Clinical trial results:
Phase II randomized study with R-DHAP +/- Bortezomib as induction therapy in relapsed/refractory Diffuse Large B-cell Lymphoma (DLBCL) patients eligible to transplantation. BR-DHAP versus R-DHAP

Summary

EudraCT number	2012-000924-16
Trial protocol	IT
Global end of trial date	20 November 2020

Results information

Result version number	v1 (current)
This version publication date	22 May 2022
First version publication date	22 May 2022

Trial information

Trial identification

Sponsor protocol code	FIL_Veral12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01805557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fondazione Italiana Linfomi (FIL) ONLUS
Sponsor organisation address	Piazza Turati 5, Alessandria, Italy,
Public contact	Segreteria, Fondazione Italiana Linfomi ONLUS, +39 0131/033151, segreteriadirezione@filinf.it
Scientific contact	Segreteria, Fondazione Italiana Linfomi ONLUS, +39 0131/033151, segreteriadirezione@filinf.it

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 March 2019
Global end of trial reached?	Yes
Global end of trial date	20 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective is to assess whether the experimental treatment achieves an absolute increase of the CR proportion of at least 20% (from 30% to 50%) with respect to the standard treatment.

Protection of trial subjects:

Therapy may be interrupted for one of the following reasons: Adverse event(s); Abnormal laboratory value(s); Abnormal test procedure result(s); Protocol deviation; Subject withdrew consent; Lost to follow-up; Administrative problems; Death; Initiation of new cancer therapy; Disease progression.

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong and Somerset West amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study will be conducted according to the ICH Guideline for Good Clinical Practice.
The protocol and its annexes are subject to review and approval by the competent Independent Ethics Committee(s) ("IEC").

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 February 2013
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	Italy: 108
Worldwide total number of subjects	108
EEA total number of subjects	108

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)	106
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One hundred and eight (108) patients recruited in Italy from February 4th, 2013, with date of last completed at November 20th, 2020

Pre-assignment

Screening details:

After providing written informed consent, patients will be evaluated for eligibility during a 28-day screening period. If they continue to meet eligibility criteria, they will be randomized to receive the first dose of BR-DHAP or R-DHAP .

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

After stratification, all patients will be randomized, with a 1:1 ratio, into two arms. The web-based randomization procedure will be completely concealed to researchers. After registering the patient at the study dedicated area, each patient will be assigned a unique ID code. The randomization procedure, based on computer generated random sequence in blocks of variable size and in random order, will be accessible, 24/24h a day, only after the baseline forms have been completely filled out.

Arms

Are arms mutually exclusive?	Yes
Arm title	ARM A R-DHAP

Arm description:

R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation

Arm type	Standard salvage therapy
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

• Rituximab 375 mg/sqm iv day 0 or 1
• Rituximab 375 mg/sqm iv 24 hours before apheresis as purging in vivo during second courses of therapy

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

Dosage and administration details:

100 mg/sqm iv day 1 in 6-hours infusion (a 3-hours infusion is allowed)

Investigational medicinal product name	Dexametasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

40 mg day 1-4

Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II o III cycle R-DHAP)

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2000 mg/sqm in 3-hours infusion iv day 2 and day 3

Arm title	ARM B Bortezomib R-DHAP

Arm description:

Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation

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

Dosage and administration details:

• Rituximab 375 mg/sqm iv day 0 or 1
• Rituximab 375 mg/sqm iv 24 hours before apheresis as purging in vivo during second courses of therapy

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

Dosage and administration details:

100 mg/sqm iv day 1 in 6-hours infusion (a 3-hours infusion is allowed)

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2000 mg/sqm in 3-hours infusion iv day 2 and day 3

Investigational medicinal product name	Dexametasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 40 mg day 1-4	
Investigational medicinal product name	Pegfilgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Pegfilgrastim 6 mg sc monodose 24 hours after the end of chemotherapy or G-CSF from day 5 till stem cell harvest during mobilization's course (II o III cycle R-DHAP)	
Investigational medicinal product name	Bortezomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Bortezomib SC 1.5 mg/sqm day 1, day 4	

Number of subjects in period 1	ARM A R-DHAP	ARM B Bortezomib R-DHAP
Started	54	54
Completed	25	29
Not completed	29	25
Toxicity	-	1
Death	-	2
Other	-	2
Progression	25	16
Clinician decision	1	-
Adverse event	2	3
Early withdrawl	-	1
Stable disease	1	-

Baseline characteristics

Reporting groups	
Reporting group title	ARM A R-DHAP
Reporting group description:	
R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation	
Reporting group title	ARM B Bortezomib R-DHAP
Reporting group description:	
Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation	

Reporting group values	ARM A R-DHAP	ARM B Bortezomib R-DHAP	Total
Number of subjects	54	54	108
Age categorical Units: Subjects			
<50	15	18	33
50-59	17	17	34
60+	22	18	40
Not recorded	0	1	1
Gender categorical Units: Subjects			
Female	24	19	43
Male	30	34	64
Not recorded	0	1	1
Disease status Units: Subjects			
Refractory/Progressed	27	27	54
Relapsed	27	26	53
Not recorded	0	1	1
First line chemotherapy Units: Subjects			
R-CHOP	42	48	90
R-mega CHOP	1	1	2
Other	11	4	15
Not recorded	0	1	1
Systemic Symptoms Units: Subjects			
Systemic Symptoms A	36	37	73
Systemic Symptoms B	18	13	31
Missing	0	3	3
Not recorded	0	1	1
Ann Arbor classification Units: Subjects			
Stage I	3	1	4
Stage II	10	9	19
Stage III	17	13	30
Stage IV	23	30	53
Missing	1	0	1

Not recorded	0	1	1
Patients with extranodal sites Units: Subjects			
No	23	19	42
Yes	31	33	64
Missing	0	1	1
Not recorded	0	1	1
IPI Units: Subjects			
Score 1	12	15	27
Score 2	17	18	35
Score 3	14	12	26
Score 4	7	2	9
Score 5	1	1	2
Missing	3	5	8
Not recorded	0	1	1
Age-Adjusted IPI Units: Subjects			
Score 1	18	23	41
Score 2	23	20	43
Score 3	10	4	14
Missing	3	6	9
Not recorded	0	1	1
Performance Status (ECOG) Units: Subjects			
ECOG 0	30	37	67
ECOG 1	14	11	25
ECOG 2	9	5	14
Missing	1	0	1
Not recorded	0	1	1
Supra-diaphragmatic nodal sites Units: Subjects			
Yes	41	34	75
No	13	19	32
Not recorded	0	1	1
Sub-diaphragmatic nodal sites Units: Subjects			
Yes	35	36	71
No	19	17	36
Not recorded	0	1	1
Extranodal sites Units: Subjects			
Yes	27	33	60
No	27	20	47
Not recorded	0	1	1
Bone marrow involvement Units: Subjects			
Positive	4	4	8
Negative	42	43	85
Not evaluable	8	6	14
Not recorded	0	1	1

Leukemia Units: Subjects			
No	0	3	3
Yes	53	50	103
Missing	1	0	1
Not recorded	0	1	1
Mediastinic syndrome Units: Subjects			
No	50	52	102
Yes	3	1	4
Missing	1	0	1
Not recorded	0	1	1

End points

End points reporting groups

Reporting group title	ARM A R-DHAP
Reporting group description:	
R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation	
Reporting group title	ARM B Bortezomib R-DHAP
Reporting group description:	
Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation	

Primary: Complete Response (CR) Rate

End point title	Complete Response (CR) Rate
End point description:	
End point type	Primary
End point timeframe:	
Evaluated by PET scan after four cycles of R-DHAP ± Bortezomib before transplantation according to Cheson criteria. At the end of the induction phase (6 months)	

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: CR proportion				
number (not applicable)	27.78	26.42		

Statistical analyses

Statistical analysis title	Complete Response (CR) Rate
Comparison groups	ARM A R-DHAP v ARM B Bortezomib R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.563 [2]
Method	Chi-squared

Notes:

[1] - Primary objective is to assess whether the experimental treatment achieves an absolute increase of the CR proportion of at least 20% (from 30% to 50%) with respect to the standard treatment.
[2] - The proportion of CR have been compared between the two arms with a chi-square test, without continuity correction, using a test critical value of 1.282 (corresponding to a one-sided p-value of 0.10) to reject the null hypothesis.

Secondary: Overall Response Rate (ORR) prior to consolidation

End point title	Overall Response Rate (ORR) prior to consolidation

End point description:

Overall response rate (ORR): a patient is defined as a responder if he has a complete or partial response, evaluated by PET/TC, after four cycles of R-DHAP ± Bortezomib

End point type	Secondary

End point timeframe:

Evaluated by PET/TC, after four cycles of R-DHAP ± Bortezomib, at the end of the induction phase (6 months).

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: ORR				
number (not applicable)	35.19	35.85		

Statistical analyses

Statistical analysis title	Overall Response Rate (ORR)
Comparison groups	ARM B Bortezomib R-DHAP v ARM A R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4714 [3]
Method	Chi-squared

Notes:

[3] - One sided P-value

Secondary: Progression free survival (PFS)

End point title	Progression free survival (PFS)

End point description:

Progression free survival (PFS): measured from the date of randomization to the date of disease progression, relapse or death from any cause. Responding patients and patients who are lost to follow up will be censored at their last assessment date. For PFS minimum follow up time required for all patients is 2 years.

End point type	Secondary

End point timeframe:

24 months

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Kaplan Meier estimates				
number (confidence interval 95%)	29.41 (17.94 to 41.83)	40.99 (27.67 to 53.84)		

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)

Statistical analysis description:

The time-to-event functions have been estimated by the Kaplan-Meier product-limit method and the difference between arms have been tested with the log-rank test, stratified by disease status.

Comparison groups	ARM A R-DHAP v ARM B Bortezomib R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0594 [4]
Method	Logrank

Notes:

[4] - Log-rank test, stratified by disease status.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS: measured from the date of randomization to the date of death from any cause. Patients alive at the time of the final analysis have been censored at the date of the last contact. OS minimum follow up time required for all patients is 2 years.

End point type	Secondary

End point timeframe:

24 months

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Kaplan Meier estimates				
number (confidence interval 95%)	43.02 (28.98 to 56.3)	52.08 (37.8 to 64.56)		

Statistical analyses

Statistical analysis title	Overall Survival (OS)

Statistical analysis description:

The time-to-event functions have been estimated by the Kaplan-Meier product-limit method and the difference between arms have been tested with the log-rank test, stratified by disease status.

Comparison groups	ARM B Bortezomib R-DHAP v ARM A R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.242 [5]
Method	Logrank

Notes:

[5] - Log-rank test, stratified by disease status.

Secondary: Toxicity

End point title	Toxicity

End point description:

Toxicity: severe, life- threatening, fatal (grade 3, 4 and 5) and/or serious adverse events are defined according to "Common Terminology Criteria for Adverse Events" (CTCAE), version 4.0, during therapy

End point type	Secondary

End point timeframe:

12 months

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: Toxicity incidence				
number (not applicable)				
Any hematological toxicity of grade >=3	88.89	90.57		
Any extra-hematological toxicity of grade >=3	25.93	32.08		

Statistical analyses

Statistical analysis title	Any hematological toxicity of grade >=3
Comparison groups	ARM A R-DHAP v ARM B Bortezomib R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.775 [6]
Method	Chi-squared

Notes:

[6] - Pearson chi2 test, within 4 cycles

Statistical analysis title	Any extra-hematological toxicity of grade >=3

Comparison groups	ARM A R-DHAP v ARM B Bortezomib R-DHAP
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.483 [7]
Method	Chi-squared

Notes:

[7] - Pearson chi2 test, within 4 cycles

Secondary: Mobilizing potential

End point title	Mobilizing potential

End point description:

Mobilizing potential: amount of CD34 + stem cell collected /Kg

End point type	Secondary

End point timeframe:

6 months

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34[8]	35[9]		
Units: CD34 + stem cell collected /Kg				
median (inter-quartile range (Q1-Q3))	6.43 (4.40 to 9.11)	6.78 (5.00 to 9.68)		

Notes:

[8] - Missing 4

[9] - Missing 4

Statistical analyses

Statistical analysis title	Mobilizing potential
Comparison groups	ARM A R-DHAP v ARM B Bortezomib R-DHAP
Number of subjects included in analysis	69
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.526
Method	Kruskal-wallis

Secondary: Number of Patients completing ASCT

End point title	Number of Patients completing ASCT

End point description:

Proportion of randomized patients successfully completing ASCT

End point type	Secondary

End point timeframe:

12 months

End point values	ARM A R-DHAP	ARM B Bortezomib R-DHAP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	54	53		
Units: percent				
number (not applicable)				
Autologus	37.04	35.85		
Allogenic	7.41	13		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

12 months

Adverse event reporting additional description:

Severe, life- threatening, fatal (grade 3, 4 and 5) and/or serious adverse events
All toxic reactions will be annotated and their grade will be assessed according to the Common Toxicity Criteria (CTC) Version

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4

Reporting groups

Reporting group title	ARM A R-DHAP

Reporting group description:

R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + R-DHAP x 2, restaging with PET evaluation

Reporting group title	ARM B Bortezomib R-DHAP

Reporting group description:

Bortezomib + R-DHAP x 2, restaging, mobilization and harvest of peripheral stem cell + Bortezomib + R-DHAP x 2, restaging with PET evaluation

Serious adverse events	ARM A R-DHAP	ARM B Bortezomib R-DHAP	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 54 (18.52%)	18 / 53 (33.96%)	
number of deaths (all causes)	31	29	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Progression disease			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary adenocarcinoma			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension and hypertension			

subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Neuropathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncopal episode			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 54 (1.85%)	3 / 53 (5.66%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fatigue			

subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 54 (1.85%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emesis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal mucositis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyloric prothesis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung adenocarcinoma			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia			
subjects affected / exposed	1 / 54 (1.85%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 54 (1.85%)	0 / 53 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney failure			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute renal failure			
subjects affected / exposed	1 / 54 (1.85%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute rhabdomyolysis			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
CMV reactivation			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	0 / 54 (0.00%)	2 / 53 (3.77%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salmonella infection			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Septic shock			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Creatinine increased			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ARM A R-DHAP	ARM B Bortezomib R-DHAP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 54 (88.89%)	48 / 53 (90.57%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	2	
Thrombosis/Embolism			
subjects affected / exposed	1 / 54 (1.85%)	1 / 53 (1.89%)	
occurrences (all)	1	2	
Nervous system disorders			
Motor neuropathy			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Sensory neuropathy			
subjects affected / exposed	0 / 54 (0.00%)	3 / 53 (5.66%)	
occurrences (all)	0	4	
Blood and lymphatic system disorders			
GB			
subjects affected / exposed	17 / 54 (31.48%)	25 / 53 (47.17%)	
occurrences (all)	32	55	
Granulocytes			
subjects affected / exposed	38 / 54 (70.37%)	34 / 53 (64.15%)	
occurrences (all)	87	81	

Hemoglobin			
subjects affected / exposed	14 / 54 (25.93%)	15 / 53 (28.30%)	
occurrences (all)	21	23	
Platelets			
subjects affected / exposed	45 / 54 (83.33%)	48 / 53 (90.57%)	
occurrences (all)	107	121	
General disorders and administration site conditions			
Mucositis			
subjects affected / exposed	0 / 54 (0.00%)	2 / 53 (3.77%)	
occurrences (all)	0	2	
Fever in documented homeless neutropenia and/or isolation			
subjects affected / exposed	1 / 54 (1.85%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Other			
subjects affected / exposed	8 / 54 (14.81%)	6 / 53 (11.32%)	
occurrences (all)	11	12	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Kidney failure			
subjects affected / exposed	3 / 54 (5.56%)	2 / 53 (3.77%)	
occurrences (all)	3	2	
Infections and infestations			
Bacterial infection			
subjects affected / exposed	1 / 54 (1.85%)	3 / 53 (5.66%)	
occurrences (all)	1	3	
Viral infectione			
subjects affected / exposed	0 / 54 (0.00%)	1 / 53 (1.89%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			

Hyperglycemia subjects affected / exposed occurrences (all)	1 / 54 (1.85%) 1	1 / 53 (1.89%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 September 2014	The main changes concerned the title of the study, because the primary objective is the evaluation of the complete response after 4 cycles of RDHAP vs BRDHAP induction. In fact, the protocol accepts a subsequent consolidation (off-protocol) with autologous or allogeneic transplantation and the previous title also included the evaluation of consolidation. In addition, some errors in the previous version have been corrected and the treatment of patients who have undergone first-line GA-CHOP is allowed. The information sheets and informed consents have been adapted to the contents of the amendment. In addition, the changes requested by the Ethics Committees of the satellite centers during the local evaluation phase have been incorporated into the information sheets. The new IB (ver. 17) of the drug under study has also been sent.
20 October 2016	The amendment relates to the risks and adverse effects section of the disclosure following the issuance of Investigator Brochure 18. The enrolment period has also been extended and the insurance policy has been adjusted accordingly. The reference for centralized histological reviews has also been updated. The information sheets and informed consents have been adapted to the contents of the amendment
11 November 2019	Due to the retirement of Dr. Umberto Vitolo, the Principal Investigator of the coordinating center of Turin (A.O.U. Città della Salute e della Scienza di Torino - S.C. Hematology) has been changed. The new PI designated is Dr. Barbara Botto.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported