Clinical trial results:
AN OPEN-LABEL, RANDOMIZED, PHASE 3 STUDY OF INOTUZUMAB OZOGAMICIN ADMINISTERED IN COMBINATION WITH RITUXIMAB COMPARED TO DEFINED INVESTIGATORS CHOICE THERAPY IN SUBJECTS WITH RELAPSED OR REFRACTORY CD22-POSITIVE AGGRESSIVE NON HODGKIN LYMPHOMA WHO ARE NOT CANDIDATES FOR INTENSIVE HIGH-DOSE CHEMOTHERAPY

Summary

EudraCT number	2010-020147-12
Trial protocol	CZ SE ES DE GB HU LT BG BE GR NL SK
Global end of trial date	28 March 2014

Results information

Result version number	v1 (current)
This version publication date	30 May 2016
First version publication date	15 August 2015

Trial information

Trial identification

Sponsor protocol code	B1931008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01232556
WHO universal trial number (UTN)	-
Other trial identifiers	Alias: 3129K5-3303

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., 001 800-718-1021, ClinicalTrials.gov_Inquiries@pfizer.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	01 June 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 March 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate efficacy as measured by overall survival (OS), with a goal of demonstrating the superiority of inotuzumab ozogamicin when administered in combination with rituximab, compared with an active comparator arm.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 April 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	54 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Belgium: 12
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Lithuania: 2
Country: Number of subjects enrolled	Canada: 22
Country: Number of subjects enrolled	Croatia: 4
Country: Number of subjects enrolled	India: 1
Country: Number of subjects enrolled	Japan: 73
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Russian Federation: 7

Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Thailand: 2
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 71
Worldwide total number of subjects	338
EEA total number of subjects	134

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)	109
From 65 to 84 years	222
85 years and over	7

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Overall study summary and the baseline characteristics summary were calculated using the ITT population. Adverse events were calculated using the safety population.

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	Inotuzumab ozogamicin plus (+) rituximab

Arm description:

Subjects received rituximab and inotuzumab ozogamicin via intravenous (IV) infusion.

Arm type	Experimental
Investigational medicinal product name	Inotuzumab ozogamicin
Investigational medicinal product code	PF-05208773
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravenous use

Dosage and administration details:

Inotuzumab ozogamicin 1.8 milligram per square meter (mg/m^2) via IV infusion on Day 2 of each 28-day cycle for a maximum of 6 cycles.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 via IV infusion on Day 1 of each 28-day cycle for a maximum of 6 cycles.

Arm title	Rituximab+gemcitabine or rituximab+bendamustine

Arm description:

Subjects received either R-bendamustine (rituximab via IV infusion and bendamustine via IV infusion) or R-gemcitabine (rituximab via IV infusion and gemcitabine via IV infusion. Choice of therapy was at the discretion of the investigator.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab 375 mg/m^2 via IV infusion on Day 1 in 28-day cycles for a maximum of 6 cycles when given in combination with bendamustine and rituximab 375 mg/m^2 via IV infusion on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 for all other cycles when given in combination with gemcitabine.

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

Dosage and administration details:

Bendamustine 120 mg/m^2 via IV infusion on Days 1 and 2 in 28-day cycles for a maximum of 6 cycles.

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

Dosage and administration details:

Gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8 and 15 of each 28-day cycle for a maximum of 6 cycles.

Number of subjects in period 1	Inotuzumab ozogamicin plus (+) rituximab	Rituximab+gemcitabine or rituximab+bendamustine
Started	166	172
Completed	7	1
Not completed	159	171
Lost to follow-up	-	2
Study terminated by sponsor	35	51
Subject died	97	97
Unspecified	6	4
Subject refused further follow-up	21	17

Baseline characteristics

Reporting groups	
Reporting group title	Inotuzumab ozogamicin plus (+) rituximab
Reporting group description:	
Subjects received rituximab and inotuzumab ozogamicin via intravenous (IV) infusion.	
Reporting group title	Rituximab+gemcitabine or rituximab+bendamustine
Reporting group description:	
Subjects received either R-bendamustine (rituximab via IV infusion and bendamustine via IV infusion) or R-gemcitabine (rituximab via IV infusion and gemcitabine via IV infusion. Choice of therapy was at the discretion of the investigator.	

Reporting group values	Inotuzumab ozogamicin plus (+) rituximab	Rituximab+gemcitabine or rituximab+bendamustine	Total
Number of subjects	166	172	338
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	68.6	66.9	
standard deviation	± 12.29	± 11.4	-
Gender categorical			
Units: Subjects			
Female	75	75	150
Male	91	97	188

End points

End points reporting groups

Reporting group title	Inotuzumab ozogamicin plus (+) rituximab
Reporting group description:	
Subjects received rituximab and inotuzumab ozogamicin via intravenous (IV) infusion.	
Reporting group title	Rituximab+gemcitabine or rituximab+bendamustine
Reporting group description:	
Subjects received either R-bendamustine (rituximab via IV infusion and bendamustine via IV infusion) or R-gemcitabine (rituximab via IV infusion and gemcitabine via IV infusion. Choice of therapy was at the discretion of the investigator.	
Subject analysis set title	Inotuzumab ozogamicin+rituximab
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received rituximab 375 mg/m^2 via IV infusion on Day 1 and inotuzumab ozogamicin 1.8 mg/m^2 via IV infusion on Day 2 of each 28-day cycle for a maximum of 6 cycles.	
Subject analysis set title	Rituximab+gemcitabine or rituximab+bendamustine
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Subjects received either R-bendamustine (rituximab 375 mg/m^2 via IV infusion on Day 1 and bendamustine 120 mg/m^2 via IV infusion on Days 1 and 2 in 28-day cycles for a maximum of 6 cycles) or R-gemcitabine (rituximab 375 mg/m^2 via IV infusion on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 for all other cycles, and gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8 and 15 of each 28-day cycle for a maximum of 6 cycles). Choice of therapy was at the discretion of the investigator.	

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description:	
OS was defined as the time from randomization to death due to any cause, censoring at the date of last contact or the end of the study. The Kaplan-Meier method was used to determine OS. The hazard ratio and corresponding 95 per cent (%) 2-sided confidence interval were calculated using stratified Cox proportional hazard regression. Intent-to-treat (ITT) Population.	
End point type	Primary
End point timeframe:	
From randomization up to 5 years after last dose or up to final study visit, whichever occurs first	

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	172		
Units: Months				
median (confidence interval 95%)	9.5 (7 to 14.5)	9.5 (7.7 to 14.1)		

Statistical analyses

Statistical analysis title	Analysis for Overall Survival

Statistical analysis description:

Primary null hypothesis: Equality of survival distributions. Sample size sufficient to have power 0.96 for an experimental/control hazard ratio of 0.6. Hazard's Ratio from stratified Cox proportional hazards model. The stratification factors are are pre-randomization investigator choice, baseline Secondary International Prognostic Index (sIPI), and best response to most recent chemo therapy. One sided stratified log-rank test was used.

Comparison groups	Inotuzumab ozogamicin+rituximab v Rituximab+gemcitabine or rituximab+bendamustine
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.708 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.083
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.44

Notes:

[1] - A one sided 0.025 level testing plan was specified with two interim analyses and final testing level at one-sided 0.023.

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS is defined as time from date of randomization to date of progressive disease (PD), (including investigator's claim of clinical progression)date of death from any cause, or initiation of a new treatment for the lymphoma due to persistent/refractory disease. The Kaplan-Meier method was used to determine PFS. The hazard ratio and corresponding 95 % 2-sided confidence interval were calculated using stratified Cox proportional hazard regression. PD requires the following: a. Appearance of any new lesion more than 1.5 centimeters (cm) in any axis during or at the end of treatment, even if other lesions are decreasing in size. b. At least a 50% increase from nadir in the sum of the product diameters of any previously involved nodes, or in a single involved node, or the size of other lesions. c. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis. ITT Population.

End point type	Secondary

End point timeframe:

From randomization up to 2 years or final study visit, whichever occurs first, including but not limited to planned assessments scheduled approximately every 12 weeks

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	172		
Units: Months				
median (confidence interval 95%)	3.7 (2.9 to 5)	3.5 (2.8 to 4.9)		

Statistical analyses

Statistical analysis title	Analysis for Progression-Free Survival (PFS)

Statistical analysis description:

Second comparison in hierarchical testing strategy was used for power calculation. HR from stratified Cox proportional hazards model. The stratification factors are are pre-randomization investigator choice, baseline sIPI, and best response to most recent chemo therapy. From one sided stratified log-rank test.

Comparison groups	Rituximab+gemcitabine or rituximab+bendamustine v Inotuzumab ozogamicin+rituximab
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.271 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.924
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.19

Notes:

[2] - A hierarchical testing strategy was specified for OS, PFS and response. PFS could be tested at the 0.023 level if the OS test result were positive. Response could be tested if both the OS and PFS test results were positive.

Secondary: Percentage of Subjects With A Best Overall Response of Complete Response (CR) or Partial Response (PR) per National Cancer Institute (NCI) International Response Criteria for Non Hodgkin Lymphoma (NHL)

End point title	Percentage of Subjects With A Best Overall Response of Complete Response (CR) or Partial Response (PR) per National Cancer Institute (NCI) International Response Criteria for Non Hodgkin Lymphoma (NHL)

End point description:

CR is defined as disappearance of all detectable clinical evidence of disease (including cleared infiltrate on repeat bone marrow aspirate/biopsy if lymphoma involvement of bone marrow before treatment). Partial Response (PR) requires the following: a. Greater than or equal to (≥)50 % decrease in SPD of the six largest dominant nodes or nodal masses. b. No increase in the size of other nodes, liver, or spleen. c. Splenic and hepatic nodules must regress by ≥50% in the SPD, or for single nodules, in the greatest transverse diameter. d. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present. e. No new sites of disease. The 95% CI was determined using the exact method based on binomial distribution. ITT Population.

End point type	Secondary

End point timeframe:

Up to 2 years from first study drug dose or up to final study visit, whichever occurs first, including but not limited to planned assessments scheduled approximately every 12 weeks

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	172		
Units: Percentage of subjects				
number (confidence interval 95%)	29.5 (22.7 to 37.08)	29.7 (22.94 to 37.08)		

Statistical analyses

Statistical analysis title	Analysis for Best overall response of CR or PR

Statistical analysis description:

Third comparison in hierarchical testing strategy was used for power calculation. Third comparison in hierarchical testing strategy was used for power calculation. The stratification factors are pre-randomization investigator choice, baseline sIPI, and best response to most recent chemo therapy.

Comparison groups	Inotuzumab ozogamicin+rituximab v Rituximab+gemcitabine or rituximab+bendamustine
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.843 [3]
Method	Cochran-Mantel-Haenszel

Notes:

[3] - A hierarchical testing strategy was specified for OS, PFS and response. PFS could be tested at the 0.023 level if the OS test result were positive. Response could be tested if both the OS and PFS test results were positive.

Secondary: Percentage of Subjects With a Best Overall Response of CR, Unconfirmed CR (unCR), PR, or Unconfirmed PR (unPR) per NCI International Response Criteria for NHL

End point title	Percentage of Subjects With a Best Overall Response of CR, Unconfirmed CR (unCR), PR, or Unconfirmed PR (unPR) per NCI International Response Criteria for NHL

End point description:

CR is defined as disappearance of all detectable clinical evidence of disease (including cleared infiltrate on repeat bone marrow aspirate/biopsy if lymphoma involvement of bone marrow before treatment). Partial Response (PR) requires the following: a. ≥50 % decrease in SPD of the six largest dominant nodes or nodal masses. b. No increase in the size of other nodes, liver, or spleen. c. Splenic and hepatic nodules must regress by ≥50% in the SPD, or for single nodules, in the greatest transverse diameter. d. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present. e. No new sites of disease. unCR and unPR means didn't have confirmatory assessment (including bone marrow assessment for CR). The 95% CI was determined using the exact method based on binomial distribution. ITT Population.

End point type	Secondary

End point timeframe:

Up to 2 years from first study drug dose or up to final study visit, whichever occurs first, including but not limited to planned assessments scheduled approximately every 12 weeks

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	172		
Units: percentage of subjects				
number (confidence interval 95%)	41 (33.4 to 48.85)	43.6 (36.07 to 51.36)		

Statistical analyses

Statistical analysis title	Analysis for CR, unCR, PR and unPR

Statistical analysis description:

Third comparison in hierarchical testing strategy was used for power calculation. The stratification factors are pre-randomization investigator choice, baseline sIPI, and best response to most recent chemo therapy.

Comparison groups	Inotuzumab ozogamicin+rituximab v Rituximab+gemcitabine or rituximab+bendamustine
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.714 [4]
Method	Cochran-Mantel-Haenszel

Notes:

[4] - A hierarchical testing strategy was specified for OS, PFS and response. PFS could be tested at the 0.023 level if the OS test result were positive. Response could be tested if both the OS and PFS test results were positive.

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever status is recorded first) until the first date that recurrence or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started. ITT population; only subjects with a CR, unCR, PR, or unPR were included in the analysis. Here, "99999" in confidence interval signifies "not estimable". The upper limit of the 95 percent (%) confidence interval could not be determined due to the large number of censored events.

End point type	Secondary

End point timeframe:

Up to 2 years from first study drug dose or up to final study visit, whichever occurs first, including but not limited to planned assessments scheduled approximately every 12 weeks

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	166	172		
Units: Months				
median (confidence interval 95%)	11.56 (7.8 to 99999)	6.93 (5.5 to 10.8)		

Statistical analyses

Statistical analysis title	Analysis for Duration of Response
Statistical analysis description:	
DOR was not part of the formal hypothesis testing strategy. HR from stratified Cox proportional hazards model. The stratification factors are pre-randomization investigator choice, baseline sIPI, and best response to most recent chemo therapy. One sided stratified log-rank test was used.	
Comparison groups	Inotuzumab ozogamicin+rituximab v Rituximab+gemcitabine or rituximab+bendamustine
Number of subjects included in analysis	338
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.142
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.25

Secondary: Health Status as Assessed by the European Quality of Life 5 Dimension (EQ-5D) Questionnaire

End point title	Health Status as Assessed by the European Quality of Life 5 Dimension (EQ-5D) Questionnaire
End point description:	
EQ-5D consists of a descriptive system and an EQ visual analogue scale. The descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 3 levels: no problems, some problems, extreme problems. The scale, the best state is marked 100 and the worst state is marked 0, is to help the subject to say how good or bad a health state is.	
End point type	Secondary
End point timeframe:	
Day 1 of each cycle and 6-9 weeks after the last dose	

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[5]	0[6]		
Units: score on a scale				

arithmetic mean (standard deviation)	()	()		

Notes:

[5] - Analysis was not performed since data was insufficient due to early termination of the study.

[6] - Analysis was not performed since data was insufficient due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Health Related Quality of Life (HRQOL) as Assessed by the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) Questionnaire

End point title	Health Related Quality of Life (HRQOL) as Assessed by the Functional Assessment of Cancer Therapy for Lymphoma (FACT-Lym) Questionnaire

End point description:

FACT-Lym is a questionnaire to record the physical well-being, social/family well-being, emotional well-being, and functional well-being. It contains 42 items (questions) covering HRQOL and common lymphoma symptoms and treatment side-effects. The questionnaire begins with 27 items covering four core HRQOL subscales: Physical Well-being (7 items), Social/Family Well-being (7), Emotional Well-being (6), and Functional Well-being (7). The FACT-Lym also includes an Additional Concerns subscale (15 items). It also asks subjects about their concerns about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment. The subjects were requested to circle one number on a 0 to 4 points scale per line to indicate how true each statement has been for him/her during the past 7 days.

End point type	Secondary

End point timeframe:

Day 1 of each cycle and 6-9 weeks after the last dose

End point values	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	0[7]	0[8]		
Units: score on a scale				
arithmetic mean (confidence interval 95%)	(to)	(to)		

Notes:

[7] - Analysis was not performed since data was insufficient due to early termination of the study.

[8] - Analysis was not performed since data was insufficient due to early termination of the study.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Treatment-Emergent Adverse Events (AEs) or Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-

threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment-Emergent Adverse Events (TEAEs) were defined as those starting on the first study drug dose date and within 56 days after the last study drug dose date. Summaries are based on safety population (subjects who received study drug). One subject in the rituximab+ inotuzumab ozogamicin arm received rituximab only, and was excluded from the safety population analysis.

End point type	Other pre-specified

End point timeframe:

First dose date up to 56 days after last dose of study drug

End point values	Inotuzumab ozogamicin plus (+) rituximab	Rituximab+gemcitabine or rituximab+bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	164	167		
Units: Percentage of Subjects				
number (not applicable)				
Subjects With AEs	98.8	100		
Subjects With SAEs	37.2	37.7		
Subjects With Grade 3 or 4 AEs	79.9	79.6		
Subjects With Grade 5 AEs	14.6	13.8		
Subjects Discontinued Due to AEs	25	18		
Subjects With Dose Reduced Due to AEs	27.4	29.3		
Subjects With Temporary Discontinuation Due to AEs	31.1	46.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs: from informed consent through and including end of treatment (EOT) visit. NonSAEs: from first dose through and including EOT visit. EOT visit = at least 42 days post last dose. Summaries include SAE/AEs from first dose up to 56 days post last dose

Adverse event reporting additional description:

AEs use safety population.1 subject in rituximab+inotuzumab arm received rituximab only(excluded from safety population).Source for SAEs, deaths is project database(PDB), safety database (SDB),respectively.Death(all causes)=fatal SAEs within 56 days post last dose;deaths resulting from AEs=fatal treatment related SAEs within 56 days post last dose.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Inotuzumab ozogamicin+rituximab

Reporting group description:

Subjects received rituximab 375 mg/m^2 via IV infusion on Day 1 and inotuzumab ozogamicin 1.8 mg/m^2 via IV infusion on Day 2 of each 28-day cycle for a maximum of 6 cycles.

Reporting group title	Rituximab+gemcitabine or rituximab+bendamustine

Reporting group description:

Subjects received either R-bendamustine (rituximab 375 mg/m^2 via IV infusion on Day 1 and bendamustine 120 mg/m^2 via IV infusion on Days 1 and 2 in 28-day cycles for a maximum of 6 cycles) or R-gemcitabine (rituximab 375 mg/m^2 via IV infusion on Days 1, 8, 15 and 22 of Cycle 1 and on Day 1 for all other cycles, and gemcitabine 1000 mg/m^2 via IV infusion on Days 1, 8 and 15 of each 28-day cycle for a maximum of 6 cycles). Choice of therapy was at the discretion of the investigator.

Serious adverse events	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 164 (37.20%)	63 / 167 (37.72%)	
number of deaths (all causes)	22	23	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelodysplastic syndrome transformation			

subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 164 (0.00%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 164 (1.83%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression	Additional description: 1 inotuzumab subject,disease progression(DP) reported as fatal event in SDB,but as Lymphoma in PDB(death and event displayed under DP and lymphoma, respectively). 2 control subjects had fatal event of DP (1related) in SDB only;not counted at PT level.		
subjects affected / exposed	15 / 164 (9.15%)	20 / 167 (11.98%)	
occurrences causally related to treatment / all	0 / 15	0 / 21	
deaths causally related to treatment / all	0 / 16	1 / 22	
Fatigue			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema due to hepatic disease			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	5 / 164 (3.05%)	4 / 167 (2.40%)	
occurrences causally related to treatment / all	1 / 5	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cough			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 164 (0.61%)	3 / 167 (1.80%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium febrile			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood bilirubin increased			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	0 / 164 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Atrial fibrillation			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depressed level of consciousness			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IIIrd nerve paralysis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraplegia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tremor			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	5 / 164 (3.05%)	7 / 167 (4.19%)	
occurrences causally related to treatment / all	2 / 6	4 / 7	
deaths causally related to treatment / all	0 / 0	1 / 1	
Neutropenia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 164 (1.22%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	2 / 2	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 164 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Haematuria			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 164 (1.22%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure acute			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
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			
Arthralgia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Groin pain			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 164 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus viraemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 164 (1.22%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection	Additional description: Lung infection reported as fatal event for 1 subject in SDP but as fatal SAE of 'Respiratory tract infection' in PDB. In this table, death and event displayed under lung and respiratory tract infection, respectively.		
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Meningitis			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	8 / 164 (4.88%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	9 / 12	0 / 1	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pneumonia fungal			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella sepsis			

subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Sepsis			
subjects affected / exposed	1 / 164 (0.61%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Sinusitis			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 164 (0.61%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal skin infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 164 (1.22%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	2 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 164 (0.61%)	0 / 167 (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			
Decreased appetite			
subjects affected / exposed	2 / 164 (1.22%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 164 (1.83%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	3 / 164 (1.83%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperuricaemia			
subjects affected / exposed	0 / 164 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Inotuzumab ozogamicin+rituximab	Rituximab+gemcitabine or rituximab+bendamustine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	155 / 164 (94.51%)	158 / 167 (94.61%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	28 / 164 (17.07%)	17 / 167 (10.18%)	
occurrences (all)	60	48	
Aspartate aminotransferase increased			
subjects affected / exposed	44 / 164 (26.83%)	18 / 167 (10.78%)	
occurrences (all)	93	54	
Blood alkaline phosphatase increased			
subjects affected / exposed	24 / 164 (14.63%)	16 / 167 (9.58%)	
occurrences (all)	57	18	
Blood bilirubin increased			
subjects affected / exposed	10 / 164 (6.10%)	4 / 167 (2.40%)	
occurrences (all)	20	5	
Blood creatinine increased			
subjects affected / exposed	5 / 164 (3.05%)	13 / 167 (7.78%)	
occurrences (all)	18	15	
Blood lactate dehydrogenase increased			
subjects affected / exposed	9 / 164 (5.49%)	4 / 167 (2.40%)	
occurrences (all)	20	10	
Gamma-glutamyltransferase increased			
subjects affected / exposed	38 / 164 (23.17%)	16 / 167 (9.58%)	
occurrences (all)	90	23	
Haemoglobin decreased			
subjects affected / exposed	4 / 164 (2.44%)	10 / 167 (5.99%)	
occurrences (all)	7	23	
Platelet count decreased			
subjects affected / exposed	9 / 164 (5.49%)	7 / 167 (4.19%)	
occurrences (all)	28	17	

Weight decreased			
subjects affected / exposed	4 / 164 (2.44%)	11 / 167 (6.59%)	
occurrences (all)	4	16	
White blood cell count decreased			
subjects affected / exposed	4 / 164 (2.44%)	12 / 167 (7.19%)	
occurrences (all)	25	80	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 164 (4.88%)	13 / 167 (7.78%)	
occurrences (all)	11	16	
Dysgeusia			
subjects affected / exposed	10 / 164 (6.10%)	8 / 167 (4.79%)	
occurrences (all)	10	8	
Headache			
subjects affected / exposed	8 / 164 (4.88%)	11 / 167 (6.59%)	
occurrences (all)	21	11	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 164 (14.63%)	43 / 167 (25.75%)	
occurrences (all)	50	123	
Leukopenia			
subjects affected / exposed	37 / 164 (22.56%)	54 / 167 (32.34%)	
occurrences (all)	167	285	
Lymphopenia			
subjects affected / exposed	28 / 164 (17.07%)	39 / 167 (23.35%)	
occurrences (all)	137	255	
Neutropenia			
subjects affected / exposed	57 / 164 (34.76%)	81 / 167 (48.50%)	
occurrences (all)	216	302	
Thrombocytopenia			
subjects affected / exposed	101 / 164 (61.59%)	64 / 167 (38.32%)	
occurrences (all)	506	189	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	13 / 164 (7.93%)	14 / 167 (8.38%)	
occurrences (all)	14	19	

Chills			
subjects affected / exposed	5 / 164 (3.05%)	9 / 167 (5.39%)	
occurrences (all)	5	9	
Fatigue			
subjects affected / exposed	55 / 164 (33.54%)	42 / 167 (25.15%)	
occurrences (all)	75	59	
Oedema peripheral			
subjects affected / exposed	17 / 164 (10.37%)	15 / 167 (8.98%)	
occurrences (all)	21	22	
Pyrexia			
subjects affected / exposed	37 / 164 (22.56%)	35 / 167 (20.96%)	
occurrences (all)	44	47	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	14 / 164 (8.54%)	13 / 167 (7.78%)	
occurrences (all)	18	18	
Constipation			
subjects affected / exposed	38 / 164 (23.17%)	33 / 167 (19.76%)	
occurrences (all)	52	54	
Diarrhoea			
subjects affected / exposed	22 / 164 (13.41%)	31 / 167 (18.56%)	
occurrences (all)	34	38	
Nausea			
subjects affected / exposed	50 / 164 (30.49%)	54 / 167 (32.34%)	
occurrences (all)	73	89	
Vomiting			
subjects affected / exposed	23 / 164 (14.02%)	32 / 167 (19.16%)	
occurrences (all)	34	46	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	12 / 164 (7.32%)	3 / 167 (1.80%)	
occurrences (all)	29	5	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	24 / 164 (14.63%)	13 / 167 (7.78%)	
occurrences (all)	27	17	

Dyspnoea			
subjects affected / exposed	9 / 164 (5.49%)	14 / 167 (8.38%)	
occurrences (all)	10	19	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 164 (3.66%)	10 / 167 (5.99%)	
occurrences (all)	6	15	
Rash			
subjects affected / exposed	8 / 164 (4.88%)	13 / 167 (7.78%)	
occurrences (all)	9	20	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 164 (4.27%)	9 / 167 (5.39%)	
occurrences (all)	12	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 164 (5.49%)	4 / 167 (2.40%)	
occurrences (all)	10	4	
Back pain			
subjects affected / exposed	10 / 164 (6.10%)	17 / 167 (10.18%)	
occurrences (all)	12	20	
Pain in extremity			
subjects affected / exposed	6 / 164 (3.66%)	10 / 167 (5.99%)	
occurrences (all)	6	12	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 164 (5.49%)	6 / 167 (3.59%)	
occurrences (all)	10	7	
Urinary tract infection			
subjects affected / exposed	9 / 164 (5.49%)	12 / 167 (7.19%)	
occurrences (all)	9	14	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	28 / 164 (17.07%)	31 / 167 (18.56%)	
occurrences (all)	37	47	
Hypercalcaemia			

subjects affected / exposed	9 / 164 (5.49%)	6 / 167 (3.59%)	
occurrences (all)	19	6	
Hypokalaemia			
subjects affected / exposed	11 / 164 (6.71%)	14 / 167 (8.38%)	
occurrences (all)	15	19	
Hypophosphataemia			
subjects affected / exposed	12 / 164 (7.32%)	12 / 167 (7.19%)	
occurrences (all)	24	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Interpretation of the results is limited by total enrollment being less than the planned total enrollment, discontinuation of some protocol activities, and shortened follow-up period which were all due to the early termination of the study.

Notes: