



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 | |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 |
| This version publication date | 07 January 2018 |
| First version publication date | 07 January 2018 |

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 | Interim |
| Date of interim/final analysis | 31 May 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 May 2016 |
| Global end of trial reached? | 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 31 May 2016. The study is ongoing.

Pre-assignment

Screening details:

Participants with a diagnosis of 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/m², 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/m²/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 | 0 | 0 |
| Not completed | 66 | 62 |
| Adverse event, serious fatal | 11 | 14 |
| Withdrawal by Participant | 8 | 7 |
| Participants in Follow-up | 42 | 39 |
| Participants on Study Treatment | 3 | - |
| Lost to follow-up | 2 | 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/m², 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 |

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

| | |
|---|---|
| End point title | Percentage of Participants Achieving an Objective Response that Lasts at Least 4 Months |
| 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 or data cutoff (Median overall follow-up 22.9 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%) | 56.3 (44.1 to 68.4) | 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 | |
| P-value | = 0.001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 43.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 29.1 |
| upper limit | 58.4 |

Notes:

[1] - 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 22.9 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%) | 15.6 (7.8 to 26.9) | 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 | |
| P-value | = 0.0046 [2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | 14.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 31.5 |

Notes:

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

Secondary: Progression-Free Survival (PFS)

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|---|---------------------------------|
| 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 17.5 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 (14.9 to 22.8) | 3.5 (2.4 to 4.6) | | |

Statistical analyses

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 | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 58 | 54 | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | -27.96 (\pm 26.877) | -8.62 (\pm 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 | |
| P-value | = 0.001 |
| Method | ANCOVA |
| Parameter estimate | Estimate of difference |
| Point estimate | -18.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -26.6 |
| upper limit | -11.2 |

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.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until disease progression, death or data cutoff (Median follow-up 22.9 months)

| End point values | Brentuximab vedotin | Methotrexate or Bexarotene | | |
|----------------------------------|---------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 43 | 13 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 15.1 (9.7 to 25.5) | 18.3 (3.5 to 18.4) | | |

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 the investigator and is defined as the time between the 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 $\geq 25\%$ increase in skin disease from baseline, or loss of response: in those with CR or PR, increase of skin score of greater than the sum of nadir plus 50% baseline score, or new tumors in patients without tumors at baseline (MF). The 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.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Until disease progression, death or data cutoff (Median follow-up 22.9 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%) | 20.6 (14.1 to 25.7) | 18.3 (3.5 to 18.9) | | |

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 26.1 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

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|-----------------|--|
| 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 EOT and during posttreatment long treatment follow-up (LTFU) - (Median follow-up 22.9 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= 20, 3) | -19.31 (± 19.861) | 0.75 (± 10.308) | | |
| Change at End of Treatment (n= 44, 37) | -14.84 (± 22.681) | -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= 6, 10) | -8.74 (± 16.910) | -4.93 (± 14.516) | | |
| Change at 12-15 months LTFU (n= 17, 15) | -18.09 (± 20.161) | -11.35 (± 17.585) | | |
| Change at 15-18 months LTFU (n= 20, 17) | -20.05 (± 17.434) | -8.58 (± 13.294) | | |

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 22.9 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= 20, 4) | 5.31 (± 9.416) | 7.88 (± 23.432) | | |
| Change at End of Treatment (n= 45, 37) | 0.15 (± 16.388) | -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= 6, 10) | 3.89 (± 19.320) | -5.32 (± 10.555) | | |
| Change at 12-15 months LTFU (n= 20, 16) | 8.99 (± 16.114) | 0.04 (± 12.272) | | |
| Change at 15-18 months LTFU (n= 16, 16) | 3.27 (± 14.116) | 3.24 (± 15.681) | | |

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 395 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) | 19 | 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 395 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 | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| 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/m², tablets, orally, once daily with meals for up to 48 weeks.

| | |
|-----------------------|---------------------|
| 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).

| Serious adverse events | Methotrexate or Bexarotene | Brentuximab vedotin | |
|---|----------------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 62 (29.03%) | 19 / 66 (28.79%) | |
| number of deaths (all causes) | 0 | 4 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lymphoma | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|--|--|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| 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 | 1 / 62 (1.61%) | 0 / 66 (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 | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 2 / 66 (3.03%) | |
| occurrences causally related to treatment / all | 2 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Extravasation | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| 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 | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|----------------|----------------|--|
| disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Stress | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Fracture | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Demyelinating polyneuropathy | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Haemolytic uraemic syndrome | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal perforation | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dermatitis bullous | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (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 | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| 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 | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Crystal arthropathy | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Superinfection bacterial | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 62 (0.00%) | 2 / 66 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 0 / 66 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Impetigo | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 1 / 66 (1.52%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotitis | | | |

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

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

| Non-serious adverse events | Methotrexate or Bexarotene | Brentuximab vedotin | |
|---|----------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 50 / 62 (80.65%) | 60 / 66 (90.91%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer pain | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 1 / 66 (1.52%) | |
| occurrences (all) | 7 | 1 | |

| | | | |
|--|------------------|------------------|--|
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 6 / 66 (9.09%) | |
| occurrences (all) | 0 | 7 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 17 / 62 (27.42%) | 18 / 66 (27.27%) | |
| occurrences (all) | 17 | 22 | |
| Asthenia | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 7 / 66 (10.61%) | |
| occurrences (all) | 9 | 10 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 62 (12.90%) | 9 / 66 (13.64%) | |
| occurrences (all) | 9 | 17 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 62 (9.68%) | 7 / 66 (10.61%) | |
| occurrences (all) | 6 | 9 | |
| Chills | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 4 / 66 (6.06%) | |
| occurrences (all) | 2 | 4 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 1 / 66 (1.52%) | |
| occurrences (all) | 4 | 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 62 (0.00%) | 7 / 66 (10.61%) | |
| occurrences (all) | 0 | 8 | |
| Cough | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 2 / 66 (3.03%) | |
| occurrences (all) | 12 | 2 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 5 / 62 (8.06%) | 2 / 66 (3.03%) | |
| occurrences (all) | 5 | 2 | |
| Anxiety | | | |

| | | | |
|--|---------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 0 / 66 (0.00%) 0 | |
| Investigations | | | |
| Weight decreased subjects affected / exposed occurrences (all) | 2 / 62 (3.23%) 2 | 6 / 66 (9.09%) 6 | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 6 | 3 / 66 (4.55%) 3 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 1 / 66 (1.52%) 1 | |
| Blood cholesterol increased subjects affected / exposed occurrences (all) | 4 / 62 (6.45%) 4 | 0 / 66 (0.00%) 0 | |
| Blood triglycerides increased subjects affected / exposed occurrences (all) | 5 / 62 (8.06%) 8 | 0 / 66 (0.00%) 0 | |
| Nervous system disorders | | | |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 6 / 66 (9.09%) 8 | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 30 / 66 (45.45%) 52 | |
| Peripheral motor neuropathy subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 4 / 66 (6.06%) 6 | |
| Dysgeusia subjects affected / exposed occurrences (all) | 0 / 62 (0.00%) 0 | 5 / 66 (7.58%) 6 | |
| Headache subjects affected / exposed occurrences (all) | 6 / 62 (9.68%) 6 | 5 / 66 (7.58%) 5 | |
| Dizziness | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 62 (1.61%) 1 | 4 / 66 (6.06%) 4 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 5 / 66 (7.58%) | |
| occurrences (all) | 6 | 11 | |
| Anaemia | | | |
| subjects affected / exposed | 6 / 62 (9.68%) | 3 / 66 (4.55%) | |
| occurrences (all) | 8 | 3 | |
| Eye disorders | | | |
| Dry eye | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 0 / 66 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 8 / 62 (12.90%) | 24 / 66 (36.36%) | |
| occurrences (all) | 8 | 32 | |
| Constipation | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 3 / 66 (4.55%) | |
| occurrences (all) | 4 | 5 | |
| Diarrhoea | | | |
| subjects affected / exposed | 4 / 62 (6.45%) | 18 / 66 (27.27%) | |
| occurrences (all) | 4 | 24 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 11 / 66 (16.67%) | |
| occurrences (all) | 3 | 14 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 2 / 62 (3.23%) | 10 / 66 (15.15%) | |
| occurrences (all) | 2 | 10 | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 3 / 62 (4.84%) | 7 / 66 (10.61%) | |
| occurrences (all) | 3 | 7 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 62 (1.61%) | 5 / 66 (7.58%) | |
| occurrences (all) | 1 | 6 | |
| Dry skin | | | |

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

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

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. |

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| 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. |
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported