Clinical trial results:
Pivotal Multicenter Trial of Moxetumomab Pasudotox in Relapsed/Refractory Hairy Cell Leukemia

Summary

EudraCT number	2014-003233-26
Trial protocol	GB ES BE IE DE CZ PL GR IT
Global end of trial date	20 September 2019

Results information

Result version number	v1 (current)
This version publication date	12 April 2020
First version publication date	12 April 2020

Trial information

Trial identification

Sponsor protocol code	CD-ON-CAT-8015-1053

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01829711
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States,
Public contact	Priti Patel, MedImmune, LLC, +1 650-264-9079, information.center@astrazeneca.com
Scientific contact	Priti Patel, MedImmune, LLC, +1 650-264-9079, information.center@astrazeneca.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	20 September 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the rate of durable complete response (CR) in multiply relapsed hairy cell leukemia (HCL) with moxetumomab pasudotox.

Protection of trial subjects:

The conduct of this clinical study met all local and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization guideline: Good Clinical Practice, and applicable regulatory requirements. Participants signed an informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 April 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Ireland: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Serbia: 2
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 35

Worldwide total number of subjects	80
EEA total number of subjects	40

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)	49
From 65 to 84 years	31
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted across 14 countries (the USA, France, Italy, Germany, Belgium, Canada, Czech Republic, Ireland, Israel, Norway, Poland, Serbia, Spain, and United Kingdom).

Pre-assignment

Screening details:

Total 89 participants were screened. Out of 89 participants, 80 participants received the study treatment.

Period 1

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

Arms

Arm title	Moxetumomab pasudotox 40 µg/kg

Arm description:

Participants received intravenous infusion of moxetumomab pasudotox 40 µg/kg on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of complete response, progressive disease, initiation of alternate therapy, or unacceptable toxicity.

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

Dosage and administration details:

Moxetumomab pasudotox 40 µg/kg was administered by IV infusion over 30 (± 10) minutes on Days 1, 3 and 5 of each 28-days cycle.

Number of subjects in period 1	Moxetumomab pasudotox 40 µg/kg
Started	80
Completed	37
Not completed	43
Adverse event, serious fatal	4
Started new therapies	17
Consent withdrawn by subject	3
Due to lack of response	1
Adverse event, non-fatal	3
Due to progression of disease	13
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Moxetumomab pasudotox 40 µg/kg
Reporting group description:	
Participants received intravenous infusion of moxetumomab pasudotox 40 µg/kg on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of complete response, progressive disease, initiation of alternate therapy, or unacceptable toxicity.	

Reporting group values	Moxetumomab pasudotox 40 µg/kg	Total	
Number of subjects	80	80	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	49	49	
From 65-84 years	31	31	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	60.3		
standard deviation	± 11.9	-	
Sex: Female, Male Units:			
Female	17	17	
Male	63	63	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	70	70	
More than one race	0	0	
Unknown or Not Reported	8	8	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5	5	
Not Hispanic or Latino	67	67	
Unknown or Not Reported	8	8	

End points

End points reporting groups

Reporting group title	Moxetumomab pasudotox 40 µg/kg

Reporting group description:

Participants received intravenous infusion of moxetumomab pasudotox 40 µg/kg on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of complete response, progressive disease, initiation of alternate therapy, or unacceptable toxicity.

Primary: Percentage of Participants with Durable Complete Response (CR) Assessed by Blinded Independent Central Review

End point title	Percentage of Participants with Durable Complete Response (CR) Assessed by Blinded Independent Central Review[1]

End point description:

Durable CR was defined as overall response that meets blood, bone marrow and imaging criteria for CR, followed by a >180 day duration of hematologic remission (HR). CR requires all of the following to be present: No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow; Resolution of any hepatomegaly, splenomegaly, and abnormal (>= 2 cm minimum length) lymphadenopathy by CT or MRI (maximum diameter of spleen should be either < 17 cm or have decreased by >25% from its baseline.); HR requires normal complete blood count (CBC) as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The Intent to treat (ITT) population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox.

End point type	Primary

End point timeframe:

Full disease assessment (CBC, bone marrow and imaging) at end of treatment (EOT; up to 24 weeks) and post EOT Day 181; CBC monthly for 6 months post EOT, every 3 months post Day 181 for first 2 years and every 6 months thereafter (approximately 6 years)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)	36.3 (25.8 to 47.8)			

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Durable CR by Investigator's Assessment

End point title	Percentage of Participants with Durable CR by Investigator's Assessment[2]

End point description:

Durable CR was defined as overall response that meets blood, bone marrow and imaging criteria for CR, followed by a >180 day duration of HR. CR requires all of the following to be present: No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow; Resolution of any hepatomegaly, splenomegaly, and abnormal (>= 2 cm minimum length) lymphadenopathy by CT or MRI (maximum diameter of spleen should be either < 17 cm or have decreased by >25% from its baseline.); HR requires normal complete blood count (CBC) as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox.

End point type	Primary

End point timeframe:

Full disease assessment (CBC, bone marrow and imaging) at end of treatment (EOT; up to 24 weeks) and post EOT Day 181; CBC monthly for 6 months post EOT, every 3 months post Day 181 for first 2 years and every 6 months thereafter (approximately 6 years)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not applicable since there were no inferential statistics, only descriptive statistics were performed for this end point.

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)	48.8 (37.4 to 60.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Minimal Residual Disease (MRD) Positive or MRD Negative CR Assessed by Blinded Independent Central Review

End point title	Percentage of Participants with Minimal Residual Disease (MRD) Positive or MRD Negative CR Assessed by Blinded Independent Central Review

End point description:

The MRD status by blinded independent review refers specifically to results of central pathologist read of bone marrow biopsy by immunohistochemistry. CR with Positive or Negative MRD requires all of following to be present: • No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow. Minimal Residual Disease: CR with HCL evident in blood or in bone marrow biopsy by immunohistochemistry. • Resolution of any hepatomegaly, splenomegaly, and abnormal (>= 2 cm minimum length) lymphadenopathy by CT or MRI. Although a normal spleen size is not defined, maximum diameter of spleen should be either < 17 cm or have decreased by >25% from its baseline. • Normal CBC as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)				
MRD negative CR	33.8 (23.6 to 45.2)			
MRD positive CR	7.5 (2.8 to 15.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with MRD Positive or MRD Negative CR by Investigator's Assessment

End point title	Percentage of Participants with MRD Positive or MRD Negative CR by Investigator's Assessment

End point description:

The MRD status by investigator refers to results of investigator assessment of bone marrow biopsy or bone marrow aspirate by immunohistochemistry and/or flow cytometry. The CR with Positive or Negative MRD requires all of the following to be present: • No evidence of leukemic cells in the peripheral blood and/or by routine H/E staining of bone marrow. Minimal Residual Disease: CR with HCL evident in blood or marrow by flow cytometry. • Resolution of any hepatomegaly, splenomegaly, and abnormal (>= 2 cm minimum length) lymphadenopathy by CT or MRI. Although a normal spleen size is not defined, the maximum diameter of the spleen should be either < 17 cm or have decreased by >25% from its baseline. • Normal CBC as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, end of treatment, and at follow-up visits every 3 months for the next 24 months and every 6 months thereafter (Approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)				
MRD negative CR	32.5 (22.4 to 43.9)			
MRD positive CR	7.5 (2.8 to 15.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to CR Assessed by Blinded Independent Central Review

End point title	Time to CR Assessed by Blinded Independent Central Review

End point description:

Time to CR was defined as the time from the start of moxetumomab pasudotox administration to the first documentation of CR. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Time to CR was evaluated for participants who achieved CR per independent central review.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (full range (min-max))	5.9 (1.8 to 13.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of CR Assessed by Blinded Independent Central Review

End point title	Duration of CR Assessed by Blinded Independent Central Review

End point description:

Duration of CR was defined as the duration from documentation of CR to the time of relapse from CR. Relapse from CR was defined as any CR criteria (blood counts, imaging or bone marrow) no longer consistent with CR. CR requires all of the following to be present: No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow; Resolution of any hepatomegaly, splenomegaly, and abnormal (>= 2 cm minimum length) lymphadenopathy by CT or MRI (maximum diameter of spleen should be either < 17 cm or have decreased by >25% from its baseline); normal CBC as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Duration of CR was evaluated for participants who achieved CR per independent central review.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (confidence interval 95%)	62.8 (35.7 to 62.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Hematologic Remission

End point title	Duration of Hematologic Remission

End point description:

Duration of HR was defined as the duration from documentation of HR to the time of relapse. HR was defined as the blood counts required for CR as normal CBC as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. Duration of HR was censored on the date of the last hematologic assessment for participants who have no documented relapse based on blood count prior to data cutoff, dropout, or initiation of alternative anticancer therapy. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Duration of HR was evaluated for participants who achieved HR.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (confidence interval 95%)	45.8 (25.9 to 71.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hematologic Remission

End point title	Time to Hematologic Remission

End point description:

Time to HR was defined as the time from the start of moxetumomab pasudotox administration to the first documentation of HR. HR was defined as the blood counts required for CR as normal CBC as exhibited by: Neutrophils >= 1.5 x 10^9/L, Platelets >= 100 x 10^9/L, and hemoglobin >= 11.0 g/dL without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Time to HR was evaluated for participants in the ITT population who achieved HR.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (full range (min-max))	1.1 (0.2 to 12.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response (OR) Assessed by Blinded Independent Central Review

End point title	Percentage of Participants With Objective Response (OR) Assessed by Blinded Independent Central Review

End point description:

The OR was defined as number of participants with a best response of CR or PR. CR requires all of following to be present: No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow; Resolution of any hepatomegaly, splenomegaly, and abnormal lymphadenopathy by CT or MRI (maximum diameter of spleen should be either <17 cm or have decreased by >25% from its baseline); normal CBC without transfusions or growth factors for at least 4 weeks. PR requires all of following for a period of at least 4 weeks: >=50% decrease or normalization (<5.0 x 10^9/L) in peripheral blood lymphocyte count and >=50% reduction in lymphadenopathy and in abnormal haepatosplenomegaly by CT or MRI from pre-treatment baseline value; normal CBC as mentioned above or 50% improvement in CBC values over baseline without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)	75.0 (64.1 to 84.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Objective Response by Investigator's Assessment

End point title	Percentage of Participants With Objective Response by Investigator's Assessment

End point description:

The OR was defined as number of participants with a best response of CR or PR. CR requires all of following to be present: No evidence of leukemic cells in peripheral blood and/or by routine H/E staining of bone marrow; Resolution of any hepatomegaly, splenomegaly, and abnormal lymphadenopathy by CT or MRI (maximum diameter of spleen should be either <17 cm or have decreased by >25% from its baseline); normal CBC without transfusions or growth factors for at least 4 weeks. PR requires all of following for a period of at least 4 weeks: >=50% decrease or normalization (<5.0 x 10^9/L) in peripheral blood lymphocyte count and >=50% reduction in lymphadenopathy and in abnormal haepatosplenomegaly by CT or MRI from pre-treatment baseline value; normal CBC as mentioned above or 50% improvement in CBC values over baseline without transfusions or growth factors for at least 4 weeks. The ITT population was analysed for this endpoint.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, end of treatment, and at follow-up visits every 3 months for the next 24 months and every 6 months thereafter (Approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of participants				
number (confidence interval 95%)	78.8 (68.2 to 87.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Objective Response Assessed by Blinded Independent Central Review

End point title	Time to Objective Response Assessed by Blinded Independent Central Review

End point description:

Time to OR was defined as the time from the start of moxetumomab pasudotox administration to the first documentation of OR (CR or PR). The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Time to OR was evaluated for participants who achieved OR per independent central review.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (full range (min-max))	5.7 (1.8 to 12.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response Assessed by Blinded Independent Central Review

End point title	Duration of Objective Response Assessed by Blinded Independent Central Review

End point description:

Duration of OR was defined as the time from the first documentation of objective response (CR or PR) to the date of relapse. Duration of OR was censored on the date of last disease assessment or hematologic assessment for participants who have no documented relapse prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox. Duration of OR was evaluated for participants who achieved OR per independent central review.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (confidence interval 95%)	66.7 (25.4 to 66.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS) Assessed by Blinded Independent Central Review

End point title	Progression-free Survival (PFS) Assessed by Blinded Independent Central Review

End point description:

The PFS was defined as the time from the start of moxetumomab pasudotox administration to the earliest date of a disease assessment showing a progressive disease/relapse, earliest date of hematologic relapse or date of death, whichever was earlier. The PFS was censored on the date of last disease assessment or hematologic assessment for participants who are alive with no documented relapse or PD prior to data cut-off, dropout, or the initiation of alternative anticancer therapy. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (confidence interval 95%)	41.5 (28.1 to 71.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF) Assessed by Blinded Independent Central Review

End point title	Time to Treatment Failure (TTF) Assessed by Blinded Independent Central Review

End point description:

The TTF was defined as the time from the start of moxetumomab pasudotox administration to the date of the first of relapse, progressive disease, initiation of alternative anticancer therapy, or death due to disease or disease-related complication. The TTF was censored on the date of last disease assessment or hematologic assessment for participants who are alive with no documented relapse or PD prior to data cut-off, dropout, or the initiation of alternative anticancer therapy and also censored for death not accompanied by relapse. The ITT population was analysed for this endpoint, which included all participants who entered into the study and treated with moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

Prior to each treatment cycle, EOT (up to 24 weeks), monthly from the EOT assessment until the Day 181 assessment (only for CBC), at follow-up visits every 3 months for the next 24 months, and every 6 months thereafter (approximately 6 years)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Months				
median (confidence interval 95%)	41.5 (28.1 to 71.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAEs) and Treatment Emergent Serious Adverse Events (TESAEs)

End point description:

An Adverse Event (AE) is any unfavourable and unintended sign, symptoms, or diseases temporally associated with use of study drug, whether or not considered related to study drug. A serious adverse event (SAE) is an AE that results in death, initial or prolonged inpatient hospitalization, life-threatening, persistent or significant disability/incapacity, congenital anomaly/birth defect, or an important medical event. TEAEs and TESAEs are defined as AEs and SAEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug. The safety population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 4-6 weeks after last dose of Cycle 6 (28-day cycle) (approximately 7 months)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Participants				
Any TEAEs	79			
Any TESAEs	28			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Participants With Abnormal Clinical Laboratory Results Reported as TEAEs

End point description:

An abnormal laboratory finding which required an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 30 days after the last dose of study drug (approximately 7 months). The safety population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 4-6 weeks after last dose of Cycle 6 (28-day cycle) (approximately 7 months)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Participants				
Anaemia	17			
Disseminated intravascular coagulation	1			
Febrile neutropenia	5			
Haemolytic uraemic syndrome	6			
Iron deficiency anaemia	1			
Leukopenia	2			
Lymphopenia	1			
Neutropenia	4			
Thrombocytopenia	3			
Activated partial thromboplastin time prolonged	1			
Lymphocyte count decreased	16			
Lymphocyte count increased	1			
Neutrophil count decreased	6			

Platelet count decreased	9			
White blood cell count decreased	8			
Aspartate aminotransferase increased	15			
Blood albumin decreased	1			
Blood alkaline phosphatase increased	4			
Blood bicarbonate decreased	2			
Blood bilirubin increased	5			
Blood creatinine increased	9			
Blood triglycerides increased	1			
Gamma-glutamyltransferase increased	1			
Lipase increased	2			
Hyperglycaemia	8			
Hyperkalaemia	6			
Hypermagnesaemia	3			
Hypernatraemia	4			
Hypertriglyceridaemia	2			
Hypoalbuminaemia	16			
Hypocalcaemia	19			
Hypoglycaemia	2			
Hypokalaemia	13			
Hypomagnesaemia	6			
Hyponatraemia	9			
Haematuria	6			
Haemoglobinuria	2			
Proteinuria	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point title	Number of Participants With Abnormal Vital Signs Reported as TEAEs

End point description:

An abnormal vital signs that were judged by the investigator to be medically significant were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 30 days after the last dose of study drug (approximately 7 months). The safety population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 4-6 weeks after last dose of Cycle 6 (28-day cycle) (approximately 7 months)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Participants				
Dyspnoea	9			
Dyspnoea exertional	3			
Hypertension	12			
Hypotension	6			
Pyrexia	25			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point title	Number of Participants with Abnormal Electrocardiogram (ECG) Reported as TEAEs

End point description:

An abnormal ECG findings that were judged by the investigator to be medically significant were reported as AEs. The TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study drug, up to 30 days after the last dose of study drug (approximately 7 months). The safety population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

From the start of study treatment (Day 1) through 4-6 weeks after last dose of Cycle 6 (28-day cycle) (approximately 7 months)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Participants				
Angina pectoris	2			
Atrial fibrillation	1			
Atrioventricular block first degree	3			
Bundle branch block left	1			
Left ventricular dysfunction	1			
Palpitations	1			
Pericardial effusion	1			
Sinus bradycardia	2			
Sinus tachycardia	6			
Supraventricular tachycardia	1			
Tachycardia	1			
Ventricular arrhythmia	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum Observed Plasma Concentration (Tmax) of Moxetumomab Pasudotox

End point title	Time to Reach Maximum Observed Plasma Concentration (Tmax) of Moxetumomab Pasudotox

End point description:

The Tmax of moxetumomab pasudotox is reported. The pharmacokinetic (PK) population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Hours				
median (full range (min-max))				
Cycle 1 Day 1 (n= 75)	0.567 (0.433 to 1.30)			
Cycle 1 Day 5 (n= 71)	0.550 (0.417 to 2.45)			
Cycle 2 Day 1 (n= 69)	0.583 (0.500 to 1.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Moxetumomab Pasudotox

End point title	Maximum Observed Plasma Concentration (Cmax) of Moxetumomab Pasudotox

End point description:

The Cmax of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

The Cmax of moxetumomab pasudotox is reported. Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 75)	192 (± 162)			
Cycle 1 Day 5 (n= 71)	435 (± 233)			
Cycle 2 Day 1 (n= 69)	379 (± 262)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Last (Tlast) Measurable Concentration of Moxetumomab Pasudotox

End point title	Time of Last (Tlast) Measurable Concentration of Moxetumomab Pasudotox

End point description:

The Tlast of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Hours				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=75)	0.841 (± 0.866)			
Cycle 1 Day 5 (n= 71)	3.37 (± 2.38)			
Cycle 2 Day 1 (n= 69)	2.16 (± 1.43)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Time of the Last Quantifiable Concentration (AUC0-last) of Moxetumomab Pasudotox

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Time of the Last Quantifiable Concentration (AUC0-last) of Moxetumomab Pasudotox

End point description:

The AUC0-last of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 75)	120 (± 261)			
Cycle 1 Day 5 (n= 71)	820 (± 721)			
Cycle 2 Day 1 (n= 69)	626 (± 610)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to 3 hours (AUC0-3hr) post end of moxetumomab pasudotox

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to 3 hours (AUC0-3hr) post end of moxetumomab pasudotox

End point description:

The AUC0-3hr of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, and 3 hr post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 6)	869 (± 200)			
Cycle 1 Day 5 (n= 54)	856 (± 370)			
Cycle 2 Day 1 (n= 37)	1030 (± 333)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of Moxetumomab Pasudotox

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to Infinity (AUC0-inf) of Moxetumomab Pasudotox

End point description:

The AUC0-inf of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point. Here, the arbitrary number "999" signifies that data for Cycle 1 Day 1 was not reported as no evaluable participants for the calculation of the concerned parameters (ie., data were not sufficient).

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 0)	999 (± 999)			
Cycle 1 Day 5 (n= 49)	1300 (± 742)			
Cycle 2 Day 1 (n= 22)	1470 (± 541)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve Extrapolated (AUCExt) of Moxetumomab Pasudotox

End point title	Area Under the Plasma Concentration-time Curve Extrapolated (AUCExt) of Moxetumomab Pasudotox

End point description:

The AUCExt of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: ng*hr/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 6) Cycle 1 Day 5 (n= 49) Cycle 2 Day 1 (n= 22)	13.2 (± 3.04) 14.3 (± 5.72) 20.2 (± 7.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Systemic Clearance (CL) of Moxetumomab Pasudotox

End point title	Systemic Clearance (CL) of Moxetumomab Pasudotox

End point description:

The CL of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point. Here, the arbitrary number "999" signifies that data for Cycle 1 Day 1 was not reported as no evaluable participants for the calculation of the concerned parameters (ie., data were not sufficient).

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6

hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: mL/hr/kg				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 0)	999 (± 999)			
Cycle 1 Day 5 (n= 49)	44.6 (± 30.5)			
Cycle 2 Day 1 (n= 22)	31.8 (± 13.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half life (t1/2) of Moxetumomab Pasudotox

End point title	Terminal Half life (t1/2) of Moxetumomab Pasudotox

End point description:

The t1/2 of moxetumomab pasudotox is reported. The PK population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox and provided at least 1 baseline and post-baseline concentration-time data point. Here, the arbitrary number "999" signifies that data for Cycle 1 Day 1 was not reported as no evaluable participants for the calculation of the concerned parameters (ie., data were not sufficient).

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (pre-dose; 5 mins and 3 hr post dose); Cycle 1 Day 5 (pre-dose; 5 mins, 1 hr, 3 hr, and 6 hrs post dose); and Cycle 2 Day 1 (pre-dose; 5 mins and 3 hr post dose)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Hours				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n= 0)	999 (± 999)			
Cycle 1 Day 5 (n= 49)	1.38 (± 0.632)			
Cycle 2 Day 1 (n= 22)	1.39 (± 0.351)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Positive Anti-drug Antibodies (ADA), Neutralizing Anti-drug Antibodies (nAb) and Specificity (CD22 and PE38) Positive to Moxetumomab Pasudotox

End point title	Percentage of Participants With Positive Anti-drug Antibodies (ADA), Neutralizing Anti-drug Antibodies (nAb) and Specificity (CD22 and PE38) Positive to Moxetumomab Pasudotox

End point description:

Participants with ADA positive, nAb positive, cluster of differentiation 22 (CD22) positive of ADA positive/NAb positive, and pseudomonas exotoxin 38 (PE38) positive of ADA positive/NAb positive to moxetumomab pasudotox at any visit are reported. The safety population was analysed for this endpoint, which included all participants who received at least 1 dose of moxetumomab pasudotox.

End point type	Secondary

End point timeframe:

Pre-infusion on Day 1 of Cycles 1, 2, 3, and 5; at the End of Treatment (4 to 6 weeks after the last dose; approximately 7 months)

End point values	Moxetumomab pasudotox 40 µg/kg			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: Percentage of Participants				
number (not applicable)				
ADA positive	87.5			
ADA and NAb positive	83.8			
Specificity CD22 positive of ADA+/NAb+	55.2			
Specificity PE38 positive of ADA+/NAb+	98.5			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For TEAEs and TESAEs: From Day 1 through 4-6 weeks after last dose of Cycle 6 (28-day cycle) (approximately 7 months)
For all-cause death data: From Day 1 through end of study (approximately 6 years)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Moxetumomab pasudotox 40 µg/kg

Reporting group description:

Participants received intravenous infusion of moxetumomab pasudotox 40 µg/kg on Days 1, 3, and 5 of each 28-day cycle for up to 6 cycles, until documentation of complete response, progressive disease, initiation of alternate therapy, or unacceptable toxicity.

Serious adverse events	Moxetumomab pasudotox 40 µg/kg		
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 80 (35.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Glioblastoma			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	5 / 80 (6.25%)			
occurrences causally related to treatment / all	2 / 5			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Cough				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypoxia				
subjects affected / exposed	2 / 80 (2.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pharyngeal cyst				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	1 / 80 (1.25%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tachypnoea				

subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haptoglobin decreased			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutrophil count decreased			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Weight increased			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Haemolytic uraemic syndrome			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences causally related to treatment / all	6 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenic colitis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Clostridium difficile colitis			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

Lung infection			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Pneumonia fungal			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis syndrome			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 80 (1.25%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Upper respiratory tract infection			
subjects affected / exposed	2 / 80 (2.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Moxetumomab pasudotox 40 µg/kg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	77 / 80 (96.25%)		
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		

Hypertension			
subjects affected / exposed	12 / 80 (15.00%)		
occurrences (all)	38		
Hypotension			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	8		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	10 / 80 (12.50%)		
occurrences (all)	30		
Chills			
subjects affected / exposed	15 / 80 (18.75%)		
occurrences (all)	18		
Face oedema			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	16		
Fatigue			
subjects affected / exposed	26 / 80 (32.50%)		
occurrences (all)	40		
Non-cardiac chest pain			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Oedema			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	5		
Oedema peripheral			
subjects affected / exposed	31 / 80 (38.75%)		
occurrences (all)	47		
Peripheral swelling			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	5		
Pyrexia			
subjects affected / exposed	22 / 80 (27.50%)		
occurrences (all)	35		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	8		
Dyspnoea			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	10		
Nasal congestion			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Oropharyngeal pain			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	8		
Pleural effusion			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	6		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	9		
Insomnia			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	9		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	17 / 80 (21.25%)		
occurrences (all)	43		
Aspartate aminotransferase increased			
subjects affected / exposed	15 / 80 (18.75%)		
occurrences (all)	38		
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	8		
Blood bilirubin increased			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	14		
Blood creatinine increased			

subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	15		
Haptoglobin decreased			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	6		
Lymphocyte count decreased			
subjects affected / exposed	16 / 80 (20.00%)		
occurrences (all)	73		
Neutrophil count decreased			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	10		
Platelet count decreased			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	18		
Weight increased			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	7		
White blood cell count decreased			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	15		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	6		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	12		
Dysgeusia			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Headache			

subjects affected / exposed	26 / 80 (32.50%)		
occurrences (all)	37		
Paraesthesia			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	8		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 80 (21.25%)		
occurrences (all)	41		
Neutropenia			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	5		
Eye disorders			
Cataract			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Dry eye			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	6		
Vision blurred			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	8		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	10 / 80 (12.50%)		
occurrences (all)	12		
Abdominal pain			
subjects affected / exposed	7 / 80 (8.75%)		
occurrences (all)	7		
Abdominal pain upper			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	5		
Constipation			
subjects affected / exposed	18 / 80 (22.50%)		
occurrences (all)	21		
Diarrhoea			

subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	17 / 80 (21.25%) 20 4 / 80 (5.00%) 5 5 / 80 (6.25%) 5 28 / 80 (35.00%) 48 14 / 80 (17.50%) 17		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Rash maculo-papular subjects affected / exposed occurrences (all)	 6 / 80 (7.50%) 12 4 / 80 (5.00%) 4 4 / 80 (5.00%) 5		
Renal and urinary disorders Haematuria subjects affected / exposed occurrences (all)	 5 / 80 (6.25%) 5		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain	 13 / 80 (16.25%) 22 12 / 80 (15.00%) 12		

subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	7		
Myalgia			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	16		
Pain in extremity			
subjects affected / exposed	12 / 80 (15.00%)		
occurrences (all)	14		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Rhinitis			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Sinusitis			
subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	5 / 80 (6.25%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	11 / 80 (13.75%)		
occurrences (all)	12		
Hyperglycaemia			
subjects affected / exposed	8 / 80 (10.00%)		
occurrences (all)	15		
Hyperkalaemia			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	8		
Hypernatraemia			

subjects affected / exposed	4 / 80 (5.00%)		
occurrences (all)	5		
Hypoalbuminaemia			
subjects affected / exposed	16 / 80 (20.00%)		
occurrences (all)	51		
Hypocalcaemia			
subjects affected / exposed	19 / 80 (23.75%)		
occurrences (all)	39		
Hypokalaemia			
subjects affected / exposed	13 / 80 (16.25%)		
occurrences (all)	22		
Hypomagnesaemia			
subjects affected / exposed	6 / 80 (7.50%)		
occurrences (all)	8		
Hyponatraemia			
subjects affected / exposed	9 / 80 (11.25%)		
occurrences (all)	17		
Hypophosphataemia			
subjects affected / exposed	19 / 80 (23.75%)		
occurrences (all)	47		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 March 2013	Stopping rules were updated for when participants redevelop Grade 3 or more severity non-hematologic toxicities after withholding study drug and re-challenge. Addition of the exclusion criterion for participants with clinically significant ophthalmologic findings during screening. Added ophthalmologic exam at baseline and follow-up visits.
20 February 2014	Modified the secondary objectives to replace relapse-free survival with TTF. Malaria infection was added as an excluded intercurrent illness. Added the exclusion criterion for participants with history of both thromboembolism and known congenital hypercoagulable conditions, participants on high dose estrogen, and participants with clinical evidence of disseminated intravascular coagulation. Updated to state that participants who experienced Grade 4 CLS and Grade 3 HUS were to be taken of off treatment instead of off study, and specified that an event of Grade 2 or more severity of hypercalcemia with calcium level corrected for serum albumin required a delay in dosing until resolution to < Grade 2. Updated time points of PK collection.
09 June 2014	Updated the length of abnormal lymphadenopathy. summarized CR duration as it is added as a secondary endpoint. Modified the eligibility criteria for participants with HCL variant and revised the eligibility criteria for prior systemic therapies. Updated the exclusion criterion regarding high dose estrogen. Revised the timing of procedures for Cycle 1 Days 1 and 5. Updated the immunogenicity evaluation. Updated the treatment plan to indicate guidelines for fluid and antihistamine administration. Added the text related to the use of non-steroidal anti-inflammatory medications.
12 August 2014	Updated the AE definition for baseline laboratory abnormality. Updated the inclusion criteria for females of childbearing potential and added the inclusion criterion pertaining to non-sterilized males. Modified the inclusion criteria related to prior systemic therapies. Uncontrolled hypertension was added to the list of conditions that are exclusionary for this study. Modified the exclusion criteria for exclusion criterion related to abnormal ECGs. Updated assessments conducted at screening, during treatment cycles, and at follow-up visits. Specified the requirement for HUS resolution. Added a criterion specifying that 6 cycles of therapy are allowed; treatment delay was specified as > 2 weeks. Specified the inclusion of bone marrow examination and cross-sectional imaging as post baseline disease assessments. Modified the statement related to the replacement of enrolled but untreated participants.
02 October 2014	Added to instructions for use of steroids. Updated the text for dose delays and dose modifications. Added the instruction on collection times of PK samples for participants who develop any grade of HUS. Added new sections to describe how bone aspirate for MRD would analyzed, the collection time points during the study, and where it would processed and analyzed.
22 January 2015	Revised immunogenicity evaluation time points. Added immunogenicity to be in line with PK evaluation upon both diagnosis and resolution of HUS and > Grade 2 CLS. Added wording regarding HUS-like event and CLS specified in the assessment of safety section. Added section of "Peripheral Blood Disease B-cell Clone Detection". Removed reference to thrombotic microangiopathy/HUS from important potential risks and added it as an identified risk.
23 April 2015	Updated the inclusion criteria for contraceptive methods. removed prior splenectomy and lymph nodes > 4 cm from the list of exclusion criteria.

06 January 2017	Updated the text related to CR with or without MRD. This text was updated for the detailed procedure of central review. Updated the text related to the assessments applicable to duration of CR are relevant to duration of hematologic remission. Clarified relapse definition. Modified the text to align with the regulatory definition of PFS.
29 March 2017	Updated the text reacted to concomitant medications. Modified the table of "Study Calendar for End of Treatment and Follow-up" related to the data collections of blood component transfusions and hematopoietic growth factors.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported