] and is defined as the time between first documentation of response and disease progression. Response Criteria was based on ISCL, USCLC and CLTF of the EORTC Consensus guidelines (Olsen, 2011). The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment. Responders in ITT population were analyzed in this outcome measure. 99999: Upper limit of Confidence Interval (CI) was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Until disease progression, death or data cutoff (Median follow-up 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	13		
Units: months				
median (confidence interval 95%)	15.1 (9.8 to 25.5)	18.4 (3.5 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR of Skin Response

End point title	DOR of Skin Response

End point description:

Duration of skin response (CR and PR) was assessed by investigator and is defined as time between first skin response to progressive disease in skin. Per mSWAT, CR is defined as 100% clearance of skin lesions. PR is defined as 50%-99% clearance of skin disease from Baseline; No new tumors in participants without tumors at Baseline -MF; No new tumors-primary cutaneous anaplastic large cell

lymphoma (pcALCL).Progressive disease is defined as ≥ 25% increase in skin disease from baseline, or loss of response: in those with CR or PR, increase of skin score of greater than sum of nadir plus 50% baseline score, or new tumors in patients without tumors at baseline (MF).ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment. Skin responders in ITT population were analyzed in this outcome measure. 99999: Upper limit of Confidence Interval (CI) was not estimable due to low number of participants with events.

End point type	Secondary

End point timeframe:

Until disease progression, death or data cutoff (Median follow-up 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	19		
Units: months				
median (confidence interval 95%)	18.9 (15.0 to 25.7)	18.3 (3.5 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

EFS was assessed by the IRF and is defined as the time from randomization until any cause of treatment failure: disease progression, discontinuation of treatment for any reason, or death due to any cause, whichever occurs first. Disease progression was based on ISCL, USCLC and CLTF of the EORTC Consensus guidelines (Olsen, 2011). The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment.

End point type	Secondary

End point timeframe:

From randomization until disease progression, death or data cutoff (Median follow-up 36.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: months				
median (full range (min-max))	9.4 (5.9 to 11.7)	2.3 (1.7 to 3.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Concentration for Brentuximab Vedotin

End point title	Cmax: Maximum Observed Concentration for Brentuximab Vedotin

End point description:

The pharmacokinetic (PK) population included participants with sufficient dose and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 pre-dose and 30 minutes after infusion in Cycles 1 and 3

End point values	pcALCL: Brentuximab vedotin	MF: Brentuximab vedotin 1.8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	50		
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 15, 50)	38.36 (± 9.427)	38.40 (± 8.912)		
Cycle 3 Day 1 (n= 12, 41)	40.14 (± 12.697)	36.69 (± 14.249)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough: Observed Concentration at the End of a Dosing Interval for Brentuximab Vedotin

End point title	Ctrough: Observed Concentration at the End of a Dosing Interval for Brentuximab Vedotin

End point description:

The PK population included participants with sufficient dose and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 pre-dose of Cycles 2 and 4

End point values	pcALCL: Brentuximab vedotin	MF: Brentuximab vedotin 1.8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	50		
Units: ug/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 11, 31)	3.57 (± 10.101)	0.58 (± 0.517)		
Cycle 4 Day 1 (n= 8, 28)	0.99 (± 0.528)	0.78 (± 0.446)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax: Maximum Observed Concentration for Monomethyl Auristatin (MMAE) for Brentuximab Vedotin

End point title	Cmax: Maximum Observed Concentration for Monomethyl Auristatin (MMAE) for Brentuximab Vedotin

End point description:

The PK population included participants with sufficient dose and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 pre-dose and 30 minutes after infusion ended in Cycles 1 and 3

End point values	pcALCL: Brentuximab vedotin	MF: Brentuximab vedotin 1.8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	50		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 13, 46)	2.53 (± 1.382)	3.34 (± 1.901)		
Cycle 3 Day 1 (n= 12, 36)	2.96 (± 1.176)	3.08 (± 1.276)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough: Observed Concentration at the End of a Dosing Interval for MMAE for Brentuximab Vedotin

End point title	Ctrough: Observed Concentration at the End of a Dosing Interval for MMAE for Brentuximab Vedotin

End point description:

The PK population included participants with sufficient dose and PK data to reliably estimate PK parameters as determined by a clinical pharmacologist. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 pre-dose of Cycles 2 and 4

End point values	pcALCL: Brentuximab vedotin	MF: Brentuximab vedotin 1.8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	50		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 2 Day 1 (n= 11, 33)	0.11 (± 0.095)	0.09 (± 0.060)		
Cycle 4 Day 1 (n= 10, 34)	0.14 (± 0.113)	0.11 (± 0.091)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Antitherapeutic Antibodies (ATA) to Brentuximab Vedotin

End point title	Number of Participants with Antitherapeutic Antibodies (ATA) to Brentuximab Vedotin

End point description:

Blood was collected and evaluated for ATA and neutralizing ATA in all participants who received brentuximab vedotin to assess immunogenicity. The Safety population included participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

Baseline up to End of Treatment (Week 52)

End point values	pcALCL: Brentuximab vedotin	MF: Brentuximab vedotin 1.8 mg/kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	50		
Units: participants				
Immunogenicity-evaluable participants	14	46		
Baseline Negative: ATA negative	8	23		
Baseline Negative: ATA positive	6	19		
Baseline Negative: Transiently Positive	4	9		
Baseline Negative: Persistently Positive	2	10		

Baseline Negative: Neutralizing ATA Positive	4	14		
Baseline Positive: ATA Negative	0	1		
Baseline Positive: ATA Positive	0	3		
Baseline Positive: Transiently Positive	0	3		
Baseline Positive: Persistently Positive	0	0		
Baseline Positive: Neutralizing ATA Positive	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Skindex-29 Questionnaire Total Score

End point title	Change from Baseline in the Skindex-29 Questionnaire Total Score

End point description:

Skindex-29 is a 29-item dermatology-specific health-related quality of life (HRQoL). The Skindex-29 incorporates a 28-day recall period and consists of 3 domains: symptoms, emotions, and functioning. The domain scores and an overall score are expressed on a 100-point scale, 0 to 100 with higher scores indicating lower levels of health- HRQoL. A negative change (reduction) from Baseline indicates improvement. The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1, 2, 4, 6, 8, 10, 12, 14, 16, at End of Treatment (EOT) and during posttreatment long treatment follow-up (LTFU) - (Median follow-up 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 2 (n= 55, 45)	-5.44 (± 11.055)	-2.49 (± 11.959)		
Change at Cycle 4 (n= 49, 30)	-14.60 (± 17.488)	-6.71 (± 9.755)		
Change at Cycle 6 (n= 40, 25)	-17.59 (± 17.770)	-5.40 (± 9.758)		
Change at Cycle 8 (n= 37, 14)	-21.73 (± 18.882)	-7.28 (± 16.769)		
Change at Cycle 10 (n= 35, 13)	-22.47 (± 21.722)	-3.71 (± 21.752)		
Change at Cycle 12 (n= 25, 8)	-23.37 (± 21.555)	-5.22 (± 17.704)		
Change at Cycle 14 (n= 25, 5)	-19.72 (± 20.980)	-7.49 (± 22.463)		
Change at Cycle 16 (n= 22, 3)	-19.35 (± 18.911)	0.75 (± 10.308)		
Change at End of Treatment (n= 47, 37)	-16.26 (± 23.281)	-0.96 (± 18.973)		

Change at 3-6 months LTFU (n= 2, 3)	-1.07 (± 3.704)	-9.48 (± 21.629)		
Change at 6-9 months LTFU (n= 6, 11)	-8.04 (± 8.800)	-9.68 (± 17.789)		
Change at 9-12 months LTFU (n= 7, 10)	-7.94 (± 15.582)	-4.93 (± 14.516)		
Change at 12-15 months LTFU (n= 25, 21)	-16.21 (± 18.438)	-11.16 (± 18.183)		
Change at 15-18 months LTFU (n= 25, 18)	-19.18 (± 19.475)	-8.53 (± 12.768)		
Change at 18-21 months LTFU (n= 22, 17))	-19.27 (± 20.962)	-5.46 (± 16.679)		
Change at 21-24 months LTFU (n= 18, 19)	-16.60 (± 19.875)	-6.86 (± 14.991)		
Change at 24-27 months LTFU (n= 20, 18)	-17.04 (± 15.982)	-9.05 (± 23.990)		
Change at 27-30 months LTFU (n= 20, 18)	-12.45 (± 19.639)	-7.97 (± 16.401)		
Change at >30 months LTFU (n= 23, 20)	-11.49 (± 22.470)	-1.07 (± 18.886)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Functional Assessment of Cancer Therapy General Questionnaire (FACT-G) Score

End point title	Change from Baseline in Functional Assessment of Cancer Therapy General Questionnaire (FACT-G) Score

End point description:

FACT-G is a 27-item general cancer QOL instrument completed by participants receiving cancer treatment. FACT-G incorporates a 7-day recall period and contains 4 primary subscales: Physical Well-Being (PWB; sum of 7 items, point range 0-28); Social/Family Well-Being (SWB, sum of 7-items, point range 0-28); Emotional Well-Being (EWB; sum of 6-items, point range 0-24); Functional Well-Being (FWB; sum of 7-items, point range 0-28); Fact-G total score=sum of PWB, SWB, EWB, FWB, point range 0-108. Higher scores for the total scales and subscales indicate better quality of life. A negative change (reduction) from Baseline indicates improvement. The ITT population included all participants who were identified as CD30+ by the Ventana anti-CD30 (Ber-H2) assay and were randomized to treatment. Here 'Number analyzed' is the number of participants with evaluable data at the specified time-point.

End point type	Secondary

End point timeframe:

Day 1 of Cycles 1, 2, 4, 6, 8, 10, 12, 14, 16, at EOT and during posttreatment (LTFU) - (Median follow-up 38.8 months)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	64	64		
Units: score on a scale				
arithmetic mean (standard deviation)				
Change at Cycle 2 (n= 56, 46)	1.43 (± 10.168)	-0.37 (± 11.723)		
Change at Cycle 4 (n= 50, 32)	1.75 (± 12.014)	1.78 (± 10.740)		

Change at Cycle 6 (n= 40, 25)	4.23 (± 14.257)	2.24 (± 13.108)		
Change at Cycle 8 (n= 37, 13)	5.96 (± 16.030)	2.54 (± 10.809)		
Change at Cycle 10 (n= 35, 13)	6.61 (± 16.971)	4.38 (± 15.040)		
Change at Cycle 12 (n= 27, 8)	7.94 (± 18.837)	8.61 (± 21.024)		
Change at Cycle 14 (n= 26, 6)	9.04 (± 14.104)	10.75 (± 13.615)		
Change at Cycle 16 (n= 22, 4)	5.08 (± 9.230)	7.88 (± 23.432)		
Change at End of Treatment (n= 47, 37)	0.35 (± 16.067)	-2.29 (± 17.171)		
Change at 3-6 months LTFU (n= 2, 2)	16.00 (± 18.385)	-2.92 (± 8.367)		
Change at 6-9 months LTFU (n= 6, 12)	-0.19 (± 19.648)	-2.59 (± 12.473)		
Change at 9-12 months LTFU (n= 7, 10)	3.62 (± 17.651)	-5.32 (± 10.555)		
Change at 12-15 months LTFU (n= 20, 16)	8.33 (± 14.918)	-1.34 (± 11.905)		
Change at 15-18 months LTFU (n= 24, 18)	3.03 (± 12.618)	2.94 (± 14.756)		
Change at 18-21 months LTFU (n= 24, 16)	3.35 (± 11.117)	-0.19 (± 14.316)		
Change at 21-24 months LTFU (n= 17, 18)	1.51 (± 5.471)	0.61 (± 14.505)		
Change at 24-27 months LTFU (n= 20, 15)	4.20 (± 7.952)	1.42 (± 17.870)		
Change at 27-30 months LTFU (n= 19, 17)	-1.57 (± 17.488)	1.93 (± 8.716)		
Change at >30 months LTFU (n= 22, 19)	-6.22 (± 15.222)	-2.85 (± 5.518)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Participants with Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

AEs and SAEs were assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. An Adverse Event (AE) is defined as any untoward medical occurrence in a clinical investigation participant administered a drug; it does not necessarily have to have a causal relationship with this treatment. A SAE is any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospitalization, results in significant disability or incapacity, is a congenital anomaly/birth defect or is a medically important event. The Safety population included participants who received at least one dose of study drug.

End point type	Secondary

End point timeframe:

First dose of study drug through 30 days after last dose of study drug (Up to 450 days)

End point values	Brentuximab vedotin	Methotrexate or Bexarotene		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	62		
Units: participants				
AEs (n= 66, 62)	63	56		
SAEs (n= 66, 62)	18	18		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug through 30 days after last dose of study drug (Up to 450 days)

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Brentuximab vedotin

Reporting group description:

Brentuximab vedotin 1.8 mg/kg, intravenous over approximately 30 minutes, once on Day 1 of each 21-day cycle and may continue as monotherapy for up to a total of 16 cycles (48 weeks).

Reporting group title	Methotrexate or Bexarotene

Reporting group description:

Methotrexate 5 to 50 mg, tablets, orally, once weekly (dose adjustment is guided by patient response and toxicity) or Bexarotene 300 mg/m^2, tablets, orally, once daily with meals for up to 48 weeks.

Serious adverse events	Brentuximab vedotin	Methotrexate or Bexarotene	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 66 (27.27%)	18 / 62 (29.03%)	
number of deaths (all causes)	4	0	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma	Additional description: One treatment-emergent death occurred in participant with lymphoma during treatment with brentuximab vedotin and is not related.		
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			

subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 66 (3.03%)	4 / 62 (6.45%)	
occurrences causally related to treatment / all	0 / 3	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extravasation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome	Additional description: One treatment-emergent death occurred in participant with pcALCL during treatment with brentuximab vedotin and is related.		
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Fatigue			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Pulmonary embolism	Additional description: One treatment-emergent death occurred in participant with pulmonary embolism during treatment with brentuximab vedotin and is not related.		
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Stress			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Pancreatitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatocellular injury			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Drug eruption			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin erosion			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crystal arthropathy			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	2 / 66 (3.03%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superinfection bacterial			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			

subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: One treatment-emergent death occurred in participant with sepsis during treatment with brentuximab vedotin and is not related.		
subjects affected / exposed	1 / 66 (1.52%)	3 / 62 (4.84%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impetigo			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital infection			

subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 66 (1.52%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			
subjects affected / exposed	0 / 66 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Brentuximab vedotin	Methotrexate or Bexarotene	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 66 (90.91%)	51 / 62 (82.26%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 66 (1.52%)	5 / 62 (8.06%)	
occurrences (all)	1	7	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 66 (9.09%)	0 / 62 (0.00%)	
occurrences (all)	7	0	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 66 (27.27%)	18 / 62 (29.03%)	
occurrences (all)	22	19	
Asthenia			
subjects affected / exposed	7 / 66 (10.61%)	5 / 62 (8.06%)	
occurrences (all)	10	9	
Pyrexia			
subjects affected / exposed	9 / 66 (13.64%)	8 / 62 (12.90%)	
occurrences (all)	17	9	
Oedema peripheral			
subjects affected / exposed	7 / 66 (10.61%)	6 / 62 (9.68%)	
occurrences (all)	9	6	
Chills			
subjects affected / exposed	4 / 66 (6.06%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Peripheral swelling			
subjects affected / exposed	1 / 66 (1.52%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	7 / 66 (10.61%)	0 / 62 (0.00%)	
occurrences (all)	8	0	
Cough			
subjects affected / exposed	2 / 66 (3.03%)	4 / 62 (6.45%)	
occurrences (all)	2	12	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 66 (3.03%)	6 / 62 (9.68%)	
occurrences (all)	2	6	
Anxiety			
subjects affected / exposed	0 / 66 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Investigations			
Weight decreased			

subjects affected / exposed	6 / 66 (9.09%)	2 / 62 (3.23%)	
occurrences (all)	6	2	
Alanine aminotransferase increased			
subjects affected / exposed	3 / 66 (4.55%)	5 / 62 (8.06%)	
occurrences (all)	3	6	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 66 (1.52%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Blood cholesterol increased			
subjects affected / exposed	0 / 66 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Blood triglycerides increased			
subjects affected / exposed	0 / 66 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	8	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	31 / 66 (46.97%)	1 / 62 (1.61%)	
occurrences (all)	53	1	
Peripheral motor neuropathy			
subjects affected / exposed	4 / 66 (6.06%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Paraesthesia			
subjects affected / exposed	6 / 66 (9.09%)	1 / 62 (1.61%)	
occurrences (all)	8	1	
Dysgeusia			
subjects affected / exposed	5 / 66 (7.58%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Headache			
subjects affected / exposed	5 / 66 (7.58%)	6 / 62 (9.68%)	
occurrences (all)	5	6	
Dizziness			
subjects affected / exposed	4 / 66 (6.06%)	1 / 62 (1.61%)	
occurrences (all)	4	1	
Blood and lymphatic system disorders			

Neutropenia			
subjects affected / exposed	5 / 66 (7.58%)	4 / 62 (6.45%)	
occurrences (all)	11	6	
Anaemia			
subjects affected / exposed	3 / 66 (4.55%)	6 / 62 (9.68%)	
occurrences (all)	3	8	
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 66 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	24 / 66 (36.36%)	9 / 62 (14.52%)	
occurrences (all)	32	9	
Vomiting			
subjects affected / exposed	11 / 66 (16.67%)	3 / 62 (4.84%)	
occurrences (all)	14	3	
Diarrhoea			
subjects affected / exposed	18 / 66 (27.27%)	4 / 62 (6.45%)	
occurrences (all)	24	4	
Constipation			
subjects affected / exposed	3 / 66 (4.55%)	5 / 62 (8.06%)	
occurrences (all)	5	5	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 66 (15.15%)	2 / 62 (3.23%)	
occurrences (all)	10	2	
Rash maculo-papular			
subjects affected / exposed	7 / 66 (10.61%)	3 / 62 (4.84%)	
occurrences (all)	7	3	
Urticaria			
subjects affected / exposed	5 / 66 (7.58%)	1 / 62 (1.61%)	
occurrences (all)	6	1	
Dry skin			
subjects affected / exposed	1 / 66 (1.52%)	4 / 62 (6.45%)	
occurrences (all)	1	4	
Pruritus			

subjects affected / exposed	11 / 66 (16.67%)	8 / 62 (12.90%)	
occurrences (all)	11	9	
Pruritus generalised			
subjects affected / exposed	7 / 66 (10.61%)	1 / 62 (1.61%)	
occurrences (all)	8	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 66 (0.00%)	5 / 62 (8.06%)	
occurrences (all)	0	6	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	6 / 66 (9.09%)	4 / 62 (6.45%)	
occurrences (all)	6	4	
Arthralgia			
subjects affected / exposed	8 / 66 (12.12%)	4 / 62 (6.45%)	
occurrences (all)	13	4	
Myalgia			
subjects affected / exposed	8 / 66 (12.12%)	2 / 62 (3.23%)	
occurrences (all)	9	3	
Muscle spasms			
subjects affected / exposed	4 / 66 (6.06%)	3 / 62 (4.84%)	
occurrences (all)	4	3	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 66 (6.06%)	2 / 62 (3.23%)	
occurrences (all)	4	2	
Skin infection			
subjects affected / exposed	2 / 66 (3.03%)	6 / 62 (9.68%)	
occurrences (all)	3	6	
Urinary tract infection			
subjects affected / exposed	4 / 66 (6.06%)	4 / 62 (6.45%)	
occurrences (all)	4	4	
Staphylococcal skin infection			
subjects affected / exposed	1 / 66 (1.52%)	5 / 62 (8.06%)	
occurrences (all)	1	5	
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	10 / 66 (15.15%)	3 / 62 (4.84%)	
occurrences (all)	15	3	
Hyperglycaemia			
subjects affected / exposed	5 / 66 (7.58%)	0 / 62 (0.00%)	
occurrences (all)	6	0	
Hyperuricaemia			
subjects affected / exposed	4 / 66 (6.06%)	2 / 62 (3.23%)	
occurrences (all)	6	2	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 66 (1.52%)	11 / 62 (17.74%)	
occurrences (all)	1	21	
Hypercholesterolaemia			
subjects affected / exposed	0 / 66 (0.00%)	4 / 62 (6.45%)	
occurrences (all)	0	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2011	Amendment 1: • The primary objective was revised to define ORR as lasting at least 4 months, and specify the study population. • The study population was modified to include only participants with a primary diagnosis of mycosis fungoides (MF) or primary cutaneous anaplastic large cell lymphoma (pcALCL). • The study population was revised to include participants who received at least 1 prior systemic therapy for their disease. • The protocol was revised to require confirmation of CD30 positivity, defined as membranous, cytoplasmic or golgi pattern of expression of the CD30 antigen by 10% or greater of either total lymphocytes or neoplastic cells at any intensity greater than zero on a scale of zero to 3+. • The protocol was revised to exclude patients with signs or symptoms of progressive multifocal leukoencephalopathy (PML) and contains instructions for the suggested management of suspected PML that include brentuximab vedotin discontinuation. • The schedule for modified severity weighted assessment tool (mSWAT) assessments was changed to include the following time points: before dose administration at Cycle 1, Day 1; at the end of every treatment cycle; within 30 days of the last dose of study drug; and at posttreatment follow-up visits. • The protocol was revised to exclude patients with known hepatitis B surface antigen-positive, or known or suspected active hepatitis C infection.
24 February 2012	Amendment 2: • The protocol was revised to include information on the occurrence of pulmonary toxicity and specifies that the concomitant use of bleomycin with brentuximab vedotin is contraindicated. • Revised recommendations for subsequent treatment for patients who complete 48 weeks of treatment with reference therapy or 16 cycles of brentuximab vedotin. • The protocol was revised to remove plan to reallocate patients to low-enrolling treatment arms for strata analysis.
04 March 2013	Amendment 3: • The protocol was revised to allow patients with stable disease (SD) to continue to receive study treatment up to the maximum treatment period (16 cycles of brentuximab vedotin or 48 weeks with methotrexate or bexarotene) at the discretion of the investigator. • The eligibility criteria was revised to allow for the enrollment of patients with pcALCL who have received prior radiation therapy or at least 1 prior systemic therapy for their disease. • A secondary objective was added to the protocol to assess duration of skin response with brentuximab vedotin. • The inclusion criterion requiring fasting serum triglycerides of <150 mg/dL before study entry was removed. • The timing of computed tomography (CT) scans was revised to align with current standard practice. • The planned analysis populations were revised to accommodate the change to the Ventana CD30 (Ber-H2) assay to determine CD30 expression for patient eligibility. • A real-time independent review performed at the time of anticipated treatment discontinuation for all patients, regardless of reason, was added. • References to ECGs were removed from the list of safety assessments in the protocol.
03 July 2013	Amendment 4: • Reverted to the text that stated that the sponsor was to be notified in the event that a participant was withdrawn from study treatment or from the study. • Revised instructions for calculating body surface area (BSA) to determine the dose of bexarotene. • The protocol was revised to require all events of peripheral neuropathy to be followed for changes in severity until resolution to baseline or study closure, whichever occurred first. • The protocol was revised to remove requirement to end safety monitoring when a patient received subsequent anticancer therapy.

02 December 2014	Amendment 5: • Updated safety information and revised the existing eligibility criteria regarding patients at risk for pancreatitis. • Language was added to the benefit and risk section summarizing the potential risk of pancreatitis in the population of patients at risk of pancreatitis and with cutaneous T-cell lymphoma (CTCL). • Eligibility criteria were updated to exclude patients with an elevated lipase value ≥3 times the upper limit of normal (ULN) with an amylase value > ULN. Allowed for Fludeoxyglucose-positron emission tomography (FDG-PET) scans and computed tomography (CT) taken within 8 weeks before signing the informed consent form (ICF) to be used as the subject FDG-PET scan, and CT scans taken within 4 weeks before signing the ICF to be used as the screening CT scan provided pre-specified conditions were met.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported