Clinical trial results:
Phase II study of ageadjusted RBAC (Rituximab, Bendamustine, Cytarabine) as induction therapy in older patients with Mantle Cell Lymphoma (MCL)

Summary

EudraCT number	2011-005739-23
Trial protocol	IT
Global end of trial date	11 September 2017

Results information

Result version number	v1 (current)
This version publication date	25 August 2022
First version publication date	25 August 2022

Trial information

Trial identification

Sponsor protocol code	FIL-RBAC500

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01662050
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	15 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2014
Global end of trial reached?	Yes
Global end of trial date	11 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to determine the activity (complete remission rate according to Cheson 2007 criteria) and safety of ageadjusted RituximabBendamustineCytarabine (RBAC500) regimen at the end of treatment in older untreated patients with MCL.

Protection of trial subjects:

1) Occurrence of relevant toxicity for two subsequent or consecutive cycles (the protocol allows for a 25% reduction of drugs dosage when an episode of relevant toxicity occurs for the first time)
2) Grade 3-4 hematological or nonhematological toxicity on day +28 of a cycle not resolving within two weeks (+28 days+14 days since last cycle)
3) Grade 3-4 hematological or nonhematological toxicity on day +28 of a cycle after the 25% dose reduction
4) Patient refusal to procede with further cycles due to perceived excessive toxicity
5) Any unpredictable drug related event that suggests against study continuation

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 March 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	Italy: 57
Worldwide total number of subjects	57
EEA total number of subjects	57

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)	5
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed at 09/11/2017.
We adopted the Bryant and Day two-stage design for calculating the sample size. At the end of the first stage, 19 pts, the trial will be stopped if there are <= 8/19 responses and >=7/19 toxicities. Otherwise, further 38 pts will be enrolled.

Pre-assignment

Screening details:

Patients with an established histological diagnosis of MCL on lymph-node biopsy, bone marrow biopsy, or extranodal tissue are eligible for entry into the study.
All patients must satisfy all the inclusion criteria and none of exclusion criteria.

Period 1

Period 1 title	Baseline (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

Patients will be treated with at least two cycles of RBAC500, recycling every 28 days.
Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment.

Arm type	Single arm study
Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dose administered: 375 mg/m2
The amount (in mg) of Rituximab to be administered will be determined based on body surface area (BSA) using a standard calculation.
Patients presenting with high lymphocyte count in the peripheral blood, defined as total lymphocytes >20000/mmc will receive the dose of Rituximab postponed after chemotherapy, 4 days after the completion of the last dose of Ara-C (+8 from the start of therapy). Patients that still have elevated lymphocyte count at that time point will avoid Rituximab for the first cycle, maintaining the same measures for subsequent cycles.

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

Dosage and administration details:

Bendamustine will be administered intravenously at a dose of 70 mg/m2 and as a 30-60 minute infusion on Days 2 and 3.

Following the first cycle, if no major complication has followed rituximab infusion, bendamustine and ara-C will be administered on day 1 following rituximab, and the complete cycle will last for 3 days, in

order to facilitate an outpatient approach.

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	Ara-C
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Ara-C will be administered intravenously at the dose of 500 mg/m2 as a 2-hour infusion, 2 hours after Bendamustine on Day 2 and 3, and once on Day 4.

Following the first cycle, if no major complication has followed rituximab infusion, bendamustine and ara-C will be administered on day 1 following rituximab, and the complete cycle will last for 3 days, in order to facilitate an outpatient approach.

Number of subjects in period 1	Single arm
Started	57
Completed	38
Not completed	19
Adverse Event	14
Medical Decision	4
Lack of efficacy	1

Baseline characteristics

Reporting groups	
Reporting group title	Baseline
Reporting group description:	
Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed (last follow-up) at 09/11/2017.	

Reporting group values	Baseline	Total	
Number of subjects	57	57	
Age categorical Units: Subjects			
Adults (18-64 years)	5	5	
From 65-84 years	52	52	
Age continuous Units: years			
median	71		
inter-quartile range (Q1-Q3)	67 to 75	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	43	43	
Ann Arbor stage Units: Subjects			
II	5	5	
III–IV	52	52	
Bone marrow involvement Units: Subjects			
Yes	36	36	
No	21	21	
Eastern Cooperative Oncology Group performance status Units: Subjects			
ECOG 0-1	54	54	
ECOG 2	3	3	
Morphological variants Units: Subjects			
Classical	43	43	
Pleomorphic	8	8	
Blastoid	6	6	
Ki67 index Units: Subjects			
<30%	35	35	
≥30%	16	16	
NA	6	6	
MIPI Units: Subjects			
Low risk	9	9	
Intermediate risk	23	23	

High risk	25	25	

Ki67 index			
Only 51 patients			
Units: percent			
median	20		
inter-quartile range (Q1-Q3)	8 to 33	-	

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description:	
Patients will be treated with at least two cycles of RBAC500, recycling every 28 days. Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment.	
Subject analysis set title	Subject analyzed
Subject analysis set type	Full analysis
Subject analysis set description:	
Fifty-seven patients recruited in Italy from 03/20/2012 , with date of last completed (last follow-up) at 09/11/2017.	

Primary: Complete response rate (CR)

End point title	Complete response rate (CR)
End point description:	
Primary efficacy end point of the study is the proportion of CR defined according to Cheson criteria (2007) at the end of treatment (6 or 4 cycles)	
End point type	Primary
End point timeframe:	
At the end of treatment (6 or 4 cycles)	

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: subject				
CR	52	52		

Statistical analyses

Statistical analysis title	Complete Response (CR) Rate
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	CR proportion
Point estimate	91
Confidence interval	
level	95 %
sides	1-sided
lower limit	85

Primary: Patients with at least a relevant one episode of relevant toxicities

End point title	Patients with at least a relevant one episode of relevant toxicities

End point description:

Relevant toxicity was defined as grade 4 cytopenia lasting for more than 6 days, grade 3–4 non haematological toxicity, or febrile neutropenia lasting for more than 3 consecutive days.

End point type	Primary

End point timeframe:

6 months

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: Subject				
Patients with relevant toxicities	23	23		

Statistical analyses

Statistical analysis title	Patients with relevant toxicities
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	114
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Proportion
Point estimate	40
Confidence interval	
level	95 %
sides	1-sided
upper limit	53

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS is measured from the time of enrollment until disease progression, relapse or death from any cause.

End point type	Secondary

End point timeframe:

30 months. The reported value corresponds to PFS% at 2-years.

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: Probability				
number (confidence interval 95%)	81 (68 to 89)	81 (68 to 89)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is measured from enrollment until death from any cause.

End point type	Secondary

End point timeframe:

30 months. The reported value corresponds to OS% at 2-years.

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: Probability				
number (confidence interval 95%)	86 (74 to 93)	86 (74 to 93)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of responses (DOR)

End point title	Duration of responses (DOR)

End point description:

DOR is measured from the first assessment that documents response (CR or PR) to the date of disease relapse or progression.

End point type	Secondary

End point timeframe:

30 months. The reported value corresponds to DOR% at 2-years.

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	57	57		
Units: Probability				
number (confidence interval 95%)	90 (85 to 94)	90 (85 to 94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of molecular response

End point title	Rate of molecular response

End point description:

Molecular response is the proportion of patients with molecular rearrangements at baseline that become negative during treatment, measured by qualitative and quantitative PCR.

End point type	Secondary

End point timeframe:

6 months

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	45[1]	45[2]		
Units: Patients				
Bone Marrow	24	24		
Peripheral Blood	35	35		

Notes:

[1] - Of 57 patients, 45 (79%) had a molecular marker

[2] - Of 57 patients, 45 (79%) had a molecular marker

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

30 months

Adverse event reporting additional description:

All subjects will be monitored for adverse events throughout the study and for 30 days after the end of treatment.
During the follow-up, patients will be monitored for adverse events every 3 months.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Single arm

Reporting group description:

Patients will be treated with at least two cycles of RBAC500, recycling every 28 days.
Patients with PD after 2 cycles will stop treatment, while all other patients will continue treatment. After 4 cycles patients that had SD after 2 cycles will be reevaluated for response and they will stop treatment if still in SD or PD. Responsive patients (CR, CRu, PR after 2 cycles; SD after 2 cycles that improved their response at the end of cycle 4) will receive a total of 6 cycles. Patients experiencing at least one episode of relevant toxicity during any of the first 4 cycles will be treated with a total of four cycles (end of treatment after 4 cycles) regardless of response to treatment.

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 57 (36.84%)		
number of deaths (all causes)	12		
number of deaths resulting from adverse events	1		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia G4, Thrombocytopenias G3			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			

subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	4 / 4			
deaths causally related to treatment / all	0 / 0			
Severe Leukopenia and Thrombocytopenias				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	2 / 57 (3.51%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Cough and fever				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Epistaxis and fever				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever				
subjects affected / exposed	3 / 57 (5.26%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Fever and cutaneous rash				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia and Temperature				

max 38° C				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia and Temperature max 38.2° C				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever, CMV reactivation and pancytopenia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonitis with fever and cought				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Melaena, with findings of severe anemia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Left cheek lesion and Melaena				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Neutropenia and fever				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Fever, Dehydration, Hypoalbuminaemia				
subjects affected / exposed	1 / 57 (1.75%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			

Chest pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction and pseudomonas aeruginosa sepsis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Pancytopenia and Epistaxis			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Severe bone pain			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
CMV Reactivation			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 57 (1.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 57 (96.49%)		
Vascular disorders			

Other hemorrhage subjects affected / exposed occurrences (all)	2 / 57 (3.51%) 5		
Cardiac disorders Supraventricular arrhythmia subjects affected / exposed occurrences (all) Ventricular arrhythmia subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	 2 / 57 (3.51%) 2 1 / 57 (1.75%) 2 1 / 57 (1.75%) 1		
Nervous system disorders Motor neuropathy subjects affected / exposed occurrences (all) Sensory neuropathy subjects affected / exposed occurrences (all)	 1 / 57 (1.75%) 2 1 / 57 (1.75%) 1		
Blood and lymphatic system disorders Platelets subjects affected / exposed occurrences (all) Leucocytes subjects affected / exposed occurrences (all) Haemoglobin subjects affected / exposed occurrences (all) Granulocytes subjects affected / exposed occurrences (all) Febrile neutropenia subjects affected / exposed occurrences (all)	 51 / 57 (89.47%) 217 52 / 57 (91.23%) 209 49 / 57 (85.96%) 190 53 / 57 (92.98%) 205 15 / 57 (26.32%) 20		
General disorders and administration			

site conditions Other toxicities subjects affected / exposed occurrences (all)	33 / 57 (57.89%) 111		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mucositis subjects affected / exposed occurrences (all)	5 / 57 (8.77%) 6 4 / 57 (7.02%) 4 3 / 57 (5.26%) 4		
Hepatobiliary disorders Liver dysfunction subjects affected / exposed occurrences (all)	1 / 57 (1.75%) 1		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	3 / 57 (5.26%) 11		
Infections and infestations Viral infection subjects affected / exposed occurrences (all) Bacterial infection subjects affected / exposed occurrences (all) Fungal infection subjects affected / exposed occurrences (all)	4 / 57 (7.02%) 4 10 / 57 (17.54%) 12 2 / 57 (3.51%) 3		
Metabolism and nutrition disorders Hyperglycemia subjects affected / exposed occurrences (all) Hyperbilirubinemia	1 / 57 (1.75%) 4		

subjects affected / exposed	1 / 57 (1.75%)		
occurrences (all)	1		
Hyperuricemia			
subjects affected / exposed	2 / 57 (3.51%)		
occurrences (all)	5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27927586