Clinical trial results:
Bendamustine and Rituximab for the treatment of Splenic Marginal Zone Lymphoma. The IELSG-36 phase II prospective study.

Summary

EudraCT number	2011-000880-28
Trial protocol	IT
Global end of trial date	30 December 2020

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022
Summary attachment (see zip file)	Synopsis IELSG36 (Synopsis_IELSG36.pdf)

Trial information

Trial identification

Sponsor protocol code	IELSG36

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02853370
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	International Extranodal Lymphoma Study Group (IELSG)
Sponsor organisation address	Ospedale Regionale di Bellinzona e Valli, Via A. Gallino, Bellinzona, Switzerland, 6500
Public contact	Segreteria Amministrativa, Fondazione Italiana Linfomi ONLUS, +39 0131/206071, segreteria@filinf.it
Scientific contact	Segreteria Amministrativa, Fondazione Italiana Linfomi ONLUS, +39 0131/206071, segreteria@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 September 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 December 2020
Global end of trial reached?	Yes
Global end of trial date	30 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of the efficacy of Rituximab-Bendamustine measured by Complete Response rate in symptomatic splenic marginal zone lymphoma patients.

Protection of trial subjects:

Guidelines for dose modifications, treatment delays and restart were included in the study protocol, in order to minimize any possible risks for the patients
All supportive therapies other than anti-cancer treatment needed for the management of patients enrolled in this study were permitted.
The following medications and support therapies may be used if needed during this study:
- Prophylaxis with levofloxacine or ciprofloxacine and fluconazole/itraconazole in case of neutropenia <1.000/mm3.
- Platelets and red blood cell transfusion were allowed, if needed, in case of Hb <8 g/dl or Plt <10.000/mm3.
-Erytropoietin therapy was allowed according to ASH/ASCO guidelines.
- G-CSF or PegG-CSF was allowed according to primary physician decision.
- Immunoglobulin assay was advised during induction therapy and follow-up; immunoglobulin replacement therapy was advised in case of IgG level <0.3-0.5 gr/dl and frequent infectious events.
-Premedication for rituximab infusion with paracetamol and diphenhydramine was suggested before each infusion of rituximab, because it might reduce infusion reactions.

Background therapy:

Patients received prophylactic treatment with valciclovir 500 mg/d and trimetroprim/Cotrimoxazole double strengths (one tablet twice daily, given three times per week) until completion of the last Rituximab-Bendamustine cycle.
In patients HBcAb+, prophylaxis against hepatitis B reactivation with Lamivudine 100 mg/die from the start of the treatment to one year after the end of the treatment.

Evidence for comparator: -	
Actual start date of recruitment	03 December 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	France: 27
Country: Number of subjects enrolled	Italy: 51
Worldwide total number of subjects	78
EEA total number of subjects	78

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)	30
From 65 to 84 years	47
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment lasted from 03 December 2021 to 13 November 2014

Pre-assignment

Screening details:

78 patients were screened and 56 patients were eligible: 16 patients were uneligible for unconfirmed diagnosis of SMZL, 3 for age >80 years, 1 for withdrawal of the Informed Consent, 1 for treatment not started and 1 urgent treatment needed.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Arm 1

Arm description:

All patients treated with Rituximab and Bendamustine

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:

Patients were treted with 375 mg/sqm on day 1 of 28 days cycles .
Patients were treated with 3 cycles of Rituximab-Bendamustine (R-B) and then restaged.
If in PR patients proceeded to the next extended phase with 3 more R-B cycles. If in CR only one more R-B cycle was be delivered.
Patients with clinical response less than PR went go off the study.

Investigational medicinal product name	Bendamustine Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients were treted with Bendamustine 90 mg/sqm on days 1-2 or days 2-3 of 28 days cycles .
Patients were treated with 3 cycles of Rituximab-Bendamustine (R-B) and then restaged.
If in PR patients proceeded to the next extended phase with 3 more R-B cycles. If in CR only one more R-B cycle was delivered.
Patients with clinical response less than PR went off the study.

Number of subjects in period 1[1]	Arm 1
Started	56
Completed	45
Not completed	11
Adverse event, serious fatal	1
Consent withdrawn by subject	3
Physician decision	1
Adverse event, non-fatal	4
Lack of efficacy	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Seventy-eight patients were enrolled in the trial, but only 56 were eligible.

Baseline characteristics

Reporting groups	
Reporting group title	Arm 1
Reporting group description:	
All patients treated with Rituximab and Bendamustine	

Reporting group values	Arm 1	Total	
Number of subjects	56	56	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	24	24	
From 65-84 years	32	32	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	23	23	
Male	33	33	
ECOG Performance Status Units: Subjects			
Grade 2	2	2	
Grade 0 -1	51	51	
Not recorded	3	3	
Bone Marrow Involvement Units: Subjects			
BM involvement	56	56	
Thoracic and / or abdominal lymphadenopathy Units: Subjects			
Thoracic and / or abdominal lymphadenopathy	34	34	
No Thoracic and / or abdominal lymphadenopathy	22	22	
Extranodal involvement Units: Subjects			
Extranodal involvement	2	2	
No extranodal involvement	54	54	
IIL Prognostic Score Units: Subjects			
Low (0)	22	22	
Intermediate(1)	14	14	
High (2-3)	19	19	

Not recorded	1	1	

End points

End points reporting groups

Reporting group title	Arm 1
Reporting group description:	
All patients treated with Rituximab and Bendamustine	

Primary: Complete Response Rate

End point title	Complete Response Rate[1]
End point description:	
Complete response rate to be be assessed by means of CT-scan, Immunophenotype in blood and bone marrow (PET-scan optional) Complete response (CR) requires the disappearance of all evidence of disease a. Regression to normal size on CT of organomegaly (splenomegaly, hepatomegaly and lymphoadenopathies) b. Normalization of the blood counts (Hb >12 g/dl; platelets >100.000/mm3; neutrophils >1.500/mm3 and no evidence of circulating clonal B-cells) c. No evidence or minor (<5%) BM infiltration detected by immunohistochemistry	
End point type	Primary
End point timeframe:	
After Cycle 3 and at the end of treatment	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Sample size was calculated with a reference CRR of 60% (p0) and an alternative CRR of 80% (p1), an alpha error of 0.05 (two sided) and a power of 0.9. A sample size of 53 evaluable patients was needed. According to Simon's optimal two-stage design, the alternative hypothesis would have been considered not reached if ≤12 CR were observed in the first 19 cases (stage1) or ≤37 CR were observed in the 53 evaluable cases (stage 2).

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: percentage				
number (confidence interval 95%)	73 (60 to 84)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response rate (ORR)

End point title	Overall Response rate (ORR)
End point description:	
Complete response + Partial Response Partial response (PR) requires regression of 50% or greater in the measurable disease manifestations and no new sites of disease. This should include: resolution or decrease in spleen size, improvement on cytopenias and resolution or decrease in lymphadenopathy if present. Bone Marrow should show a decrease in the level of lymphoid infiltration and improvement of the haemopoietic reserve	
End point type	Secondary

End point timeframe:

After cycle 3 and at the end of treatment

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	91 (80 to 97)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year Progression Free Survival (PFS)

End point title	3-year Progression Free Survival (PFS)

End point description:

PFS was measured from time of study entry until lymphoma relapse/progression, or death from any cause

End point type	Secondary

End point timeframe:

From study entry until 3 years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	90 (77 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-years Duration of Response (DOR)

End point title	3-years Duration of Response (DOR)

End point description:

DOR was measured from time of documentation of tumour response to disease progression

End point type	Secondary

End point timeframe:

From the first documented response to the first documented progression/relapse until 3 years from study entry

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	93 (81 to 98)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-years Event Free Survival (EFS)

End point title	3-years Event Free Survival (EFS)

End point description:

EFS is measured from time of study entry until any treatment failure, including disease progression/relapse, histological transformation or initiation of new anti-lymphoma therapy or death from any cause

End point type	Secondary

End point timeframe:

From study entry until 3 years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	80 (65 to 89)			

Statistical analyses

No statistical analyses for this end point

Secondary: 3-years Overall Survival Rate

End point title	3-years Overall Survival Rate

End point description:

End point type	Secondary

End point timeframe:

3 years from treatment start

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	96 (84 to 98)			

Statistical analyses

No statistical analyses for this end point

Secondary: 5 years Progression Free Survival (PFS)

End point title	5 years Progression Free Survival (PFS)

End point description:

PFS was measured from time of study entry until lymphoma relapse/progression, or death from any cause

End point type	Secondary

End point timeframe:

From study entryt until five years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	83 (71 to 91)			

Statistical analyses

No statistical analyses for this end point

Secondary: 5 years Overall Survival (OS)

End point title	5 years Overall Survival (OS)

End point description:

OS was measured from the date of protocol treatment start until date of death irrespective of cause

End point type	Secondary

End point timeframe:

From the date of protocol treatment start until five years after

End point values	Arm 1			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: Percentage				
number (confidence interval 95%)	93 (82 to 97)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the date of informed consent signature until 30 days after end of treatment	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	5.1
Reporting groups	
Reporting group title	Safety Population
Reporting group description: All patients who have received at least one dose of treatment will be considered as Safety Population	

Serious adverse events	Safety Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 56 (25.00%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	1		
Investigations			
Pancytopenia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant peripheral nerve sheath tumor			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myelodysplastic syndrome			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Angioplasty			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Infusion related reaction			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
paraneoplastic fever			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Coagulation disorders			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 56 (7.14%)		
occurrences causally related to treatment / all	5 / 5		
deaths causally related to treatment / all	0 / 0		
Anaemia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Erythroderma			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Sepsis			

subjects affected / exposed	2 / 56 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Lung infection			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 56 (89.29%)		
Investigations			
Investigations			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	4		
Nervous system disorders			
central nervous system			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	24 / 56 (42.86%)		
occurrences (all)	42		
Leukopenia			
subjects affected / exposed	28 / 56 (50.00%)		
occurrences (all)	82		
Neutropenia			
subjects affected / exposed	31 / 56 (55.36%)		
occurrences (all)	98		

Thrombocytopenia subjects affected / exposed occurrences (all)	26 / 56 (46.43%) 51		
General disorders and administration site conditions General disorder subjects affected / exposed occurrences (all)	13 / 56 (23.21%) 22		
Gastrointestinal disorders Gastrointestinal disorder subjects affected / exposed occurrences (all)	23 / 56 (41.07%) 37		
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	4 / 56 (7.14%) 10		
Skin and subcutaneous tissue disorders Skin disorder subjects affected / exposed occurrences (all)	10 / 56 (17.86%) 19		
Infections and infestations Infections subjects affected / exposed occurrences (all)	7 / 56 (12.50%) 17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 May 2012	This was an administrative amendment and its main purpose was to include the cooperative group LYSA, born in February 2012 from the fusion of two research groups that had already been working for several decades, the GELA (the Adult Lymphoma Study Group) and the GOELAMS (Groupe Ouest-Est d'etudes des Leucémies Aigues et autres Maladies du Sang
04 July 2012	The main purpose of this amendment was to add : - adequate methods of contraception in the inclusion criteria; - major surgery and renal impairement in the exclusion criteria; - allopurinol and vaccination against yellow fever as prohibited concomitant medications;
06 June 2013	This amendment was issued to implement several changes: 1. Inclusion of additional tests (blood and bone marrow samples) after cycle 3, 4, 6 and during follow-up for MRD assessment. 2. Detailed description of the central review of the diagnosis 3. Change of contact of safety officer and inclusion of an appendix on procedures for reporting SAE/AE/SUSAR. 4. Additional Appendix detailing the management of AEs related to progressive multifocal leukoencephalopathy (PML) occurring in patients treated with anti-CD20 including rituximab. 5. Appendix containing guidelines for the use of granulocyte colony-stimulating factor.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not applicable

Notes: