Clinical trial results:
Study Phase II Non-randomized Prospective Open to Assess the Combination of Rituximab, Bendamustine, Mitoxantrone, Dexamethasone (R-BMD) in Patients With Follicular Lymphoma Refractory or Relapsed

Summary

EudraCT number	2008-005687-13
Trial protocol	ES
Global end of trial date	29 July 2016

Results information

Result version number	v1 (current)
This version publication date	17 July 2021
First version publication date	17 July 2021
Summary attachment (see zip file)	R-BMD (CAM4-8-6955.pdf)

Trial information

Trial identification

Sponsor protocol code	R-BMDGELTAMO08

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01133158
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GELTAMO
Sponsor organisation address	H. MARQUES DE VALDECILLA SERVICIO DE HEMATOLOGIA, SANTANDER, Spain, 39008
Public contact	GELTAMO, Grupo Español de Linfomas y Transplante Autólogo de Médula Ósea , 0034 913195780, dm@geltamo.com
Scientific contact	GELTAMO, Grupo Español de Linfomas y Transplante Autólogo de Médula Ósea , 0034 913195780, sc@geltamo.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	29 July 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2013
Global end of trial reached?	Yes
Global end of trial date	29 July 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the combination of efficacy and safety of the combination of rituximab, bendamustine, mitoxantrone, dexamethasone in the treatment of patients with Follicular Lymphoma who are refractory or in relapse.

Protection of trial subjects:

Patients eligible for inclusion were those aged 1875 years who had been previously diagnosed (lymph node or tissue biopsy) by a local pathologist and fulfilled the following criteria: FL grade, 13a; Eastern Cooperative Oncology Group (ECOG) score, ≤2; Ann Arbor stage, I–IV; Follicular Lymphoma International Prognostic Index (FLIPI), 05. Patients to whom any of the following exclusion criteria applied were considered ineligible: previous radiotherapy treatment; relapse after autologous stem cell transplantation central nervous system involvement; previous or concomitant malignant disease; clinical suspicion or histological confirmation of transformed lymphoma (in the staging bone marrow biopsy performed on each patient or in a new lymph node or tissue biopsy performed prior to inclusion in some patients with clinical suspicion of transformation); previous or active infection with hepatitis B virus, hepatitis C virus, or HIV; other serious immunosuppressive conditions; organ function deficits (liver, kidney, or heart) unrelated to lymphom

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 July 2009
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	Spain: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	32
From 65 to 84 years	28
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixtyone patients were enrolled and assessed. After exclusion of one screen failure, 60 patients (median age,
62.5 years; range, 3276) received treatment according to
the study protocol

Period 1

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

Arms

Arm title	Experimental: R-BMD

Arm description:

Patient will receive Rituximab, Bendamustina, Mitoxantrone and Dexametasona

Rituximab, Bendamustine, Mitoxantrone, Dexamethasone: Bendamustine: 90 mg/m2/day, days 1 and 2 of each cycle, iv Mitoxantrone: 6 mg/m2/day, day 1 of each cycle, iv DEXAMETHASONE 20 mg / day, days 1 through 5 of each cycle, od Rituximab: 375 mg / m 2 / day, day 1 of each cycle, iv

Arm type	Experimental
Investigational medicinal product name	RITUXIMAB
Investigational medicinal product code	
Other name	Rituxan®
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Rituximab: 375 mg / m 2 / day, day 1 of each cycle, iv

Investigational medicinal product name	BENDAMUSTINE
Investigational medicinal product code	
Other name	Bendeka, Belrapzo, Treanda
Pharmaceutical forms	Injection
Routes of administration	Injection

Dosage and administration details:

90 mg/m2/day, days 1 and 2 of each cycle

Investigational medicinal product name	MITOXANTRONE
Investigational medicinal product code	
Other name	Novantrone
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

6 mg/m2/day, day 1 of each cycle

Investigational medicinal product name	DEMAMETHASONE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Tablet
Routes of administration	Oral use, Intravenous use

Dosage and administration details:
Dexamethasone 20 mg / day, days 1 through 5 of each cycle

Number of subjects in period 1	Experimental: R-BMD
Started	60
Completed	60

Baseline characteristics

Reporting groups

Reporting group title	OVERALL STUDY

Reporting group description: -

Reporting group values	OVERALL STUDY	Total	
Number of subjects	60	60	
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)	32	32	
From 65-84 years	28	28	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	30	30	
Male	30	30	

Subject analysis sets

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

Number of Participants analyzed in the Maintenance Rituximab Arm reflects all participants who received at least one dose of Rituximab during maintenance, and had available data for response during that phase

Reporting group values	Overall trial		
Number of subjects	60		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	32		
From 65-84 years	28		
85 years and over	0		

Gender categorical Units: Subjects			
Female	30		
Male	30		

End points

End points reporting groups

Reporting group title	Experimental: R-BMD

Reporting group description:

Patient will receive Rituximab, Bendamustina, Mitoxantrone and Dexametasona

Rituximab, Bendamustine, Mitoxantrone, Dexamethasone: Bendamustine: 90 mg/m2/day, days 1 and 2 of each cycle, iv Mitoxantrone: 6 mg/m2/day, day 1 of each cycle, iv DEXAMETHASONE 20 mg / day, days 1 through 5 of each cycle, od Rituximab: 375 mg / m 2 / day, day 1 of each cycle, iv

Subject analysis set title	Overall trial
Subject analysis set type	Full analysis

Subject analysis set description:

Number of Participants analyzed in the Maintenance Rituximab Arm reflects all participants who received at least one dose of Rituximab during maintenance, and had available data for response during that phase

Primary: Response Rate: Primary End points

End point title	Response Rate: Primary End points

End point description:

The primary endpoint is the number of Participants with Response according to the criteria of the International Workshop to Standardize Response Criteria for NHL

Complete Remission (CR):

Nodes returned to normal (if GTD >15 mm before therapy, GTD now ≤15 mm; if GTD 11-15 and SA >10 mm before therapy, SA now ≤10 mm) All (non-nodal) target lesions completely resolved

Partial Remission (PR) SPD of target lesions decreased ≥50% from baseline Spleen and liver nodules regress by 50% in SPD or single lesion in GTD

Stable Disease (SD) Not enough shrinkage for PR Not enough growth for PD

Progressive Disease (PD):

SPD increase ≥50% from nadir (smallest value seen during trial) in nodal target lesions overall or in any single nodal target lesion

End point type	Primary

End point timeframe:

7 YEARS

End point values	Experimental: R-BMD	Overall trial		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	60	60		
Units: CR/uCR	60	60		

Statistical analyses

Statistical analysis title	Complete analisis
Comparison groups	Experimental: R-BMD v Overall trial

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	other
P-value	= 50
Method	Logrank
Parameter estimate	TTP

Secondary: Secondary End points

End point title	Secondary End points

End point description:

Secondary Endpoints Included an Assessment of the Following Parameters: Progression-Free Survival, Disease-Free Survival, Global Survival, Duration of the Response.
Secondary endpoints were toxicity, the role of rituximab maintenance to prolong the response and delay the next treatment, OS and PFS.

End point type	Secondary

End point timeframe:

7 years

End point values	Experimental: R-BMD			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: OS and PFS	60			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

9 years

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	All patients

Reporting group description: -

Serious adverse events	All patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 60 (41.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Left ventricular systolic dysfunction			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tachycardia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Surgery			
subjects affected / exposed	3 / 60 (5.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Pancytopenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection			
subjects affected / exposed	12 / 60 (20.00%)		
occurrences causally related to treatment / all	0 / 20		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 60 (100.00%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 60 (71.67%)		
occurrences (all)	144		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	18 / 60 (30.00%)		
occurrences (all)	58		

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