Clinical trial results:
A Phase 2 Open-label Study of MEDI-551 and Bendamustine vs Rituximab and Bendamustine in Adults With Relapsed or Refractory CLL

Summary

EudraCT number	2011-002566-21
Trial protocol	DE BE IT PL
Global end of trial date	08 January 2016

Results information

Result version number	v1 (current)
This version publication date	05 May 2017
First version publication date	05 May 2017

Trial information

Trial identification

Sponsor protocol code	CD-ON-MEDI-551-1019

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01466153
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 Clinical Study Information Center, AstraZeneca, +1 1-877-240-9479, information.center@astrazenca.com
Scientific contact	AstraZeneca Clinical Study Information Center, AstraZeneca, +1 1-877-240-9479, information.center@astrazenca.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	08 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the ORR, including CR and PR, in adult subjects with progressive CLL, including small lymphocytic lymphoma (SLL) treated with up to 6 cycles of MEDI-551 in combination with bendamustine versus rituximab in combination with bendamustine.

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. Subjects 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	07 February 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 31
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	159
EEA total number of subjects	87

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)	72
From 65 to 84 years	87
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 182 subjects were screened in this study, of which 159 subjects were randomized.

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 + Bendamustine

Arm description:

Rituximab was administered on Day 2 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of rituximab in each cycle.

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

Dosage and administration details:

Bendamustine infusion was administered as 70 mg/m^2 for all 6 cycles.

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

Dosage and administration details:

Rituximab was administered at the dose of 375 mg/m^2 for first cycle and then 500 mg/m^2 for subsequent cycles.

Arm title	MEDI-551 2 mg/kg + Bendamustine

Arm description:

MEDI-551 2 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.

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

Dosage and administration details:

MEDI-551 infusion was administered as 2 mg/kg for all 6 cycles.

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

Dosage and administration details:

Bendamustine infusion was administered as 70 mg/m^2 for all 6 cycles.

Arm title	MEDI-551 4 mg/kg + Bendamustine

Arm description:

MEDI-551 4 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.

Arm type	Experimental
Investigational medicinal product name	Bendamustine
Investigational medicinal product code	
Other name	Treanda
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bendamustine infusion was administered as 70 mg/m^2 for all 6 cycles.

Investigational medicinal product name	MEDI-551
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

MEDI-551 infusion was administered as 4 mg/kg for all 6 cycles.

Number of subjects in period 1	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine
Started	62	36	61
Completed	33	12	36
Not completed	29	24	25
Withdrawal of Consent	2	-	-
Adverse event, non-fatal	14	13	17
Investigator Discretion	3	2	2
Other-Unspecified	6	4	2
Randomized-Not Treated	2	3	4
Disease Progression	2	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Rituximab + Bendamustine
Reporting group description:	
Rituximab was administered on Day 2 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of rituximab in each cycle.	
Reporting group title	MEDI-551 2 mg/kg + Bendamustine
Reporting group description:	
MEDI-551 2 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.	
Reporting group title	MEDI-551 4 mg/kg + Bendamustine
Reporting group description:	
MEDI-551 4 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.	

Reporting group values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine
Number of subjects	62	36	61
Age categorical Units: Subjects			
Adults (18-64 years)	34	17	21
From 65-84 years	28	19	40
Age Continuous Units: YEARS			
arithmetic mean	63.4	65.1	66.3
standard deviation	± 8.8	± 8.7	± 8.9
Gender, Male/Female Units: Subjects			
Female	16	14	18
Male	46	22	43

Reporting group values	Total		
Number of subjects	159		
Age categorical Units: Subjects			
Adults (18-64 years)	72		
From 65-84 years	87		
Age Continuous Units: YEARS			
arithmetic mean			
standard deviation	-		
Gender, Male/Female Units: Subjects			
Female	48		
Male	111		

End points

End points reporting groups

Reporting group title	Rituximab + Bendamustine
Reporting group description:	
Rituximab was administered on Day 2 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of rituximab in each cycle.	
Reporting group title	MEDI-551 2 mg/kg + Bendamustine
Reporting group description:	
MEDI-551 2 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.	
Reporting group title	MEDI-551 4 mg/kg + Bendamustine
Reporting group description:	
MEDI-551 4 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.	

Primary: Objective Response Rate

End point title	Objective Response Rate
End point description:	
ORR, defined as the proportion of subjects with complete response (CR) or partial response (PR) out of total number of subjects. Responses were assessed by using National Cancer Institute - Working Group guidelines on CLL. Intent-to-treat (ITT) population includes all subjects who are randomized into the study.	
End point type	Primary
End point timeframe:	
From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)	

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Percentage of Subjects				
number (confidence interval 95%)	59.7 (46.4 to 71.9)	52.8 (35.5 to 69.6)	63.9 (50.6 to 75.8)	

Statistical analyses

Statistical analysis title	Rituximab+bendamustine vs MEDI-551+bendamustine
Comparison groups	Rituximab + Bendamustine v MEDI-551 4 mg/kg + Bendamustine

Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4475
Method	Cochran-Mantel-Haenszel

Secondary: Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs) and Adverse Events of Special Interest (AESIs)

End point title	Number of Subjects with Treatment Emergent Adverse Events (TEAEs), Treatment Emergent Serious Adverse Events (TESAEs) and Adverse Events of Special Interest (AESIs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a subject who received study drug (MEDI-551). A serious adverse event (SAE) was an AE resulting in any of these outcomes: death; initial or prolonged inpatient hospitalization; life-threatening experience; persistent or significant disability/incapacity; congenital anomaly. Treatment-emergent are events between use of study drug and Day 90 that were absent before treatment or that worsened relative to pre-treatment state. An AESIs was one of scientific and medical interest specific to understanding of study product and may have required close monitoring and rapid communication by investigator to the sponsor. Treatment emergent AESIs were collected from the time of dosing through Day 90 after the last dose of study drug. Hepatic function abnormality and infusion reactions resulting in discontinuation were considered as AESIs in this study. The safety population includes all subjects who received any investigational product.

End point type	Secondary

End point timeframe:

From time of consent to 90 days post last dose

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	33	57	
Units: Subjects				
TEAEs	58	33	57	
TESAEs	19	16	19	
AESIs	2	4	6	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Clinical Laboratory Parameters Reported as AEs

End point title	Number of Subjects With Abnormal Clinical Laboratory Parameters Reported as AEs

End point description:

An abnormal laboratory finding which required an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation were reported as an adverse event. Laboratory evaluations (haematology, serum chemistry and

urinalysis) of blood and urine samples were performed. The safety population includes all subjects who received any investigational product.

End point type	Secondary

End point timeframe:

From time of consent to 90 days post last dose

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	33	57	
Units: Subjects				
Hyperbilirubinaemia	0	2	1	
Hypercalcaemia	1	0	0	
Hypercholesterolaemia	1	0	1	
Hyperglycaemia	4	2	1	
Hyperkalaemia	2	1	2	
Hyperlipidaemia	0	1	0	
Hypermagnesaemia	1	0	0	
Hyperphosphataemia	0	1	1	
Hypertriglyceridaemia	1	0	0	
Hyperuricaemia	3	5	2	
Hypoalbuminaemia	2	0	2	
Hypocalcaemia	3	1	1	
Hypokalaemia	6	1	4	
Hypomagnesaemia	2	2	1	
Hyponatraemia	2	1	0	
Alanine Aminotransferase Increased	1	0	3	
Aspartate Aminotransferase Increased	1	0	3	
Blood Alkaline Phosphatase Increased	1	1	2	
Blood Bilirubin Increased	0	1	1	
Blood Cholesterol Decreased	0	0	1	
Blood Creatinine Decreased	1	0	0	
Blood Creatinine Increased	1	2	1	
Blood Immunoglobulin G Decreased	0	0	1	
Blood Lactate Dehydrogenase Increased	4	0	0	
Blood Urea Increased	1	1	0	
Gamma-Glutamyltransferase Increased	1	1	2	
Hepatic enzyme Increased	1	0	0	
Anaemia	18	7	9	
Eosinophilia	0	0	1	
Lymphopenia	4	3	1	
Neutropenia	28	10	19	
Thromobocytopenia	12	6	10	
Activated Partial Thromboplastin Time Prolonged	2	0	0	
Blood Fibrinogen Increased	1	0	0	
Haemoglobin Decreased	0	1	0	
Lymphocyte Count Decreased	3	0	2	
Neutrophil Count Decreased	9	1	3	

Platelet Count Decreased	2	2	3	
Prothrombin Time Shortened	1	0	0	
Haematuria	0	2	1	
Proteinuria	0	1	0	
White Blood Cells in Urine	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Abnormal Vital Signs and Electrocardiogram Reported as AEs

End point title	Number of Subjects With Abnormal Vital Signs and Electrocardiogram Reported as AEs

End point description:

AEs observed in subjects with clinically significant ECG abnormalities were assessed. The safety population includes all subjects who received any investigational product.

End point type	Secondary

End point timeframe:

From time of consent to 90 days post last dose

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	60	33	57	
Units: Subjects				
Atrial Fibrillation	1	2	1	
Atrioventricular Block	1	0	0	
Palpitations	0	0	2	
Sinus Bradycardia	1	0	0	
Sinus Tachycardia	1	0	0	
Tachycardia	2	1	1	
Pyrexia	20	11	14	
Dyspnoea	9	2	4	
Dyspnoea Exertional	3	1	0	
Hypertension	1	0	1	
Hypotension	5	2	6	
Orthostatic Hypotension	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Complete Response Rate

End point title	Complete Response Rate

End point description:

Complete response was as per IWG was complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. Intent-to-treat (ITT) population includes all subjects who are randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Percentage of Subjects				
number (confidence interval 95%)	6.5 (1.8 to 15.7)	5.6 (0.7 to 18.7)	11.5 (4.7 to 22.2)	

Statistical analyses

Statistical analysis title	Rituximab+bendamustine vs MEDI-551+bendamustine
Comparison groups	Rituximab + Bendamustine v MEDI-551 4 mg/kg + Bendamustine
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3206
Method	Cochran-Mantel-Haenszel

Secondary: Minimal Residual Disease Negative Complete Response (CR) rate

End point title	Minimal Residual Disease Negative Complete Response (CR) rate

End point description:

The MRD-negative CR rate was defined as the percentage of subjects who achieved CR and became MRD-negative as determined by flow cytometry. CR as per International Working Group (IWG) was complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. Intent-to-treat (ITT) population includes all subjects who are randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Percentage of Subjects				
number (confidence interval 95%)	1.6 (0 to 8.7)	5.6 (0.7 to 18.7)	4.9 (1 to 13.7)	

Statistical analyses

Statistical analysis title	Rituximab+bendamustine vs MEDI551+bendamustine
Comparison groups	Rituximab + Bendamustine v MEDI-551 4 mg/kg + Bendamustine
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	Cochran-Mantel-Haenszel

Secondary: Time to Response

End point title	Time to Response

End point description:

Time to response was evaluated using the Kaplan-Meier method.
Intent-to-treat (ITT) population includes all subjects who are randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Months				
median (confidence interval 95%)	2.1 (1.9 to 2.6)	1.9 (1.7 to 2.9)	2.1 (1.9 to 3.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression (TTP)

End point title	Time to Disease Progression (TTP)

End point description:

TTP was defined as the time from onset of treatment with study drug until first evidence/diagnosis of progressive disease or – in the absence of any diagnosis of progressive disease – until the subject´s death. Intent-to-treat (ITT) population includes all subjects who are randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Months				
median (confidence interval 95%)	15.4 (12 to 27.2)	15 (5.8 to 23.3)	16.1 (12.5 to 24)	

Statistical analyses

Statistical analysis title	Rituximab+bendamustine vs MEDI-551+bendamustine
Comparison groups	Rituximab + Bendamustine v MEDI-551 4 mg/kg + Bendamustine
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9527
Method	Logrank

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS was measured from the start of treatment with study drug until the first documentation of disease progression or death due to any cause, whichever occurred first. Kaplan-Meier method was used for evaluation. Intent-to-treat (ITT) population includes all subjects who are randomized into the study.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Months				
median (confidence interval 95%)	14.8 (11.4 to 23.5)	15 (5.8 to 22.1)	16.1 (12.5 to 21.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was determined as the time from the start of treatment with study drug until death due to any cause. For subjects who were alive at the end of the study or lost to follow-up, OS was censored on the last date when the subject was known be alive. Kaplan-Meier method was used for evaluation. Intent-to-treat (ITT) population includes all subjects who are randomized into the study. In this section, 99999 represents that median was not reached and the upper and/or lower limit of the 95% confidence interval was not calculable because an insufficient number of subjects reached the event at the final time point for assessment.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

End point values	Rituximab + Bendamustine	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62	36	61	
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	99999 (23.9 to 99999)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects who developed detectable anti-drug antibodies (ADA)

End point title	Number of Subjects who developed detectable anti-drug antibodies (ADA)[1]

End point description:

A subject was considered ADA-positive across the study if they had a positive reading at any time point during the study. The safety population includes all subjects who received any investigational product. Subjects whom ADA samples were available were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

From treatment administration (Day 1) until disease progression, death, initiation of alternative therapy, withdrawal of consent, or end of study (up to 24 months)

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: ADA was analyzed only for 'MEDI-551 2 mg/kg + Bendamustine' and 'MEDI-551 4 mg/kg + Bendamustine' arms

End point values	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	57		
Units: Subjects	4	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Terminal Half life (t1/2) of MEDI-551

End point title	Terminal Half life (t1/2) of MEDI-551[2]

End point description:

Terminal phase elimination half-life (T1/2) was the time required for half of the drug to be eliminated from the serum. The safety population includes all subjects who received any investigational product. Subjects whom PK samples were available were analyzed for this endpoint.

End point type	Secondary

End point timeframe:

Pre-infusion and 1 hour post infusion on Days 2 and 8, Days 15 and 22 of cycle 1

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: ADA was analyzed only for 'MEDI-551 2 mg/kg + Bendamustine' and 'MEDI-551 4 mg/kg + Bendamustine' arms

End point values	MEDI-551 2 mg/kg + Bendamustine	MEDI-551 4 mg/kg + Bendamustine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	38		
Units: Day				
arithmetic mean (standard deviation)	17.2 (± 9.56)	22 (± 14.4)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 90 days after the last dose of study drug

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Rituximab + Bendamustine

Reporting group description:

Rituximab was administered on Day 2 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of rituximab in each cycle.

Reporting group title	MEDI-551 4 mg/kg + Bendamustine

Reporting group description:

MEDI-551 4 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.

Reporting group title	MEDI-551 2 mg/kg + Bendamustine

Reporting group description:

MEDI-551 2 mg/kg was administered on Days 2 and 8 of Cycle 1 and then on Day 1 of up to 5 subsequent 28-day cycle. Bendamustine was administered on Day 1 and Day 2 of every cycle (total 6 cycles). Bendamustine was administered before the administration of MEDI-551 in each cycle.

Serious adverse events	Rituximab + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	MEDI-551 2 mg/kg + Bendamustine
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 60 (31.67%)	19 / 57 (33.33%)	16 / 33 (48.48%)
number of deaths (all causes)	3	3	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bowen's disease			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Squamous cell carcinoma			

subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Inflammation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Female genital tract fistula			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			

subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Cough			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Epistaxis			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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	1 / 60 (1.67%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Respiratory tract inflammation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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			
Haemoglobin decreased			

subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Platelet count decreased			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 60 (1.67%)	5 / 57 (8.77%)	5 / 33 (15.15%)
occurrences causally related to treatment / all	1 / 1	5 / 14	5 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Atrioventricular block			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Cardiac failure			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Nervous system disorders			
Coma			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Syncope			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Abdominal lymphadenopathy			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Febrile neutropenia			
subjects affected / exposed	6 / 60 (10.00%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	5 / 6	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Neutropenia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Thrombocytopenia			

subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Uveitis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Intestinal obstruction			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Nausea			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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 / 60 (3.33%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Renal failure			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Bronchitis			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis norovirus			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Pneumonia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	4 / 33 (12.12%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonia pseudomonal			
subjects affected / exposed	0 / 60 (0.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia viral			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Rhinovirus infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Sepsis			
subjects affected / exposed	3 / 60 (5.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Skin infection			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Viral myocarditis			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Dehydration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	0 / 33 (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
Diabetes mellitus			

subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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
Tumour lysis syndrome			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	0 / 33 (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

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

Non-serious adverse events	Rituximab + Bendamustine	MEDI-551 4 mg/kg + Bendamustine	MEDI-551 2 mg/kg + Bendamustine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 60 (96.67%)	54 / 57 (94.74%)	31 / 33 (93.94%)
Vascular disorders			
Flushing			
subjects affected / exposed	4 / 60 (6.67%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	7	1	3
Hypotension			
subjects affected / exposed	4 / 60 (6.67%)	6 / 57 (10.53%)	2 / 33 (6.06%)
occurrences (all)	4	7	2
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	20 / 60 (33.33%)	7 / 57 (12.28%)	4 / 33 (12.12%)
occurrences (all)	31	17	4
Chest discomfort			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Chills			
subjects affected / exposed	11 / 60 (18.33%)	7 / 57 (12.28%)	6 / 33 (18.18%)
occurrences (all)	15	10	7
Fatigue			
subjects affected / exposed	18 / 60 (30.00%)	20 / 57 (35.09%)	14 / 33 (42.42%)
occurrences (all)	38	30	19
Oedema peripheral			

subjects affected / exposed	3 / 60 (5.00%)	7 / 57 (12.28%)	2 / 33 (6.06%)
occurrences (all)	4	7	3
Peripheral swelling			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	2	2	2
Pyrexia			
subjects affected / exposed	20 / 60 (33.33%)	14 / 57 (24.56%)	11 / 33 (33.33%)
occurrences (all)	27	23	14
Immune system disorders			
Cytokine release syndrome			
subjects affected / exposed	0 / 60 (0.00%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	0	2	1
Hypogammaglobulinaemia			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 60 (18.33%)	19 / 57 (33.33%)	5 / 33 (15.15%)
occurrences (all)	13	24	9
Dysphonia			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	2 / 33 (6.06%)
occurrences (all)	1	0	2
Dyspnoea			
subjects affected / exposed	9 / 60 (15.00%)	4 / 57 (7.02%)	2 / 33 (6.06%)
occurrences (all)	13	5	2
Dyspnoea exertional			
subjects affected / exposed	3 / 60 (5.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences (all)	4	0	1
Epistaxis			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Nasal congestion			
subjects affected / exposed	3 / 60 (5.00%)	3 / 57 (5.26%)	1 / 33 (3.03%)
occurrences (all)	4	4	1
Oropharyngeal pain			

subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Pleural effusion			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Pulmonary congestion			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	2	2	0
Upper-airway cough syndrome			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Rhinorrhoea			
subjects affected / exposed	3 / 60 (5.00%)	3 / 57 (5.26%)	1 / 33 (3.03%)
occurrences (all)	3	3	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	5 / 60 (8.33%)	4 / 57 (7.02%)	0 / 33 (0.00%)
occurrences (all)	5	5	0
Depression			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	3 / 33 (9.09%)
occurrences (all)	2	2	3
Insomnia			
subjects affected / exposed	6 / 60 (10.00%)	5 / 57 (8.77%)	2 / 33 (6.06%)
occurrences (all)	7	5	2
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	3 / 57 (5.26%)	0 / 33 (0.00%)
occurrences (all)	3	4	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	3 / 57 (5.26%)	0 / 33 (0.00%)
occurrences (all)	4	4	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	3	2	2
Blood creatinine increased			

subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	1	1	3
Blood lactate dehydrogenase increased			
subjects affected / exposed	4 / 60 (6.67%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences (all)	7	0	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	4	2	1
Lymphocyte count decreased			
subjects affected / exposed	3 / 60 (5.00%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	8	2	0
Neutrophil count decreased			
subjects affected / exposed	9 / 60 (15.00%)	3 / 57 (5.26%)	1 / 33 (3.03%)
occurrences (all)	16	6	3
Platelet count decreased			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	2 / 33 (6.06%)
occurrences (all)	4	2	2
Weight decreased			
subjects affected / exposed	5 / 60 (8.33%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences (all)	6	0	1
White blood cell count decreased			
subjects affected / exposed	3 / 60 (5.00%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	3	2	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 60 (1.67%)	3 / 57 (5.26%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Infusion related reaction			
subjects affected / exposed	14 / 60 (23.33%)	37 / 57 (64.91%)	21 / 33 (63.64%)
occurrences (all)	25	123	64
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	2 / 33 (6.06%)
occurrences (all)	1	0	2
Tachycardia			

subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	2	1	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 60 (8.33%)	7 / 57 (12.28%)	3 / 33 (9.09%)
occurrences (all)	5	10	6
Dysgeusia			
subjects affected / exposed	5 / 60 (8.33%)	1 / 57 (1.75%)	3 / 33 (9.09%)
occurrences (all)	7	1	3
Headache			
subjects affected / exposed	7 / 60 (11.67%)	5 / 57 (8.77%)	6 / 33 (18.18%)
occurrences (all)	9	6	9
Neuropathy peripheral			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	1	1	1
Paraesthesia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	3	2	0
Sciatica			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Restless legs syndrome			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	2	1	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 60 (30.00%)	9 / 57 (15.79%)	7 / 33 (21.21%)
occurrences (all)	64	13	20
Febrile neutropenia			
subjects affected / exposed	4 / 60 (6.67%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	5	1	0
Leukopenia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	26	1	0
Lymphopenia			

subjects affected / exposed	4 / 60 (6.67%)	1 / 57 (1.75%)	3 / 33 (9.09%)
occurrences (all)	26	5	7
Neutropenia			
subjects affected / exposed	28 / 60 (46.67%)	19 / 57 (33.33%)	10 / 33 (30.30%)
occurrences (all)	78	58	44
Thrombocytopenia			
subjects affected / exposed	12 / 60 (20.00%)	10 / 57 (17.54%)	5 / 33 (15.15%)
occurrences (all)	76	21	8
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	1	2	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	4	1	2
Abdominal distension			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	1	1	2
Abdominal pain			
subjects affected / exposed	7 / 60 (11.67%)	7 / 57 (12.28%)	3 / 33 (9.09%)
occurrences (all)	8	15	3
Abdominal pain upper			
subjects affected / exposed	5 / 60 (8.33%)	3 / 57 (5.26%)	1 / 33 (3.03%)
occurrences (all)	6	3	1
Constipation			
subjects affected / exposed	20 / 60 (33.33%)	10 / 57 (17.54%)	9 / 33 (27.27%)
occurrences (all)	23	11	11
Diarrhoea			
subjects affected / exposed	13 / 60 (21.67%)	11 / 57 (19.30%)	5 / 33 (15.15%)
occurrences (all)	20	15	5
Dyspepsia			

subjects affected / exposed	1 / 60 (1.67%)	4 / 57 (7.02%)	2 / 33 (6.06%)
occurrences (all)	1	5	2
Flatulence			
subjects affected / exposed	3 / 60 (5.00%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences (all)	3	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 60 (5.00%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	4	2	0
Gingival pain			
subjects affected / exposed	1 / 60 (1.67%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	1	1	1
Haemorrhoids			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	29 / 60 (48.33%)	29 / 57 (50.88%)	13 / 33 (39.39%)
occurrences (all)	45	47	23
Vomiting			
subjects affected / exposed	13 / 60 (21.67%)	7 / 57 (12.28%)	7 / 33 (21.21%)
occurrences (all)	14	7	8
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	0	2	2
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	2 / 33 (6.06%)
occurrences (all)	2	2	2
Erythema			
subjects affected / exposed	4 / 60 (6.67%)	6 / 57 (10.53%)	0 / 33 (0.00%)
occurrences (all)	4	6	0
Hyperhidrosis			
subjects affected / exposed	7 / 60 (11.67%)	2 / 57 (3.51%)	3 / 33 (9.09%)
occurrences (all)	7	3	3
Night sweats			

subjects affected / exposed	5 / 60 (8.33%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences (all)	6	0	1
Pruritus			
subjects affected / exposed	9 / 60 (15.00%)	6 / 57 (10.53%)	5 / 33 (15.15%)
occurrences (all)	13	6	9
Rash erythematous			
subjects affected / exposed	3 / 60 (5.00%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences (all)	3	0	0
Rash			
subjects affected / exposed	4 / 60 (6.67%)	8 / 57 (14.04%)	4 / 33 (12.12%)
occurrences (all)	7	10	6
Rash pruritic			
subjects affected / exposed	1 / 60 (1.67%)	3 / 57 (5.26%)	0 / 33 (0.00%)
occurrences (all)	1	3	0
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	4 / 60 (6.67%)	0 / 57 (0.00%)	0 / 33 (0.00%)
occurrences (all)	5	0	0
Haematuria			
subjects affected / exposed	0 / 60 (0.00%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	0	1	2
Pollakiuria			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	1	2	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 60 (11.67%)	4 / 57 (7.02%)	1 / 33 (3.03%)
occurrences (all)	7	4	1
Back pain			
subjects affected / exposed	5 / 60 (8.33%)	5 / 57 (8.77%)	4 / 33 (12.12%)
occurrences (all)	5	8	4
Bone pain			
subjects affected / exposed	4 / 60 (6.67%)	5 / 57 (8.77%)	1 / 33 (3.03%)
occurrences (all)	4	9	1
Muscle spasms			

subjects affected / exposed	5 / 60 (8.33%)	7 / 57 (12.28%)	1 / 33 (3.03%)
occurrences (all)	9	9	1
Muscular weakness			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	3	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 60 (0.00%)	2 / 57 (3.51%)	2 / 33 (6.06%)
occurrences (all)	0	2	2
Musculoskeletal pain			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	2 / 33 (6.06%)
occurrences (all)	2	2	2
Myalgia			
subjects affected / exposed	3 / 60 (5.00%)	4 / 57 (7.02%)	0 / 33 (0.00%)
occurrences (all)	6	5	0
Neck pain			
subjects affected / exposed	1 / 60 (1.67%)	2 / 57 (3.51%)	2 / 33 (6.06%)
occurrences (all)	1	2	2
Pain in extremity			
subjects affected / exposed	4 / 60 (6.67%)	3 / 57 (5.26%)	2 / 33 (6.06%)
occurrences (all)	4	3	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	4 / 60 (6.67%)	4 / 57 (7.02%)	3 / 33 (9.09%)
occurrences (all)	4	4	4
Conjunctivitis			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	2	1	0
Lung infection			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	2	1	1
Nasopharyngitis			
subjects affected / exposed	3 / 60 (5.00%)	4 / 57 (7.02%)	2 / 33 (6.06%)
occurrences (all)	5	5	3
Pneumonia			
subjects affected / exposed	0 / 60 (0.00%)	4 / 57 (7.02%)	1 / 33 (3.03%)
occurrences (all)	0	5	1

Rhinitis			
subjects affected / exposed	2 / 60 (3.33%)	0 / 57 (0.00%)	2 / 33 (6.06%)
occurrences (all)	2	0	2
Sinusitis			
subjects affected / exposed	3 / 60 (5.00%)	6 / 57 (10.53%)	1 / 33 (3.03%)
occurrences (all)	3	6	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 60 (6.67%)	1 / 57 (1.75%)	3 / 33 (9.09%)
occurrences (all)	4	1	4
Urinary tract infection			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	0 / 33 (0.00%)
occurrences (all)	8	3	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 60 (21.67%)	6 / 57 (10.53%)	4 / 33 (12.12%)
occurrences (all)	17	6	4
Dehydration			
subjects affected / exposed	1 / 60 (1.67%)	0 / 57 (0.00%)	3 / 33 (9.09%)
occurrences (all)	1	0	3
Hyperglycaemia			
subjects affected / exposed	4 / 60 (6.67%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	4	1	3
Hyperkalaemia			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	1 / 33 (3.03%)
occurrences (all)	2	3	1
Hyperuricaemia			
subjects affected / exposed	3 / 60 (5.00%)	2 / 57 (3.51%)	5 / 33 (15.15%)
occurrences (all)	5	2	6
Hypoalbuminaemia			
subjects affected / exposed	2 / 60 (3.33%)	2 / 57 (3.51%)	0 / 33 (0.00%)
occurrences (all)	3	2	0
Hypocalcaemia			
subjects affected / exposed	3 / 60 (5.00%)	1 / 57 (1.75%)	1 / 33 (3.03%)
occurrences (all)	3	1	1
Hypokalaemia			

subjects affected / exposed	6 / 60 (10.00%)	4 / 57 (7.02%)	1 / 33 (3.03%)
occurrences (all)	7	4	1
Hypomagnesaemia			
subjects affected / exposed	2 / 60 (3.33%)	1 / 57 (1.75%)	2 / 33 (6.06%)
occurrences (all)	2	1	2
Hyponatraemia			
subjects affected / exposed	2 / 60 (3.33%)	0 / 57 (0.00%)	1 / 33 (3.03%)
occurrences (all)	2	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2012	- The bendamustine dose used in another CLL study was corrected from 90 mg/m^2 to 70 mg/m^2 - Inclusion Criterion were revised from stating study subjects must be eligible for chemotherapy to stating that study subjects must be eligible for bendamustine/rituximab therapy to be included in the study - Inclusion Criterion for description of symptomatic disease was expanded to include enlarging adenopathy and increasing cytopenias. The additional indications were added in accordance with the diagnostic, treatment and response criteria in Hallek et al, 2008. - Exclusion Criterion for describing excluded prior therapies was removed to correctly state the intention of the sponsor to permit any prior therapy. - Exclusion Criterion was added to exclude any subject who had exposure to bendamustine within 180 days before study enrollment. There is a high likelihood that patients who have received bendamustine in the last 180 days are resistant to it; therefore it is unethical to provide the same therapy - The lists of acceptable treatments for infusion reactions and for pretreatment of subjects who experienced infusion reactions were revised. In addition to acetaminophen and antihistamines, corticosteroids are permitted. Steroids are considered standard, acceptable adjunctive treatments for infusion reactions. - The listed procedure of MEDI-551 PK sample was revised to list pre-dose and post-dose samples separately to emphasize that pre-dose and post-dose samples must be taken on Day 1 of each cycle and on Day 8 of Cycle 1. - The procedure of pregnancy test (urine β hCG) and in visit descriptions was revised to include the restriction to women of childbearing potential. This was done as an aid to the investigator staff and to avoid needless testing. - Information about the composition and operation of the study DMC was revised to reflect the current plan.
07 July 2012	Exploratory objective changed from, "To conduct exploratory pharmacogenomic analyses" to "To examine the association of FcγR polymorphisms with MEDI-551 treatment effects and complete elimination of minimal residual disease. Clarified primary endpoint ORR, is defined as the proportion of subjects with CR or PR according to the International Workshop on Chronic Lymphocytic Leukemia's update of the National Cancer Institute - Working Group 1996 guidelines on CLL. The dosing section updated with Phase 1 protocol MI-CP204 results. Changes to inclusion criteria: Eligible subjects must have had a minimum of one course of chemotherapy with rituximab, because rituximab is considered the standard of care for CLL; Confirmation of CLL and presence of symptomatic disease defined in more detail; The definition of adequate hematological function criterion for absolute neutrophil count (ANC) was lowered from a minimum of 1,500/mm^3 to 1,000/mm^3; CLL is a disease that commonly presents with cytopenias resulting from disease-overloaded marrow with limited hematopoietic function; the majority of subjects present with ANC below 1500/mm3; Therefore, the ANC requirement has been lowered to permit increased access of study drug to subjects; Investigators are permitted to supplement subjects with GCSF at their discretion to minimize the duration of neutropenia so as to minimize the risk of infection; Serum creatinine limits modified to ≤ 1.5 mg/dL or calculated creatinine clearance ≥ 60 mL/minute as determined by the Cockcroft-Gault equation to provide limits more appropriate to this population. Changes to exclusion criteria: Subjects suspected of having Richter's transformation or high-grade disease, current pregnancy or lactation and history of yellow fever vaccination; cautions regarding potential of interaction of bendamustine with CYP1A2 inhibitors and inducers of CYP1A2 were added; the DMC's plan for recommendation for the dose selected (2 mg/kg or 4 mg/kg) was clarified.

09 May 2013	-All subjects were given oral acetaminophen & diphenhydramine methylprednisolone IV 30-60 min prior to first infusion of MEDI-551 was added. -MEDI-551/rituximab on Day2 of Cycle1,followed by 2nd dose of bendamustine. -Prophylaxis before rituximab infusion was at investigator's discretion added. -Potential risks of MEDI-551 were updated. 3 exploratory objectives were added -Inclusion Criteria •Recovered from any acute side effects resulting from previous anticancer therapy was removed. •Hemoglobin & platelet count lowered to ≥8g/dL & ≥50000/mm^3. Alternative hemoglobin level & platelet count were eliminated for simplify entry requirements. •Adequate organ function was revised: bilirubin level revised from <2mg/dL to <2×ULN, calculated creatinine clearance lowered to ≥50 mL/min. •Use of birth control after study drug was extend beyond 90 days. •Duration of contraception was modified to at least Day1 through 90 days after the last dose of study drug. -Exclusion Criteria •Was changed to History of Grade 4 anaphylactic reaction to any component of MEDI-551, rituximab/bendamustine formulations Grade of anaphylactic reaction was defined. •Exclusions related to hepatitis B&C was split into 2 exclusion criteria; Exclusion relates to hepatitis C. -Conditions were added to reasons for permanent discontinuation from study drug: •Grade 4 febrile neutropenia or sepsis, regardless of attribution & treatment arm. •Grade 3 or higher toxicity attributed to MEDI-551. •Delay in start of a cycle by greater than 7 days. •Grade 4 infusion reaction by MEDI-551. -Subjects received mandatory premedication before the first dose of MEDI-551 was restated. Other premedication was permitted as clinically indicated, or in accordance with institutional guidelines for administration of a MAb. -Prophylactic antibiotics allowed & recommended in subjects with medical history of recurrent or severe infections." -The schedule of study procedures was updated -Futility analysis added.
19 October 2015	Details about Blinded central independent review was removed from rationale from "Study Design, dose and control group" as well as the section on Blinding. The following text was removed from the planned analysis section: "Two formal analyses are planned for the study. The first analysis will be performed once all subjects have discontinued from the study-specific chemoimmunotherapies. This will occur approximately 6 months post randomization of the last subject randomized into the study."

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported