Clinical trial results:
A Phase 2 Randomized Open-label Study of MEDI-551 in Adults With Relapsed or Refractory DLBCL

Summary

EudraCT number	2011-002565-38
Trial protocol	DE CZ ES HU IT PL
Global end of trial date	17 July 2016

Results information

Result version number	v1 (current)
This version publication date	21 February 2018
First version publication date	21 February 2018

Trial information

Trial identification

Sponsor protocol code	CD-ON-MEDI-551-1088

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01453205
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	MedImmune, LLC
Sponsor organisation address	One MedImmune Way, Gaithersburg, United States, MD 20878
Public contact	AstraZeneca, AstraZeneca Clinical Study Information Center,, +1 18772409479, information.center@astrazenca.com
Scientific contact	AstraZeneca, AstraZeneca Clinical Study Information Center,, +1 18772409479, information.center@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 July 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the overall response rate (ORR), including partial response (PR) and complete response (CR), of participants treated with MEDI-551 when used in combination with ifosfamide-carboplatin-etoposide (ICE) or dexamethasone-cytarabine-cisplatin (DHAP) versus rituximab in combination with ICE or DHAP in participants with relapsed or refractory diffuse large B-cell lymphoma (DLBCL).

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	27 February 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 84
Country: Number of subjects enrolled	Canada: 8
Country: Number of subjects enrolled	Czech Republic: 7
Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Poland: 13
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Turkey: 7
Worldwide total number of subjects	187
EEA total number of subjects	73

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)	138
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted from 27Feb2012 to 17Jun2016.

Pre-assignment

Screening details:

A total of 256 participants were screened, of which 187 participants were randomized in the study.

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	Rituximab+ ICE/DHAP

Arm description:

Participants received Rituximab in combination with ifosfamide + carboplatin + etoposide (ICE) or dexamethasone + cisplatin + cytarabine (DHAP) for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). Rituximab (375 mg/m^2) was administered intravenous (IV) on 2 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of rituximab, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of rituximab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Arm type	Active comparator
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab (375 mg/m^2) was administered intravenous (IV) on 2 days before the start of Cycle 1 and on Day 1 of each cycle.

Arm title	MEDI-551 2 mg/kg + ICE/DHAP

Arm description:

Participants received MEDI-551 (2 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (2 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Arm type	Experimental
Investigational medicinal product name	MEDI-551 2 mg/kg
Investigational medicinal product code	
Other name	Inebilizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MEDI-551 (2 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle.

Arm title	MEDI-551 4 mg/kg + ICE/DHAP

Arm description:

Participants received MEDI-551 (4 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (4 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Arm type	Experimental
Investigational medicinal product name	MEDI-551 4 mg/kg
Investigational medicinal product code	
Other name	Inebilizumab
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MEDI-551 (4 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle.

Number of subjects in period 1	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP
Started	80	52	55
Completed	0	0	1
Not completed	80	52	54
Adverse event, serious fatal	24	22	18
Consent withdrawn by subject	8	3	-
Unspecified	45	27	35
Lost to follow-up	3	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab+ ICE/DHAP

Reporting group description:

Participants received Rituximab in combination with ifosfamide + carboplatin + etoposide (ICE) or dexamethasone + cisplatin + cytarabine (DHAP) for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). Rituximab (375 mg/m^2) was administered intravenous (IV) on 2 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of rituximab, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of rituximab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 2 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (2 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (2 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 4 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (4 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (4 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects	80	52	55
Age Categorical Units: Subjects			
< 65 YEARS	60	35	43
>= 65 YEARS	20	17	12
Age Continuous Units: YEARS			
arithmetic mean	56.4	56.9	55.9
standard deviation	± 12.3	± 11.4	± 11.6
Gender, Male/Female Units: Subjects			
Female	35	19	24
Male	45	33	31

Reporting group values	Total		
Number of subjects	187		

Age Categorical Units: Subjects			
< 65 YEARS	138		
>= 65 YEARS	49		
Age Continuous Units: YEARS arithmetic mean standard deviation	 -		
Gender, Male/Female Units: Subjects			
Female	78		
Male	109		

Subject analysis sets

Subject analysis set title	MEDI-551
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were received MEDI-551 2 mg/kg or 4 mg/kg by IV infusion. Recommended MEDI-551 dose was selected based on the DMC reviews. As there is no data available for the 107 participants presented for the endpoint accepted dose of MEDI-551, I have included the arbitrary value of '99999' for Age continuous field (arithmetic mean and the standard deviation).

Reporting group values	MEDI-551		
Number of subjects	107		
Age Categorical Units: Subjects			
< 65 YEARS			
>= 65 YEARS			
Age Continuous Units: YEARS arithmetic mean standard deviation	 56.4 ± 11.8		
Gender, Male/Female Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Rituximab+ ICE/DHAP

Reporting group description:

Participants received Rituximab in combination with ifosfamide + carboplatin + etoposide (ICE) or dexamethasone + cisplatin + cytarabine (DHAP) for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). Rituximab (375 mg/m^2) was administered intravenous (IV) on 2 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of rituximab, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of rituximab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 2 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (2 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (2 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 4 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (4 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (4 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of MEDI-551, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Subject analysis set title	MEDI-551
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants were received MEDI-551 2 mg/kg or 4 mg/kg by IV infusion. Recommended MEDI-551 dose was selected based on the DMC reviews. As there is no data available for the 107 participants presented for the endpoint accepted dose of MEDI-551, I have included the arbitrary value of '99999' for Age continuous field (arithmetic mean and the standard deviation).

Primary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

Objective Response Rate, defined as the proportion of participants with a best response of complete response (disappearance of all evidence of disease) or partial response (regression of measurable disease and no new sites) according to the International Working Group criteria. The analysis for this end point was based on Intent-To-Treat (ITT) population, which included all participants who were randomized into the study.

End point type	Primary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: Percentage of participants				
number (confidence interval 95%)	47.5 (36.2 to 59.0)	46.2 (32.2 to 60.5)	43.6 (30.3 to 57.7)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Rituximab+ ICE/DHAP v MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5543
Method	Cochran-Mantel-Haenszel

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

Progression-free survival (PFS) is defined as the time from randomization until the first documentation of disease progression or death due to any cause, whichever occurs first. PFS (months) = (Date of PD/death or censoring – Date of randomization + 1) / (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: months				
median (full range (min-max))	6.1 (0.0 to 39.2)	6.6 (0.0 to 31.3)	7.7 (0 to 14.8)	

Statistical analyses

Statistical analysis title	Rituximab vs Inebilizumab 4 mg/kg
Comparison groups	Rituximab+ ICE/DHAP v MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8567
Method	Logrank

Secondary: Event-Free Survival (EFS)

End point title	Event-Free Survival (EFS)

End point description:

Event-Free Survival (EFS) is defined as the time from randomization until the first documentation of EFS events which include disease progression, initiation of alternative antitumor treatment or death due to any cause, whichever occurs first. EFS (months) = (Date of EFS or censoring – Date of randomization + 1) / (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: months				
median (full range (min-max))	4.7 (0.0 to 39.2)	4.2 (0.0 to 31.3)	5.9 (0.0 to 14.8)	

Statistical analyses

Statistical analysis title	Rituximab vs Inebilizumab 4 mg/kg
Comparison groups	Rituximab+ ICE/DHAP v MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7412
Method	Logrank

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall survival defined as the time from randomization until death due to any cause. OS (months) = (Date of death or censoring – Date of randomization + 1) / (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study. '99999' indicates value was not estimable.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: months				
median (confidence interval 95%)	99999 (15.6 to 99999)	99999 (14.2 to 99999)	23.0 (12.8 to 99999)	

Statistical analyses

Statistical analysis title	Rituximab vs Inebilizumab 4 mg/kg
Comparison groups	Rituximab+ ICE/DHAP v MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9996
Method	Logrank

Secondary: Time to Progression (TTP)

End point title	Time to Progression (TTP)

End point description:

Time to Progression (TTP) defined as the time from randomization until the first documentation of disease progression. TTP (months) = (Date of PD or censoring – Date of randomization + 1) / (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: months				
median (full range (min-max))	4.9 (0.0 to 11.1)	4.2 (0.0 to 31.3)	5.9 (0.0 to 14.0)	

Statistical analyses

Statistical analysis title	Rituximab vs Inebilizumab 4 mg/kg
Comparison groups	Rituximab+ ICE/DHAP v MEDI-551 4 mg/kg + ICE/DHAP
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1686
Method	Logrank

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

Time to response (TTR) defined as the time from randomization until the first documentation of disease response. Only participants who have achieved objective response (confirmed CR or confirmed PR) assessed by investigator were evaluated for TTR. TTR (months) = (Date of first disease response – Date of randomization + 1) / (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	32	30	
Units: months				
median (full range (min-max))	1.7 (0.9 to 3.8)	2.3 (1.5 to 3.4)	2.3 (1.6 to 6.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

Duration of Response (DR) defined as time from start of first documented objective response (confirmed Complete Response [CR] or confirmed Partial Response [PR]) to first documented disease progression. Only participants who have achieved objective response assessed by investigator were evaluated. DR calculated as (months) = (Date of PD or censoring – Date of first disease response + 1)/ (365.25/12). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study. '99999' indicates value was not estimable.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	42	32	30	
Units: months				
median (confidence interval 95%)	99999 (4.9 to 99999)	7.1 (4.1 to 99999)	7.9 (4.6 to 12.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Best Overall Response Assessed by Blinded Independent Central Review (BICR)

End point title	Number of Participants with Best Overall Response Assessed by Blinded Independent Central Review (BICR)

End point description:

The best overall response was calculated, based upon the disease assessments recorded during the study visits, and summarized with the number of participants for the following categories: complete response (CR), partial response (PR), stable disease (SD), progessive disease (PD), and not evaluable (NE). The analysis for this end point was based on ITT population, which included all participants who were randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	80	52	55	
Units: Number of particpants				
COMPLETE RESPONSE (CR)	20	6	12	
PARTIAL RESPONSE (PR)	18	18	12	
STABLE DISEASE (SD)	17	12	14	
PROGRESSIVE DISEASE (PD)	5	5	5	
UNKNOWN	20	11	12	

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptable Dose of MEDI-551

End point title	Acceptable Dose of MEDI-551

End point description:

Acceptable dose for MEDI-551 was evaluated based on the benefit-risk analysis. The analysis for this end point was based on all participants who were randomized into the study and received MEDI-551.

End point type	Secondary

End point timeframe:

After the administration of the first dose of MEDI-551(7 days before the Cycle 1) to last dose of MEDI-551 (Cycle 3 Day 1) (each cycle of 21 days)

End point values	MEDI-551			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: milligram per kilogram (mg/kg)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

An Adverse Event (AE) is any unfavourable and unintended signs, symptoms, or diseases temporally associated with use of study drug, whether or not considered related to study drug. SAE is any AE that resulted in death, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, life-threatening, a congenital anomaly/birth defect, or an important medical event. TEAEs are defined as AEs present at baseline that worsened in intensity after administration of study drug, or events absent at baseline that emerged after administration of study

drug, up to 90 days after the end of treatment (EOT). The analysis for this end point was based on safety population, which included all participants who received any study treatment.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	52	54	
Units: Number of participants				
TEAEs	78	51	52	
TESAEs	33	25	27	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Hematology/Coagulation Laboratory Results

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Hematology/Coagulation Laboratory Results

End point description:

An abnormal laboratory finding that was judged by the investigator to be medically significant was reported as an AE. TEAEs were defined as events present at baseline that worsened in intensity after administration of inebilizumab, or events absent at baseline that emerged after administration of inebilizumab, for the period extending to 90 days after the EOT. The analysis for this end point was based on safety population, which included all participants who received any study treatment.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	52	54	
Units: Number of participants				
Anaemia	47	32	33	
Febrile neutropenia	16	9	12	
Granulocytopenia	3	0	2	
Leukopenia	9	6	10	
Lymphopenia	4	2	3	
Neutropenia	30	15	20	

Pancytopenia	2	0	3	
Thromobocytopenia	49	24	29	
Activated partial thromboplastin time prolonged	0	2	0	
Blood immunoglobulin g decreased	0	1	0	
Blood immunoglobulin m decreased	0	1	0	
Haemoglobin decreased	0	1	0	
Immunoglobulins decreased	0	1	0	
Lymphocyte count decreased	9	4	3	
Neutrophil count decreased	7	6	8	
Platelet count decreased	12	8	10	
Platelet count increased	0	1	0	
White blood cell count decreased	6	5	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Chemistry Laboratory Results (include Urinalysis)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Chemistry Laboratory Results (include Urinalysis)

End point description:

An abnormal laboratory findings that was judged by the investigator to be medically significant was reported as an AE. TEAEs were defined as events present at baseline that worsened in intensity after administration of inebilizumab, or events absent at baseline that emerged after administration of inebilizumab, for the period extending to 90 days after the end of study treatment. The analysis for this end point was based on safety population, which included all participants who received any study treatment.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	52	54	
Units: Number of participants				
Hyperbilirubinaemia	1	0	0	
Hypernatraemia	3	1	1	
Hyperphosphataemia	0	0	2	
Hypertriglyerideaemia	1	0	0	
Hyperuricaemia	5	4	1	
Hypoalbuminaemia	3	4	3	
Hypocalcaemia	11	6	7	
Hypoglycaemia	1	1	1	
Hypokalaemia	24	13	14	

Hypomagnesaemia	17	6	11	
Hyponatraemia	8	2	2	
Hypophosphataemia	4	3	3	
Hypoproteinaemia	0	0	1	
Alanine aminotransferase increased	7	2	4	
Aspartate aminotransferase increased	5	2	6	
Blood alkaline phosphatase increased	2	0	1	
Blood bicarbonate decreased	1	0	0	
Blood bilirubin increased	1	1	1	
Blood chloride increased	0	1	0	
Blood creatinine increased	10	5	7	
Blood lactate dehydrogenase increased	2	1	1	
Blood magnesium decreased	2	0	0	
Blood potassium decreased	2	0	0	
Blood uric acid decreased	0	1	0	
Blood uric acid increased	1	1	0	
Gamma-glutamyltransferase increased	9	3	3	
Hepatic enzyme increased	1	0	1	
Protein total decreased	0	1	1	
Transaminases increased	1	2	0	
Dysuria	2	1	3	
Hematuria	2	3	0	
Glucose urine present	0	1	1	
Proteinuria	0	1	1	
Urine sodium increased	0	0	1	
Calcium deficiency	0	0	1	
Electrolyte imbalance	2	0	0	
Hypercalcaemia	2	1	0	
Hyperglycaemia	12	9	2	
Hyperkalaemia	2	2	1	
Hypermagnesaemia	3	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Vital Signs and ECG Abnormalities

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs) Related to Vital Signs and ECG Abnormalities

End point description:

Vital signs included parameters such as heart rate, blood pressure, temperature, and respiratory rate. An abnormal vital signs and ECG findings that was judged by the investigator to be medically significant was reported an AE. TEAEs were defined as events present at baseline that worsened in intensity after administration of inebilizumab, or events absent at baseline that emerged after administration of inebilizumab, for the period extending to 90 days after the end of study treatment. The analysis for this end point was based on safety population, which included all participants who received any study treatment.

End point type	Secondary

End point timeframe:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

End point values	Rituximab+ ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	52	54	
Units: Number of participants				
Arrhythmia	0	0	2	
Atrial fibrillation	1	1	2	
Bradycardia	3	1	2	
Extrasystoles	0	1	0	
Palpitations	2	1	0	
Sinus arrhythmia	0	0	1	
Sinus bradycardia	1	2	1	
Systolic dysfunction	0	0	1	
Tachycardia	3	1	2	
Pyrexia	17	14	11	
Blood pressure increased	0	0	1	
Carbon dioxide decreased	1	0	0	
Electrocardiogram abnormal	0	0	1	
Electrocardiogram QT prolonged	0	2	2	
Heart rate irregular	1	0	0	
Weight decreased	0	1	1	
Weight increased	1	0	1	
Dyspnoea	11	7	8	
Dyspnoea exertional	0	3	1	
Hypertension	5	2	3	
Hypotension	10	4	8	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants who Developed Detectable MEDI-551 Anti-drug Antibodies

End point title	Number of Participants who Developed Detectable MEDI-551 Anti-drug Antibodies[1]

End point description:

A participant was considered ADA-positive across the study if they had a positive reading (titer of 50 or higher) at any time point during the study. The analysis for this end point was based on safety population, which included all participants who received any study treatment.

End point type	Secondary

End point timeframe:

7 days before the start of Cycle 1, Day 1 of each subsequent Cycle, EOT, and post EOT on Days 30, 60, 90 and 270 (up to 36 months from the randomization of last participant)

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: This end point is related to MEDI-551. Therefore, it is applicable for "MEDI-551 2 mg/kg +

ICE/DHAP" and "MEDI-551 4 mg/kg + ICE/DHAP" arms only.

End point values	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: Number of participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Serum Concentration of MEDI-551

End point title	Mean Serum Concentration of MEDI-551[2]

End point description:

The mean serum concentration of MEDI-551 were observed. Participants who received MEDI-551 were analysed for this end point. Here, "n" is number of participants analysed at this time point.

End point type	Secondary

End point timeframe:

Cycle 1 Day -7 Post dose, pre-dose and postdose on Day 1, post-dose on Days 4, 8, 15 of Cycle 1, pre-dose and postdose on Day 1 of Cycle 2 and Cycle 3

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: This end point is related to MEDI-551. Therefore, it is applicable for "MEDI-551 2 mg/kg + ICE/DHAP" and "MEDI-551 4 mg/kg + ICE/DHAP" arms only.

End point values	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: mcg/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day-7 Post Dose (n= 46, 50)	47.0 (± 23.7)	83.8 (± 21.9)		
Cycle 1 Day 1 Pre Dose (n= 46, 52)	16.7 (± 5.81)	33.1 (± 16.3)		
Cycle 1 Day 1 Post Dose (n= 46, 51)	64.8 (± 26.4)	116 (± 41.3)		
Cycle 1 Day 4 (n= 43, 45)	38.8 (± 14.6)	71.9 (± 23.0)		
Cycle 1 Day 8 (n= 44, 48)	30.6 (± 9.69)	69.3 (± 25.1)		
Cycle 1 Day 15 (n= 40, 43)	19.4 (± 6.19)	44.7 (± 25.0)		
Cycle 2 Day 1 Pre Dose (n= 40, 44)	15.0 (± 5.45)	30.9 (± 14.3)		
Cycle 2 Day 1 Post Dose (n= 40, 43)	52.3 (± 18.7)	112 (± 32.6)		
Cycle 3 Day 1 Pre Dose (n= 26, 26)	14.0 (± 6.50)	36.4 (± 18.7)		
Cycle 3 Day 1 Post Dose (n= 25, 25)	52.4 (± 16.9)	116 (± 30.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Half-life (T1/2) of MEDI-551

End point title	Half-life (T1/2) of MEDI-551[3]

End point description:

Terminal elimination half-life (T1/2) is the time required for half of the drug to be eliminated from the serum. Participants who received MEDI-551 were analysed for this end point. Here, "n" is number of participants analysed at this time point.

End point type	Secondary

End point timeframe:

Cycle 1 and EOT (Day 21 of Cycle 3 [each cycle of 21 days] or earlier cycles if treatment stopped before Cycle 3)

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: This end point is related to MEDI-551. Therefore, it is applicable for "MEDI-551 2 mg/kg + ICE/DHAP" and "MEDI-551 4 mg/kg + ICE/DHAP" arms only.

End point values	MEDI-551 2 mg/kg + ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	54		
Units: Day				
arithmetic mean (standard deviation)				
Cycle 1 n= (36, 43)	14.4 (± 5.09)	16.5 (± 10.5)		
End of Treatment n= (9,17)	18.9 (± 4.34)	20.2 (± 5.73)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From treatment administration (Day1) to 90 days after the end of study treatment (up to approximately 36 months from the randomization of last participant)

Adverse event reporting additional description:

AE were reported for safety population, which included all participants who received any study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Rituximab+ ICE/DHAP

Reporting group description:

Participants received Rituximab in combination with ifosfamide + carboplatin + etoposide (ICE) or dexamethasone + cisplatin + cytarabine (DHAP) for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). Rituximab (375 mg/m^2) was administered intravenous (IV) on 2 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of rituximab, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of rituximab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 4 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (4 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (4 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of Inebilizumab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Reporting group title	MEDI-551 2 mg/kg + ICE/DHAP

Reporting group description:

Participants received MEDI-551 (2 mg/kg) in combination with ICE or DHAP for 3 cycles (21-day cycles) and were followed until end of the study (36 months after the date of randomization for last participant, or date the sponsor stops the trial, whichever occurs first). MEDI-551 (2 mg/kg) was administered IV on 7 days before the start of Cycle 1 and on Day 1 of each cycle. After completion of MEDI-551, IV infusion of ICE as: ifosfamide 5 g/ m^2 continuously for 24 hours with mesna on Day 2; carboplatin AUC=5 mg/mL x min (800 mg maximum) on Day 2; etoposide 100 mg/ m^2 on Days 1, 2, and 3 in 21-day cycles. After completion of Inebilizumab, IV infusion of DHAP as: dexamethasone 40 mg on Days 1, 2, 3, and 4; cisplatin 100 mg/m^2 continuously for 24 hours on Day 1; cytarabine 2 g/m^2 in 3-hour infusion repeated after 12 hours (2 doses) on Day 2 in 21-day cycles.

Serious adverse events	Rituximab+ ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 79 (41.77%)	27 / 54 (50.00%)	25 / 52 (48.08%)
number of deaths (all causes)	24	18	22
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system lymphoma			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Tumour haemorrhage			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Fatigue			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple organ dysfunction syndrome			

subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	1 / 79 (1.27%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal inflammation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 79 (0.00%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicidal ideation			

subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Overdose			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Angina pectoris			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Coma hepatic			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Dizziness			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Memory impairment			

subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disseminated intravascular coagulation			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	11 / 79 (13.92%)	9 / 54 (16.67%)	8 / 52 (15.38%)
occurrences causally related to treatment / all	8 / 11	10 / 10	9 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			

subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 54 (5.56%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	4 / 5	2 / 3	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	5 / 79 (6.33%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	6 / 7	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombotic microangiopathy			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			

subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic colitis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 79 (2.53%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 79 (3.80%)	2 / 54 (3.70%)	3 / 52 (5.77%)
occurrences causally related to treatment / all	3 / 3	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	1 / 79 (1.27%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	1 / 1	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis viral			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter sepsis			

subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	3 / 79 (3.80%)	4 / 54 (7.41%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 3	5 / 5	0 / 1
deaths causally related to treatment / all	0 / 2	2 / 2	0 / 0
Septic shock			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 1
Staphylococcal sepsis			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			

subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 79 (0.00%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Rituximab+ ICE/DHAP	MEDI-551 4 mg/kg + ICE/DHAP	MEDI-551 2 mg/kg + ICE/DHAP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 79 (98.73%)	52 / 54 (96.30%)	49 / 52 (94.23%)
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 79 (6.33%)	3 / 54 (5.56%)	2 / 52 (3.85%)
occurrences (all)	9	10	2
Hypotension			
subjects affected / exposed	10 / 79 (12.66%)	8 / 54 (14.81%)	3 / 52 (5.77%)
occurrences (all)	12	9	4
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	9 / 79 (11.39%)	11 / 54 (20.37%)	12 / 52 (23.08%)
occurrences (all)	12	15	21
Chills			
subjects affected / exposed	6 / 79 (7.59%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences (all)	9	2	1
Fatigue			
subjects affected / exposed	22 / 79 (27.85%)	15 / 54 (27.78%)	20 / 52 (38.46%)
occurrences (all)	32	20	33
Mucosal inflammation			
subjects affected / exposed	7 / 79 (8.86%)	3 / 54 (5.56%)	3 / 52 (5.77%)
occurrences (all)	7	5	3
Oedema			
subjects affected / exposed	5 / 79 (6.33%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences (all)	6	2	2
Oedema peripheral			
subjects affected / exposed	10 / 79 (12.66%)	5 / 54 (9.26%)	6 / 52 (11.54%)
occurrences (all)	12	7	9
Pyrexia			
subjects affected / exposed	17 / 79 (21.52%)	9 / 54 (16.67%)	12 / 52 (23.08%)
occurrences (all)	24	10	16
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	10 / 79 (12.66%)	8 / 54 (14.81%)	9 / 52 (17.31%)
occurrences (all)	12	8	12

Dyspnoea			
subjects affected / exposed	11 / 79 (13.92%)	7 / 54 (12.96%)	7 / 52 (13.46%)
occurrences (all)	15	8	11
Dyspnoea exertional			
subjects affected / exposed	0 / 79 (0.00%)	1 / 54 (1.85%)	3 / 52 (5.77%)
occurrences (all)	0	2	3
Epistaxis			
subjects affected / exposed	5 / 79 (6.33%)	1 / 54 (1.85%)	3 / 52 (5.77%)
occurrences (all)	5	1	5
Hiccups			
subjects affected / exposed	2 / 79 (2.53%)	2 / 54 (3.70%)	3 / 52 (5.77%)
occurrences (all)	2	3	3
Oropharyngeal pain			
subjects affected / exposed	6 / 79 (7.59%)	4 / 54 (7.41%)	0 / 52 (0.00%)
occurrences (all)	7	4	0
Pleural effusion			
subjects affected / exposed	5 / 79 (6.33%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	5	2	0
Pulmonary embolism			
subjects affected / exposed	2 / 79 (2.53%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Rhinorrhoea			
subjects affected / exposed	6 / 79 (7.59%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	6	1	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	7 / 79 (8.86%)	2 / 54 (3.70%)	5 / 52 (9.62%)
occurrences (all)	8	2	5
Confusional state			
subjects affected / exposed	3 / 79 (3.80%)	3 / 54 (5.56%)	1 / 52 (1.92%)
occurrences (all)	3	4	1
Insomnia			
subjects affected / exposed	8 / 79 (10.13%)	8 / 54 (14.81%)	4 / 52 (7.69%)
occurrences (all)	9	8	4
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	7 / 79 (8.86%)	4 / 54 (7.41%)	2 / 52 (3.85%)
occurrences (all)	13	7	2
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 79 (6.33%)	6 / 54 (11.11%)	2 / 52 (3.85%)
occurrences (all)	11	13	2
Blood creatinine increased			
subjects affected / exposed	10 / 79 (12.66%)	7 / 54 (12.96%)	5 / 52 (9.62%)
occurrences (all)	17	17	8
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 79 (2.53%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Electrocardiogram qt prolonged			
subjects affected / exposed	0 / 79 (0.00%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences (all)	0	2	2
Gamma-glutamyltransferase increased			
subjects affected / exposed	9 / 79 (11.39%)	3 / 54 (5.56%)	3 / 52 (5.77%)
occurrences (all)	15	4	8
Lymphocyte count decreased			
subjects affected / exposed	9 / 79 (11.39%)	3 / 54 (5.56%)	4 / 52 (7.69%)
occurrences (all)	27	7	13
Neutrophil count decreased			
subjects affected / exposed	7 / 79 (8.86%)	8 / 54 (14.81%)	5 / 52 (9.62%)
occurrences (all)	8	16	8
Platelet count decreased			
subjects affected / exposed	12 / 79 (15.19%)	10 / 54 (18.52%)	8 / 52 (15.38%)
occurrences (all)	31	23	38
White blood cell count decreased			
subjects affected / exposed	6 / 79 (7.59%)	6 / 54 (11.11%)	4 / 52 (7.69%)
occurrences (all)	13	22	9
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	11 / 79 (13.92%)	6 / 54 (11.11%)	7 / 52 (13.46%)
occurrences (all)	32	6	9

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 79 (1.27%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences (all)	1	2	1
Bradycardia			
subjects affected / exposed	3 / 79 (3.80%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences (all)	3	2	1
Sinus bradycardia			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	1	1	3
Tachycardia			
subjects affected / exposed	3 / 79 (3.80%)	2 / 54 (3.70%)	1 / 52 (1.92%)
occurrences (all)	3	3	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	11 / 79 (13.92%)	7 / 54 (12.96%)	8 / 52 (15.38%)
occurrences (all)	12	9	10
Dysgeusia			
subjects affected / exposed	3 / 79 (3.80%)	3 / 54 (5.56%)	5 / 52 (9.62%)
occurrences (all)	3	3	5
Headache			
subjects affected / exposed	14 / 79 (17.72%)	8 / 54 (14.81%)	7 / 52 (13.46%)
occurrences (all)	19	10	7
Neuropathy peripheral			
subjects affected / exposed	5 / 79 (6.33%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences (all)	5	3	2
Presyncope			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	3	1	1
Syncope			
subjects affected / exposed	2 / 79 (2.53%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences (all)	3	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	47 / 79 (59.49%)	33 / 54 (61.11%)	32 / 52 (61.54%)
occurrences (all)	113	111	87
Febrile neutropenia			

subjects affected / exposed	6 / 79 (7.59%)	3 / 54 (5.56%)	2 / 52 (3.85%)
occurrences (all)	6	4	2
Granulocytopenia			
subjects affected / exposed	3 / 79 (3.80%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	5	4	0
Leukopenia			
subjects affected / exposed	8 / 79 (10.13%)	10 / 54 (18.52%)	6 / 52 (11.54%)
occurrences (all)	10	31	8
Lymphopenia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 54 (5.56%)	2 / 52 (3.85%)
occurrences (all)	22	4	18
Neutropenia			
subjects affected / exposed	27 / 79 (34.18%)	18 / 54 (33.33%)	15 / 52 (28.85%)
occurrences (all)	50	45	30
Thrombocytopenia			
subjects affected / exposed	47 / 79 (59.49%)	28 / 54 (51.85%)	24 / 52 (46.15%)
occurrences (all)	172	114	71
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	4 / 79 (5.06%)	3 / 54 (5.56%)	0 / 52 (0.00%)
occurrences (all)	4	3	0
Eye disorders			
Dry eye			
subjects affected / exposed	4 / 79 (5.06%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences (all)	4	0	1
Vision blurred			
subjects affected / exposed	2 / 79 (2.53%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 79 (5.06%)	2 / 54 (3.70%)	6 / 52 (11.54%)
occurrences (all)	5	3	9
Abdominal pain upper			
subjects affected / exposed	5 / 79 (6.33%)	4 / 54 (7.41%)	2 / 52 (3.85%)
occurrences (all)	5	4	2
Constipation			

subjects affected / exposed	23 / 79 (29.11%)	18 / 54 (33.33%)	17 / 52 (32.69%)
occurrences (all)	38	27	23
Diarrhoea			
subjects affected / exposed	19 / 79 (24.05%)	13 / 54 (24.07%)	15 / 52 (28.85%)
occurrences (all)	26	16	17
Dry mouth			
subjects affected / exposed	4 / 79 (5.06%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences (all)	4	0	1
Dyspepsia			
subjects affected / exposed	4 / 79 (5.06%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	4	1	1
Gastrooesophageal reflux disease			
subjects affected / exposed	6 / 79 (7.59%)	5 / 54 (9.26%)	0 / 52 (0.00%)
occurrences (all)	8	5	0
Haemorrhoids			
subjects affected / exposed	4 / 79 (5.06%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	4	1	2
Nausea			
subjects affected / exposed	43 / 79 (54.43%)	25 / 54 (46.30%)	23 / 52 (44.23%)
occurrences (all)	75	42	45
Oral pain			
subjects affected / exposed	2 / 79 (2.53%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Stomatitis			
subjects affected / exposed	5 / 79 (6.33%)	0 / 54 (0.00%)	2 / 52 (3.85%)
occurrences (all)	5	0	2
Vomiting			
subjects affected / exposed	26 / 79 (32.91%)	14 / 54 (25.93%)	14 / 52 (26.92%)
occurrences (all)	37	21	28
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 79 (7.59%)	8 / 54 (14.81%)	5 / 52 (9.62%)
occurrences (all)	7	8	7
Night sweats			
subjects affected / exposed	2 / 79 (2.53%)	4 / 54 (7.41%)	1 / 52 (1.92%)
occurrences (all)	3	4	1

Petechiae			
subjects affected / exposed	4 / 79 (5.06%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	5	1	2
Pruritus			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	3	1	1
Rash			
subjects affected / exposed	3 / 79 (3.80%)	6 / 54 (11.11%)	0 / 52 (0.00%)
occurrences (all)	4	8	0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 79 (1.27%)	4 / 54 (7.41%)	3 / 52 (5.77%)
occurrences (all)	4	5	5
Dysuria			
subjects affected / exposed	2 / 79 (2.53%)	3 / 54 (5.56%)	1 / 52 (1.92%)
occurrences (all)	2	3	3
Haematuria			
subjects affected / exposed	2 / 79 (2.53%)	0 / 54 (0.00%)	3 / 52 (5.77%)
occurrences (all)	3	0	3
Pollakiuria			
subjects affected / exposed	4 / 79 (5.06%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences (all)	4	0	2
Renal failure			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences (all)	4	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 79 (5.06%)	1 / 54 (1.85%)	4 / 52 (7.69%)
occurrences (all)	4	2	5
Back pain			
subjects affected / exposed	12 / 79 (15.19%)	4 / 54 (7.41%)	2 / 52 (3.85%)
occurrences (all)	15	4	2
Bone pain			
subjects affected / exposed	7 / 79 (8.86%)	7 / 54 (12.96%)	8 / 52 (15.38%)
occurrences (all)	8	9	9
Muscle spasms			

subjects affected / exposed	3 / 79 (3.80%)	0 / 54 (0.00%)	1 / 52 (1.92%)
occurrences (all)	4	0	1
Muscular weakness			
subjects affected / exposed	1 / 79 (1.27%)	3 / 54 (5.56%)	4 / 52 (7.69%)
occurrences (all)	1	3	4
Musculoskeletal chest pain			
subjects affected / exposed	3 / 79 (3.80%)	0 / 54 (0.00%)	2 / 52 (3.85%)
occurrences (all)	4	0	2
Myalgia			
subjects affected / exposed	6 / 79 (7.59%)	1 / 54 (1.85%)	4 / 52 (7.69%)
occurrences (all)	7	1	8
Neck pain			
subjects affected / exposed	3 / 79 (3.80%)	0 / 54 (0.00%)	3 / 52 (5.77%)
occurrences (all)	3	0	3
Pain in extremity			
subjects affected / exposed	6 / 79 (7.59%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	6	1	5
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 79 (1.27%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	1	1	2
Oral herpes			
subjects affected / exposed	4 / 79 (5.06%)	0 / 54 (0.00%)	2 / 52 (3.85%)
occurrences (all)	5	0	2
Pneumonia			
subjects affected / exposed	2 / 79 (2.53%)	2 / 54 (3.70%)	0 / 52 (0.00%)
occurrences (all)	2	2	0
Rhinitis			
subjects affected / exposed	2 / 79 (2.53%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	2	1	2
Upper respiratory tract infection			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	3 / 52 (5.77%)
occurrences (all)	1	0	3
Urinary tract infection			
subjects affected / exposed	7 / 79 (8.86%)	3 / 54 (5.56%)	3 / 52 (5.77%)
occurrences (all)	10	3	3

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 79 (15.19%)	8 / 54 (14.81%)	7 / 52 (13.46%)
occurrences (all)	14	11	7
Dehydration			
subjects affected / exposed	1 / 79 (1.27%)	0 / 54 (0.00%)	3 / 52 (5.77%)
occurrences (all)	1	0	3
Fluid overload			
subjects affected / exposed	2 / 79 (2.53%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	2	1	1
Hyperglycaemia			
subjects affected / exposed	12 / 79 (15.19%)	2 / 54 (3.70%)	8 / 52 (15.38%)
occurrences (all)	23	4	22
Hyperkalaemia			
subjects affected / exposed	2 / 79 (2.53%)	1 / 54 (1.85%)	2 / 52 (3.85%)
occurrences (all)	2	1	2
Hypermagnesaemia			
subjects affected / exposed	3 / 79 (3.80%)	0 / 54 (0.00%)	2 / 52 (3.85%)
occurrences (all)	5	0	2
Hypernatraemia			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	1 / 52 (1.92%)
occurrences (all)	3	1	1
Hyperuricaemia			
subjects affected / exposed	5 / 79 (6.33%)	1 / 54 (1.85%)	4 / 52 (7.69%)
occurrences (all)	6	1	5
Hypoalbuminaemia			
subjects affected / exposed	3 / 79 (3.80%)	3 / 54 (5.56%)	4 / 52 (7.69%)
occurrences (all)	3	3	4
Hypocalcaemia			
subjects affected / exposed	11 / 79 (13.92%)	7 / 54 (12.96%)	6 / 52 (11.54%)
occurrences (all)	31	8	9
Hypokalaemia			
subjects affected / exposed	24 / 79 (30.38%)	14 / 54 (25.93%)	13 / 52 (25.00%)
occurrences (all)	50	28	23
Hypomagnesaemia			

subjects affected / exposed	17 / 79 (21.52%)	11 / 54 (20.37%)	6 / 52 (11.54%)
occurrences (all)	37	19	10
Hyponatraemia			
subjects affected / exposed	8 / 79 (10.13%)	2 / 54 (3.70%)	2 / 52 (3.85%)
occurrences (all)	11	2	3
Hypophosphataemia			
subjects affected / exposed	4 / 79 (5.06%)	3 / 54 (5.56%)	3 / 52 (5.77%)
occurrences (all)	10	3	4
Tumour lysis syndrome			
subjects affected / exposed	3 / 79 (3.80%)	1 / 54 (1.85%)	0 / 52 (0.00%)
occurrences (all)	3	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 February 2013	The Protocol was amended to update the exploratory objectives; Randomization plan and schedule of data monitoring committee (DMC) reviews updated; Number of study centers was increased from 50 to 106; Russia, and Israel were added; and Australia was removed, reflecting current strategy for enrolling the study. The choice of ifosfamide-carboplatin-etoposide (ICE) or dexamethasone-cytarabine-cisplatin (DHAP) as the chemotherapy regimen was made for each participant by the investigator as per institutional standard of care; Study-stopping criteria updated; Updated inclusion and exclusion criteria, withdrawal criteria, and specified replacement of participants criteria. Rituximab was added to ICE and DHAP. Updated treatment assignment and treatment regimen to improve study design. Added information related to MEDI-551 preparation and administration, dose modification for toxicity management, and concomitant medication to improve participants safety. The scheduled of procedures was updated.
11 March 2014	The minimum dose of methylprednisolone was administered before the first infusion of MEDI-551 was changed from 50 mg to 60 mg (or its equivalent), as this is the standard dose for this purpose; Three additional exploratory objectives were added; The total number of participants to be enrolled was increased from 170 to 180; Inclusion Criteria, exclusion Criteria, withdrawal Criteria, dose modification for toxicity management, permitted concomitant medications, schedule of study procedures were updated.
06 March 2015	Previous evaluations of "Full-body fluorodeoxyglucose-positron emission tomography (FDG-PET) scan and chest, abdomen, pelvis, and neck CT scan, unless participant discontinued for progressive disease (PD), tumor measurements, and disease response evaluation" at End of Treatment (+ 14 Days) and Day 60 Post EOT (+/- 7 Days) were changed to evaluation of "Chest, abdomen, pelvis, and neck CT scan, unless participant discontinued for PD" at End of Treatment and Day 90 Post EOT (+/- 14 Days) and evaluation of "Full-body FDG-PET scan (or CT-Pet scan)" at End of Treatment (+ 14 Days). The evaluation of Full-body FDG-PET scan was deleted from Long-term safety evaluations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported