Clinical trial results:
An Open-Label, Randomized Phase 3 Study of Inotuzumab Ozogamicin Compared to a Defined Investigator's Choice in Adult Patients with Relapsed or Refractory CD22-Positive Acute Lymphoblastic Leukemia (ALL)

Summary

EudraCT number	2011-005491-41
Trial protocol	HU CZ SK SE ES GB DE FI IT NL BE
Global end of trial date	

Results information

Result version number	v1
This version publication date	23 March 2017
First version publication date	23 March 2017

Trial information

Trial identification

Sponsor protocol code	B1931022

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01564784
WHO universal trial number (UTN)	-

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	Interim
Date of interim/final analysis	08 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 March 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the study were to compare hematological remission rate (complete remission and complete remission with incomplete hematologic recovery), as assessed by the independent external Endpoint Adjudication Committee (EAC), and overall survival in patients with relapsed or refractory cluster of differentiation (CD) 22 positive B-cell ALL randomized to receive inotuzumab ozogamicin or Investigator's choice of chemotherapy.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants. The final protocol, any amendments and informed consent documentation were reviewed and approved by the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each of the investigational centres participating in the study.

Background therapy: -

Evidence for comparator:

The choice of a comparator was complicated by the small patient population, the heterogeneity of the population, and the lack of an appropriate universal comparator. In the salvage setting, multiple miscellaneous regimens are used ranging from single agents to combination therapies such as combinations with cytarabine (conventional or high-dose), hyper-cyclophosphamide, vincristine, doxorubicin and dexamethasone, combinations with methotrexate and/or asparaginase, etc. Patients with Philadelphia chromosome positive (Ph+) ALL are treated with combinations including tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib. In the second and later salvage settings, treatments used will depend on responses to the treatments used in the frontline and first salvage settings further complicating the choice of comparator in these multiply-treated patients. In the patient population eligible for this study, it was expected that most patients would have been treated with intensive combination chemotherapy including anthracyclines and that physicians would select therapies, such as those shown above, or experimental therapies based on the patient's condition, prior therapies, as well as standard
practice. Therefore, the comparator arm included a defined list of 3 induction chemotherapy regimens commonly used in relapsed and refractory ALL, from which the investigator chose the optimal regimen for the patient: fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF) (FLAG); mitoxantrone and cytarabine (MXN/Ara-C); or, high dose cytarabine (HIDAC). To avoid potential bias the investigator must have chosen the treatment of choice before patient randomization.

Actual start date of recruitment	02 August 2012
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	Australia: 2

Country: Number of subjects enrolled	China: 12
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Italy: 26
Country: Number of subjects enrolled	Japan: 19
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Poland: 12
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Singapore: 3
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 149
Worldwide total number of subjects	307
EEA total number of subjects	115

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)	261
From 65 to 84 years	46
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants were screened locally for characterization of leukemia, including CD22 immunophenotyping (flow cytometry) from peripheral blood or bone marrow aspirate obtained within 28 days of randomization. If CD22 immunophenotyping was negative per local laboratory results, central results may have been used for determining eligibility.

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

Arm description:

Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

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

Dosage and administration details:

Inotuzumab ozogamicin was administered intravenously at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

Arm title	Defined Investigator’s Choice of Chemotherapy

Arm description:

Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator’s choice.

Arm type	Active comparator

Investigational medicinal product name	Participants were treated with FLAG, MXN/Ara-C, or HIDAC, according to the Investigator's choice.
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants treated with FLAG received cytarabine 2 g/m^2/day intravenous (IV) infusion over 4 hours on Day 1 (could be omitted per local standard of care), fludarabine 30 mg/m^2/day 30-minute IV infusion followed 4 hours later with cytarabine 2 g/m^2/day IV infusion over 4 hours on Days 2 to 6, and G-CSF 5 µg/kg/day or per local standard of care. Participants treated with MXN/Ara-C received mitoxantrone 12 mg/m^2 (dose could be reduced to 8 mg/m^2 based on patient age, comorbidities and prior anthracycline use) IV over 20 minutes on Day 1, cytarabine 200 mg/m^2/day continuous IV infusion over 7 days from Day 1 and mitoxantrone 12 mg/m^2 IV over 20 minutes on Days 2 to 3. Participants treated with HIDAC received cytarabine 3 g/m^2 IV over 1 to 3 hours every 12 hours for up to 12 doses starting on Day 1 of up to 6. For participants ≥55 years of age, the dose of cytarabine could be reduced up to 1.5 g/m^2. For participants over 60 years of age, the dose was reduced to 1.5 g/m^2.

Number of subjects in period 1	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy
Started	164	143
Completed	0	0
Not completed	164	143
Adverse event, serious fatal	122	120
Ongoing in study	39	15
Unspecified	1	-
Subject refused further follow-up	1	7
Lost to follow-up	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Inotuzumab Ozogamicin
Reporting group description:	
Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).	
Reporting group title	Defined Investigator's Choice of Chemotherapy
Reporting group description:	
Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator's choice.	

Reporting group values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy	Total
Number of subjects	164	143	307
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	134	127	261
From 65-84 years	30	16	46
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	45.9	45.6	
standard deviation	± 17.07	± 16.32	-
Gender, Male/Female			
Units: Subjects			
Female	73	51	124
Male	91	92	183

End points

End points reporting groups

Reporting group title	Inotuzumab Ozogamicin

Reporting group description:

Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

Reporting group title	Defined Investigator's Choice of Chemotherapy

Reporting group description:

Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator's choice.

Subject analysis set title	Inotuzumab Ozogamicin
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

Subject analysis set title	Defined Investigator's Choice of Chemotherapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator's choice.

Subject analysis set title	Defined Investigator's Choice of Chemotherapy
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator's choice.

Primary: Percentage of Participants with Hematologic Remission (complete remission [CR]/complete remission with incomplete hematologic recovery [CRi]) as Assessed by the EAC

End point title	Percentage of Participants with Hematologic Remission (complete remission [CR]/complete remission with incomplete hematologic recovery [CRi]) as Assessed by the EAC

End point description:

CR was disappearance of leukemia indicated by <5 % marrow blasts & absence of peripheral blood leukemic blasts, with recovery of hematopoiesis defined by absolute neutrophil count (ANC) ≥1000/µL & platelets ≥100,000/µL. C1 extramedullary disease status (i.e. complete disappearance of measurable/non-measurable extramedullary disease with the following exceptions: for participants with at least 1 measurable lesion, all nodal masses >1.5 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤1.5 cm in GTD; all nodal masses ≥1 cm & ≤1.5 cm in GTD at baseline must have regressed to <1 cm GTD or reduced by 75% in sum of products of greatest diameters, no new lesions, spleen/other previously enlarged organs must have regressed in size & not be palpable) was required. CRi was defined as CR except ANC <1000/µL &/or platelets <100,000/µL.
ITT218 population - included the intention-to-treat (ITT) population (all participants randomized) for the

initial 218 participants.

End point type	Primary

End point timeframe:

Screening, Day 16 to 28 of Cycles 1, 2 and 3, then every 1 to 2 cycles (or as clinically indicated) up to approximately 4 weeks (end of treatment [EoT]) from the last dose

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	109		
Units: Percentage of Participants				
number (confidence interval 95%)	80.7 (72.1 to 87.7)	29.4 (21 to 38.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis of CR/CRi
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	218
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	1-sided p-value based on Chi-square test
Parameter estimate	Rate difference
Point estimate	51.4
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	38.4
upper limit	64.3

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]

End point description:

OS was defined as the time from randomization to date of death due to any cause. Participants last known to be alive were censored at date of last contact.

End point type	Primary

End point timeframe:

Up to 5 years after randomization or 2 years from randomization of the last patient, whichever occurs first.
Analysis population = ITT population - included all participants randomized.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analyzed for all participants randomized (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Months				
median (confidence interval 95%)	7.7 (6 to 9.2)	6.7 (4.9 to 8.3)		

Statistical analyses

Statistical analysis title	Statistical Analysis of OS
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0203
Method	1-sided stratified log-rank p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.578
upper limit	1.026

Secondary: Duration of Remission (DoR) for Patients Who Achieved CR/CRi (per Investigator Assessment)

End point title	Duration of Remission (DoR) for Patients Who Achieved CR/CRi (per Investigator Assessment)

End point description:

DoR was defined as time from date of first response in responders (CR/CRi per Investigator assessment) to date of PFS event (i.e. death, progressive disease [objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status] or starting new induction therapy or post-therapy stem cell transplant [SCT] without achieving CR/CRi). Responders without PFS events were censored at the last valid disease assessment including follow-up.
Analysis population = ITT218 population

End point type	Secondary

End point timeframe:

Up to 2 years from randomization

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	84	32		
Units: Months				
median (confidence interval 95%)	5.4 (4.2 to 8)	3.5 (2.9 to 6.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis of DoR
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0031
Method	1-sided stratified log-rank p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.502
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.303
upper limit	0.832

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)[2]

End point description:

PFS was defined as time from date of randomization to earliest date of the following events: death, progressive disease (objective progression, relapse from CR/CRi or treatment discontinuation due to global deterioration of health status) and starting new induction therapy or post-therapy SCT without achieving CR/CRi. Participants without a PFS event at time of analysis were censored at the last valid disease assessment. In addition, participants with documentation of an event after an unacceptably long interval (>28 weeks if there was post-baseline disease assessment, or >12 weeks if there was no post-baseline assessment) since the previous disease assessment were censored at the time of the previous assessment (date of randomization if no post-baseline assessment). Post-study treatment follow-up disease assessments was included. 2-sided 95% confidence interval (CI) calculated based on the Brookmeyer and Crowley method.
Analysis population = ITT population.

End point type	Secondary

End point timeframe:

Up to 2 years from randomization

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analysed for all participants randomised (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Months				
median (confidence interval 95%)	5 (3.7 to 5.6)	1.8 (1.5 to 2.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis of PFS
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	1-sided stratified log-rank p-value
Parameter estimate	Hazard ratio (HR)
Point estimate	0.452
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.336
upper limit	0.609

Secondary: Percentage of Participants who had a Hematopoietic Stem-Cell Transplant (HSCT)

End point title	Percentage of Participants who had a Hematopoietic Stem-Cell Transplant (HSCT)[3]

End point description:

HSCT rate was defined as the percentage of participants who underwent SCT following treatment with inotuzumab ozogamicin or Investigator's choice of chemotherapy.
Analysis population = ITT population.

End point type	Secondary

End point timeframe:

From first dose date to start of post induction therapy

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analyzed for all participants randomized (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Percentage of Participants				
number (confidence interval 95%)	43.3 (35.6 to 51.2)	11.1 (6.7 to 17)		

Statistical analyses

Statistical analysis title	Statistical Analysis of HSCT
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	1-sided p-value based on Chi-square test
Parameter estimate	Rate difference
Point estimate	32.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	23.2
upper limit	41.2

Secondary: Percentage of Participants Achieving MRD Negativity (Based on Central Laboratory Analysis) in Patients Achieving a CR/CRi (per EAC Assessment)

End point title	Percentage of Participants Achieving MRD Negativity (Based on Central Laboratory Analysis) in Patients Achieving a CR/CRi (per EAC Assessment)

End point description:

MRD analysis was performed at least once in participants with prior assessment of CR or CRi. Bone marrow aspirates, collected at screening and during the study, were sent to the central laboratory and analyzed using multiparametric flow cytometry. The antibody combinations were designed to maximize discrimination between normal and abnormal cells of B-cell lineage and similar maturational stage and included antibodies detecting cluster of differentiation (CD) 9, CD10, CD13, CD19, CD20, CD33, CD34, CD38, CD45, CD58, CD66c, and CD123. A peripheral blood sample was provided if a participant had an inadequate bone marrow aspirate at screening. MRD negativity was considered to have been achieved if the lowest value of MRD from the first date of CR/CRi to EoT was <1 × 10^-4 blasts/nucleated cells. Analysis population = ITT218 population.

End point type	Secondary

End point timeframe:

Up to approximately 4 weeks (EoT) from last dose of study drug

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88	32		
Units: Percentage of Participants				
number (confidence interval 95%)	78.4 (68.4 to 86.5)	28.1 (13.7 to 46.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis of MRD Negativity
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	1-sided p-value based on Chi-Square test

Secondary: Cytogenetic Status (Based on Local Laboratory Analysis) of Participants with CR/CRi (per EAC Assessment)

End point title	Cytogenetic Status (Based on Local Laboratory Analysis) of Participants with CR/CRi (per EAC Assessment)

End point description:

Karyotyping was required locally, at screening and at least once during the study in participants who had abnormal cytogenetics at baseline and who achieved CR/CRi. Data presented below are for participants who achieved CR/CRi per EAC and had abnormal karyotype at screening.
Analysis population = ITT218 population.

End point type	Secondary

End point timeframe:

Up to approximately 4 weeks (EoT) from last dose of study drug

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	88[4]	32[5]		
Units: Percentage of Participants				
number (confidence interval 95%)				
Abnormal at screening in CR/CRi subjects (Group 1)	61.4 (50.4 to 71.6)	68.8 (50 to 83.9)		
Abnormal after remission in Group 1 subjects	3.7 (0.5 to 12.7)	18.2 (5.2 to 40.3)		

Notes:

[4] - n = 54 for participants who achieved CR/CRi per EAC and had abnormal karyotype at screening.

[5] - n = 22 for participants who achieved CR/CRi per EAC and had abnormal karyotype at screening.

Statistical analyses

Statistical analysis title	Statistical Analysis of Cytogenetics
Statistical analysis description: Abnormal after remission	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.216
Method	1-sided p-value based on Chi-Square test

Statistical analysis title	Statistical Analysis of Cytogenetics
Statistical analysis description: Abnormal at Screening	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3168
Method	1-sided p-value based on Chi-Square test

Secondary: Maximum Observed Inotuzumab Ozogamicin Serum Concentration (Cmax) and Pre-Dose Inotuzumab Ozogamicin Serum Concentration (Ctrough) Following Single (Cycle 1 Day 1) and Multiple (Cycle 4 Day 1) Dosing

End point title	Maximum Observed Inotuzumab Ozogamicin Serum Concentration (Cmax) and Pre-Dose Inotuzumab Ozogamicin Serum Concentration (Ctrough) Following Single (Cycle 1 Day 1) and Multiple (Cycle 4 Day 1) Dosing[6]

End point description:

Blood samples were collected and analyzed for inotuzumab ozogamicin serum concentrations using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) method with a lower limit of quantification of 1.0 nanograms per milliliter (ng/mL). Cmax was the maximum observed concentration occurring between 0-8 hours post-dose. Ctrough was the concentration prior to subsequent dose (pre-dose) occurring after 8 hours. n = number of observations (non-missing concentrations).
Analysis population = Pharmacokinetic (PK) evaluable population - included all participants with available PK data.

End point type	Secondary

End point timeframe:

Days 1, 4, 8, and 15 of Cycle 1, Days 1 and 8 of Cycle 2 and Day 1 of Cycle 4

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants from the Inotuzumab Ozogamicin treatment arm were planned to be analyzed for this end point.

End point values	Inotuzumab Ozogamicin			
Subject group type	Reporting group			
Number of subjects analysed	163			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cmax (Cycle 1 Day 1, 1 hour post-dose) (n=128)	211 (± 232)			
Ctrough (Cycle 4 Day 1, pre-dose) (n=46)	57.9 (± 29.8)			
Cmax (Cycle 4 Day 1, 1 hour post-dose) (n=37)	308 (± 362)			

Statistical analyses

No statistical analyses for this end point

Secondary: Between Treatment Comparison of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30 (EORTC QLQ-C30) Score

End point title	Between Treatment Comparison of European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, Core 30 (EORTC QLQ-C30) Score[7]

End point description:

This questionnaire is comprised of 30 questions in total. Within the 30 questions are 9 multi-item scales and 6 single-item measures. There are 5 functional scales; physical, role, cognitive, emotional and social, 3 symptom scales; fatigue, pain and nausea and vomiting, and also a global health status/quality of life (QOL) scale. There are 5 single item measures assessing additional symptoms commonly reported by cancer patients (loss of appetite, insomnia, constipation, diarrhea, and dyspnea) and a single item concerning perceived financial impact of the disease.
Analysis population = ITT population.

End point type	Secondary

End point timeframe:

Day 1 of each cycle prior to dosing and EoT

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analyzed for all participants randomized (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)				

Physical Functioning	75 (72.1 to 77.8)	68.1 (63.4 to 72.7)		
Role Functioning	64.7 (60.8 to 68.7)	53.4 (46.3 to 60.4)		
Emotional Functioning	77.4 (75 to 79.7)	79.6 (75.7 to 83.6)		
Cognitive Functioning	85.3 (83.1 to 87.4)	82.5 (78.9 to 86.1)		
Social Functioning	68.1 (64.3 to 72)	59.8 (53.1 to 66.5)		
Global Health Status	62.1 (59.1 to 65.1)	57.8 (52.6 to 63)		
Dyspnoea	14.7 (11.8 to 17.7)	19.4 (14.1 to 24.8)		
Insomnia	25.4 (21.9 to 28.8)	27.1 (21.1 to 33.1)		
Appetite Loss	17.6 (14.4 to 21.1)	26.3 (19.9 to 32.7)		
Constipation	12.1 (9.2 to 15)	10.7 (5.6 to 15.7)		
Diarrhoea	5.9 (3.9 to 7.8)	8.9 (5.2 to 12.6)		
Financial Difficulties	29.5 (25.9 to 33)	32 (25.7 to 38.2)		
Fatigue	35 (31.7 to 38.3)	39.4 (33.9 to 44.9)		
Nausea and Vomiting	8.7 (6.6 to 10.8)	10.4 (6.6 to 14.2)		
Pain	21.3 (18 to 24.6)	22 (16.2 to 27.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Physical Functioning	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0139
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.4
upper limit	12.3

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30

Statistical analysis description: Role Functioning	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0065
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	11.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.2
upper limit	19.5

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Emotional Functioning	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3307
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.9
upper limit	2.3

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Cognitive Functioning	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1904
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	2.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	7

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Social Functioning	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0336
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	16.1

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Global Health Status	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1572
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	10.3

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30

Statistical analysis description:	
Dyspnoea	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1281
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	1.4

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description:	
Insomnia	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6207
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.7
upper limit	5.2

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description:	
Appetite Loss	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0193
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-8.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-16
upper limit	-1.4

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Constipation	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6249
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	7.3

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Diarrhoea	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1534
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.2
upper limit	1.1

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30

Statistical analysis description: Financial Difficulties	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4915
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.7
upper limit	4.7

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Fatigue	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1789
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.8
upper limit	2

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description: Nausea and Vomiting	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator’s Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4578
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-6
upper limit	2.7

Statistical analysis title	Statistical Analysis of EORTC QLQ-C30
Statistical analysis description:	
Pain	
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8428
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.3
upper limit	6

Secondary: Between Treatment Comparison of EuroQol Five Dimension Health Questionnaire (EQ-5D) Index Score

End point title	Between Treatment Comparison of EuroQol Five Dimension Health Questionnaire (EQ-5D) Index Score[8]

End point description:

The EQ-5D self-report questionnaire is a standardized measure of health status developed by the EuroQoL Group. It consists of the EQ-5D descriptive system and a visual analogue scale (VAS), EQ-VAS. The EQ-5D descriptive system measures a participants' health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no problems", "some problems", and "extreme problems". The EQ-VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health state.
Analysis population = ITT population.

End point type	Secondary

End point timeframe:

Day 1 of each cycle prior to dosing and EoT

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analyzed for all participants randomized (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	0.8 (0.77 to 0.82)	0.76 (0.73 to 0.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis of EQ-5D
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.171
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	0.07

Secondary: Between Treatment Comparison of EQ-5D VAS

End point title	Between Treatment Comparison of EQ-5D VAS[9]

End point description:

The EQ-5D self-report questionnaire is a standardized measure of health status developed by the EuroQoL Group. It consists of the EQ-5D descriptive system and a visual analogue scale (VAS), EQ-VAS. The EQ-5D descriptive system measures a participants' health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels, reflecting "no problems", "some problems", and "extreme problems". The EQ-VAS records the respondent's self-rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state); higher scores indicate a better health state.
Analysis population = ITT population.

End point type	Secondary

End point timeframe:

Day 1 of each cycle prior to dosing and EoT

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The baseline period arm for Defined Investigator's Choice of Chemotherapy includes only those participants treated (i.e. the safety population). This outcome measure was analyzed for all participants randomized (i.e. the intention-to-treat [ITT] population).

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	164	162		
Units: Score on a scale				
arithmetic mean (confidence interval 95%)	67.1 (64 to 70.2)	62.5 (57.6 to 67.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis of EQ-5D VAS
Comparison groups	Inotuzumab Ozogamicin v Defined Investigator's Choice of Chemotherapy
Number of subjects included in analysis	326
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1172
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	4.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	10.4

Secondary: Percentage of Participants with Veno-Occlusive Liver Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS) Following Post Study HSCT

End point title	Percentage of Participants with Veno-Occlusive Liver Disease (VOD)/Sinusoidal Obstruction Syndrome (SOS) Following Post Study HSCT

End point description:

VOD/SOS was defined as the occurrence of 2 out of the following 3 clinical criteria: 1) total serum bilirubin level >34 micromoles per liter (µmol/L) (>2.0 milligrams per deciliter [mg/dL]), 2) an increase in liver size from baseline or development of right upper quadrant pain of liver origin and 3) sudden weight gain >2.5% (eg, within a 72 hour period) because of fluid accumulation in the weeks following infusion of study drug or chemotherapy, or HSCT conditioning/preparative therapy, or development of ascites not present at baseline following such exposures AND the absence of other explanations for these signs and symptoms, OR development of bilirubin elevation, weight gain, or hepatomegaly plus histologic abnormalities on liver biopsy demonstrating hepatocyte necrosis in zone 3 of the liver acinus, sinusoidal fibrosis, and centrilobular hemorrhage, with or without fibrosis of the terminal hepatic venules.
Analysis population = Safety population.

End point type	Secondary

End point timeframe:

Up to 2 years from randomization

End point values	Inotuzumab Ozogamicin	Defined Investigator's Choice of Chemotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	32		
Units: Percentage of Participants				
number (not applicable)	22.1	3.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAEs were assessed from informed consent up to at least 28 calendar days after last dose of investigational product. AEs were recorded on or after Cycle 1 Day 1 but within 42 days of last dose (all-causality) and all treatment-related AEs thereafter.

Adverse event reporting additional description:

An event may appear as both an AE & SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 participant & non-serious in another participant, or 1 participant may have experienced both a serious & non-serious event.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Defined Investigator's Choice of Chemotherapy

Reporting group description:

Patients received fludarabine, cytarabine, granulocyte-colony stimulating factor (FLAG), mitoxantrone + cytarabine (MXN/Ara-C), or high-dose cytarabine (HIDAC), according to the Investigator's choice.

Reporting group title	Inotuzumab Ozogamicin

Reporting group description:

Participants were treated with inotuzumab ozogamicin at a starting dose of 1.8 mg/m^2 (according to body surface area) per cycle with a divided-dose regimen using 3 weekly administrations. Participants received 0.8 mg/m^2/cycle on Week 1 (Day 1), followed by 0.5 mg/m^2 on Week 2 (Day 8) and Week 3 (Day 15) of a 21-day cycle, and administered as an intravenous infusion over 60 minutes. For participants who achieved a CR or CRi, or to allow recovery from toxicity, the length of Cycle 1 could be extended up to 28 days (ie, 1 week treatment-free interval starting on Day 21). For participants who achieved CR or CRi, the inotuzumab ozogamicin dose administered on Week 1 was reduced to 0.5 mg/m^2 (for a total cycle dose of 1.5 mg/m^2/cycle) for Cycles 2 through 6 (maximum number of cycles permitted). For Cycles 2 through 6, the cycle length was 28 days for all patients (regardless of remission status).

Serious adverse events	Defined Investigator's Choice of Chemotherapy	Inotuzumab Ozogamicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	71 / 143 (49.65%)	84 / 164 (51.22%)	
number of deaths (all causes)	16	24	
number of deaths resulting from adverse events	4	4	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	3 / 143 (2.10%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombophlebitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 143 (0.00%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	5 / 143 (3.50%)	8 / 164 (4.88%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 5	1 / 11	
Fatigue			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure	Additional description: In the 'Investigator Choice' treatment arm 'Multiple organ dysfunction syndrome' appears as a fatal event for 2 participants in the		

	Safety Data Warehouse, but as fatal SAEs of 'Multi-organ failure' in the clinical database.		
subjects affected / exposed	2 / 143 (1.40%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 3	2 / 3	
deaths causally related to treatment / all	1 / 2	0 / 0	
Pain			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 143 (2.10%)	5 / 164 (3.05%)	
occurrences causally related to treatment / all	1 / 3	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Epistaxis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal stenosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	6 / 143 (4.20%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	3 / 7	1 / 2	
deaths causally related to treatment / all	1 / 3	1 / 2	

Respiratory tract oedema			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	3 / 143 (2.10%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Myocardial infarction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Headache			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
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	27 / 143 (18.88%)	19 / 164 (11.59%)	
occurrences causally related to treatment / all	27 / 31	14 / 23	
deaths causally related to treatment / all	0 / 0	0 / 0	

Leukopenia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 143 (1.40%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 143 (0.70%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	1 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ascites			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis haemorrhagic			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ileal perforation			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Intra-abdominal haemorrhage			

subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal ulcer			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 143 (0.70%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic vein thrombosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	3 / 143 (2.10%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive liver disease			
subjects affected / exposed	1 / 143 (0.70%)	22 / 164 (13.41%)	
occurrences causally related to treatment / all	0 / 1	26 / 28	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Dermatitis allergic			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
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	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone infarction			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Adenoviral upper respiratory infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 143 (0.70%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile colitis			
subjects affected / exposed	1 / 143 (0.70%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corona virus infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus chorioretinitis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis necroticans			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal sepsis			

subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	2 / 143 (1.40%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	2 / 143 (1.40%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungaemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Klebsiella infection			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	2 / 143 (1.40%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Necrotising fasciitis fungal			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	4 / 143 (2.80%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	4 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	0 / 143 (0.00%)	10 / 164 (6.10%)	
occurrences causally related to treatment / all	0 / 0	5 / 13	
deaths causally related to treatment / all	0 / 0	1 / 3	
Pneumonia fungal			
subjects affected / exposed	3 / 143 (2.10%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	2 / 143 (1.40%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pseudomonal sepsis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	10 / 143 (6.99%)	4 / 164 (2.44%)	
occurrences causally related to treatment / all	4 / 12	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 3	
Septic embolus			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	3 / 143 (2.10%)	3 / 164 (1.83%)	
occurrences causally related to treatment / all	1 / 3	3 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
Serratia bacteraemia			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis fungal			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 143 (0.70%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic mycosis			
subjects affected / exposed	1 / 143 (0.70%)	0 / 164 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 143 (0.70%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection fungal			

subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	0 / 143 (0.00%)	1 / 164 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	0 / 143 (0.00%)	2 / 164 (1.22%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Defined Investigator's Choice of Chemotherapy	Inotuzumab Ozogamicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	143 / 143 (100.00%)	159 / 164 (96.95%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 143 (5.59%)	9 / 164 (5.49%)	
occurrences (all)	8	12	
Hypotension			
subjects affected / exposed	22 / 143 (15.38%)	12 / 164 (7.32%)	
occurrences (all)	27	13	
General disorders and administration			

site conditions			
Asthenia			
subjects affected / exposed	14 / 143 (9.79%)	14 / 164 (8.54%)	
occurrences (all)	16	20	
Chest pain			
subjects affected / exposed	9 / 143 (6.29%)	3 / 164 (1.83%)	
occurrences (all)	9	3	
Chills			
subjects affected / exposed	17 / 143 (11.89%)	18 / 164 (10.98%)	
occurrences (all)	22	21	
Fatigue			
subjects affected / exposed	24 / 143 (16.78%)	41 / 164 (25.00%)	
occurrences (all)	28	76	
Mucosal inflammation			
subjects affected / exposed	19 / 143 (13.29%)	6 / 164 (3.66%)	
occurrences (all)	21	7	
Oedema peripheral			
subjects affected / exposed	13 / 143 (9.09%)	13 / 164 (7.93%)	
occurrences (all)	16	19	
Pain			
subjects affected / exposed	8 / 143 (5.59%)	12 / 164 (7.32%)	
occurrences (all)	10	12	
Pyrexia			
subjects affected / exposed	57 / 143 (39.86%)	49 / 164 (29.88%)	
occurrences (all)	90	76	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	23 / 143 (16.08%)	22 / 164 (13.41%)	
occurrences (all)	28	25	
Dyspnoea			
subjects affected / exposed	18 / 143 (12.59%)	10 / 164 (6.10%)	
occurrences (all)	20	13	
Epistaxis			
subjects affected / exposed	11 / 143 (7.69%)	24 / 164 (14.63%)	
occurrences (all)	11	27	
Oropharyngeal pain			

subjects affected / exposed	10 / 143 (6.99%)	6 / 164 (3.66%)	
occurrences (all)	10	6	
Pleural effusion			
subjects affected / exposed	8 / 143 (5.59%)	3 / 164 (1.83%)	
occurrences (all)	8	4	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 143 (7.69%)	8 / 164 (4.88%)	
occurrences (all)	14	8	
Depression			
subjects affected / exposed	9 / 143 (6.29%)	4 / 164 (2.44%)	
occurrences (all)	9	4	
Insomnia			
subjects affected / exposed	22 / 143 (15.38%)	24 / 164 (14.63%)	
occurrences (all)	25	24	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	18 / 143 (12.59%)	25 / 164 (15.24%)	
occurrences (all)	26	35	
Aspartate aminotransferase increased			
subjects affected / exposed	16 / 143 (11.19%)	37 / 164 (22.56%)	
occurrences (all)	23	61	
Blood alkaline phosphatase increased			
subjects affected / exposed	10 / 143 (6.99%)	22 / 164 (13.41%)	
occurrences (all)	10	29	
Gamma-glutamyltransferase increased			
subjects affected / exposed	12 / 143 (8.39%)	35 / 164 (21.34%)	
occurrences (all)	12	48	
Lipase increased			
subjects affected / exposed	1 / 143 (0.70%)	15 / 164 (9.15%)	
occurrences (all)	1	31	
White blood cell count decreased			
subjects affected / exposed	9 / 143 (6.29%)	10 / 164 (6.10%)	
occurrences (all)	13	18	
Injury, poisoning and procedural complications			

Contusion			
subjects affected / exposed	3 / 143 (2.10%)	10 / 164 (6.10%)	
occurrences (all)	3	11	
Fall			
subjects affected / exposed	4 / 143 (2.80%)	11 / 164 (6.71%)	
occurrences (all)	5	13	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	16 / 143 (11.19%)	6 / 164 (3.66%)	
occurrences (all)	21	6	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 143 (11.19%)	12 / 164 (7.32%)	
occurrences (all)	17	14	
Headache			
subjects affected / exposed	38 / 143 (26.57%)	45 / 164 (27.44%)	
occurrences (all)	45	58	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	79 / 143 (55.24%)	54 / 164 (32.93%)	
occurrences (all)	191	160	
Febrile neutropenia			
subjects affected / exposed	52 / 143 (36.36%)	27 / 164 (16.46%)	
occurrences (all)	66	33	
Leukopenia			
subjects affected / exposed	54 / 143 (37.76%)	47 / 164 (28.66%)	
occurrences (all)	119	174	
Lymphopenia			
subjects affected / exposed	35 / 143 (24.48%)	31 / 164 (18.90%)	
occurrences (all)	76	116	
Neutropenia			
subjects affected / exposed	66 / 143 (46.15%)	79 / 164 (48.17%)	
occurrences (all)	126	246	
Thrombocytopenia			
subjects affected / exposed	86 / 143 (60.14%)	80 / 164 (48.78%)	
occurrences (all)	297	286	
Eye disorders			

Dry eye			
subjects affected / exposed	8 / 143 (5.59%)	1 / 164 (0.61%)	
occurrences (all)	8	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	2 / 143 (1.40%)	10 / 164 (6.10%)	
occurrences (all)	3	14	
Abdominal pain			
subjects affected / exposed	26 / 143 (18.18%)	19 / 164 (11.59%)	
occurrences (all)	29	23	
Abdominal pain upper			
subjects affected / exposed	12 / 143 (8.39%)	11 / 164 (6.71%)	
occurrences (all)	12	12	
Constipation			
subjects affected / exposed	34 / 143 (23.78%)	28 / 164 (17.07%)	
occurrences (all)	39	31	
Diarrhoea			
subjects affected / exposed	54 / 143 (37.76%)	30 / 164 (18.29%)	
occurrences (all)	66	34	
Dyspepsia			
subjects affected / exposed	9 / 143 (6.29%)	3 / 164 (1.83%)	
occurrences (all)	11	3	
Nausea			
subjects affected / exposed	68 / 143 (47.55%)	52 / 164 (31.71%)	
occurrences (all)	89	72	
Stomatitis			
subjects affected / exposed	9 / 143 (6.29%)	5 / 164 (3.05%)	
occurrences (all)	12	6	
Vomiting			
subjects affected / exposed	35 / 143 (24.48%)	25 / 164 (15.24%)	
occurrences (all)	39	41	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	23 / 143 (16.08%)	35 / 164 (21.34%)	
occurrences (all)	41	66	
Skin and subcutaneous tissue disorders			

Erythema			
subjects affected / exposed	9 / 143 (6.29%)	7 / 164 (4.27%)	
occurrences (all)	10	9	
Pruritus			
subjects affected / exposed	10 / 143 (6.99%)	8 / 164 (4.88%)	
occurrences (all)	11	9	
Rash			
subjects affected / exposed	27 / 143 (18.88%)	14 / 164 (8.54%)	
occurrences (all)	32	15	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 143 (4.90%)	9 / 164 (5.49%)	
occurrences (all)	7	10	
Back pain			
subjects affected / exposed	10 / 143 (6.99%)	16 / 164 (9.76%)	
occurrences (all)	10	20	
Bone pain			
subjects affected / exposed	10 / 143 (6.99%)	3 / 164 (1.83%)	
occurrences (all)	10	3	
Pain in extremity			
subjects affected / exposed	16 / 143 (11.19%)	13 / 164 (7.93%)	
occurrences (all)	19	14	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	13 / 143 (9.09%)	4 / 164 (2.44%)	
occurrences (all)	14	4	
Pneumonia			
subjects affected / exposed	12 / 143 (8.39%)	4 / 164 (2.44%)	
occurrences (all)	13	5	
Sinusitis			
subjects affected / exposed	8 / 143 (5.59%)	4 / 164 (2.44%)	
occurrences (all)	9	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	18 / 143 (12.59%)	19 / 164 (11.59%)	
occurrences (all)	25	23	

Fluid overload			
subjects affected / exposed	8 / 143 (5.59%)	2 / 164 (1.22%)	
occurrences (all)	8	2	
Hyperglycaemia			
subjects affected / exposed	12 / 143 (8.39%)	11 / 164 (6.71%)	
occurrences (all)	19	19	
Hypoalbuminaemia			
subjects affected / exposed	7 / 143 (4.90%)	10 / 164 (6.10%)	
occurrences (all)	14	13	
Hypocalcaemia			
subjects affected / exposed	15 / 143 (10.49%)	11 / 164 (6.71%)	
occurrences (all)	29	19	
Hypokalaemia			
subjects affected / exposed	33 / 143 (23.08%)	25 / 164 (15.24%)	
occurrences (all)	49	37	
Hypomagnesaemia			
subjects affected / exposed	12 / 143 (8.39%)	10 / 164 (6.10%)	
occurrences (all)	14	13	
Hyponatraemia			
subjects affected / exposed	9 / 143 (6.29%)	5 / 164 (3.05%)	
occurrences (all)	13	8	
Hypophosphataemia			
subjects affected / exposed	10 / 143 (6.99%)	9 / 164 (5.49%)	
occurrences (all)	19	10	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2012	Inclusion and exclusion criteria were added or modified. The assessment of bone marrow biopsies was only required for patients with inadequate hematologic recovery. Patient follow-up time for survival was extended. Requirement for effective contraception was extended to 90 days post therapy. Redundant/unnecessary laboratory tests were removed. Administrative corrections and clarifications were made throughout the protocol.
24 June 2013	Removed time to progression as a secondary endpoint. Dose of inotuzumab ozogamicin was reduced to 0.5 mg/m^2 at Day 1 of Cycle 2 and beyond in patients achieving either CR or CRi. Revised sites required for study completion from 100 to 190. Changed the statistical power for testing CR/CRi from 88 to 89%. Allowed immunohistochemistry for the determination of CD22 expression at screening in patients with inadequate bone marrow aspirate and no circulating blasts. Added collection of an additional bone marrow sample for analysis of leukemic blast phenotype/genotype by other test methods. Changed the timing of disease assessment to allow bone marrow recovery for patients in the control arm. Updated background information with clinical data for inotuzumab ozogamicin from prior/ongoing studies in patients with relapsed or refractory ALL. Revised and clarified some inclusion/exclusion criteria. Updated study drug administration tables. Modified dose reduction schema to allow for drug related toxicities in the inotuzumab ozogamicin arm. Updated section on destruction of partially used or empty drug vials. Clarified disease assessment including time of radiographic assessment and bone marrow biopsy. Updated SAE reporting section. Added additional details on the sample size calculation. Implemented administrative corrections and clarifications throughout the protocol.
28 March 2014	Updated the inotuzumab ozogamicin clinical background section. Increased the total sample size from 292 to 325 patients due to higher number of patients in the control arm withdrawing from treatment before start of chemotherapy than initially anticipated and loss of follow-up data in the control arm. Capped the percentage of patients with Ph+ ALL that had failed TKI-based therapies at approximately 20% of the study patient population to reflect the relapsed and refractory ALL adult population. Clarified recommendations to reduce the risk of VOD/SOS for patients proceeding to HSCT; these recommendations included avoidance of hepatotoxic myeloablative regimens for subsequent HSCT and limiting the number of cycles of inotuzumab ozogamicin treatment in patients proceeding to HSCT. Modified CD22 immunophenotyping performed at screening such that patients were eligible for the study if they were considered to be CD22-positive based on assessment by the central laboratory even if they were considered to be CD22-negative based on assessment by the local laboratory. Added requirement for medications used as prophylaxis for hepatotoxicities or for the treatment of VOD/SOS to be reported for up to 2 years from randomization. Implemented administrative corrections and clarifications throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported