Clinical trial results:
Randomized phase II study of treatment with R-CHOP vs Bortezomib-R-CAP for young patients with poor IPI diffuse large B-cell lymphoma.

Summary

EudraCT number	2012-005138-12
Trial protocol	ES
Global end of trial date	08 August 2018

Results information

Result version number	v1 (current)
This version publication date	03 July 2021
First version publication date	03 July 2021
Summary attachment (see zip file)	BR-CAP (BRCAP-GELTAMO12_Clinical_Study_Report_FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	BRCAP-GELTAMO12

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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 Trasplante Autólogo de Médula Ósea, 0034 913195780NA, dm@geltamo.com
Scientific contact	GELTAMO, Grupo Español de Linfomas y Trasplante Autólogo de Médula Ósea, 0034 913195780NA, 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	08 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the proportion of patients with event-free survival at 2 years in patients diagnosed of DLBCL with aIPI > 1 or aIPI=1 with elevated levels of beta 2-mcroglobulin (above UNL).
UNL= Upper Normal Limit.

Protection of trial subjects:

Once trial treatment is initiated, pre-treatment visits will be conducted at the start of each cycle, weekly visits at 60 days after the end of the 6 treatment cycles, and follow-up visits every 3 months after the end of the 6 treatment cycles.
safety visits 60 days after the end of the 6 treatment cycles and follow-up visits every 3 months for the first 2 years and every 6 months until the 5th year.
2 years and every 6 months until the 5th year.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	29 March 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	Spain: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	121
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Authorisation 26/03/2013, Start of rehearsal 03/10/2013, First Patient Inclusion 03/10/2013, End of recruitment 17/02/2016, End of trial in Spain 08/08/2018

Pre-assignment

Screening details:

Patients diagnosed with primary diffuse DLBCL
2.- Age between 18 and 70 years.
3.- Age adjusted IPI higher than 1 or equal 1, with high levels of beta-2-microglobulin (above UNL)
4.- Neoplasic B lymphocytes for CD20 positivity.
5.- ECOG 0-3 6.- More than 12 weeks of life expectancy.
7.- Signed Informed Consent.

Pre-assignment period milestones

Number of subjects started	121
Number of subjects completed	121

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	EXPERIMENTAL ARM BR-CAP21X2

Arm description:

Six cycles of treatment with bortezomib were administered subcutaneously at a dose of 1.3 mg/m2 on days 1, 8, and 15, followed by rituximab iv at a dose of 375 mg/m2 on day 1 followed by chemotherapy: cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + prednisone 100 mg oral on days 1-5. The cycles were administered every 21 days

Arm type	Experimental
Investigational medicinal product name	BORTEZOMIB
Investigational medicinal product code	PR-1
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection in cartridge
Routes of administration	Injection

Dosage and administration details:

6 cycles administered every 21 days. Bortezomib will be administered on days 1-8-15.
1.3 mg/m² sc.

Investigational medicinal product name	RITUXIMAB
Investigational medicinal product code	PR-6
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

(Comparator) 6 cycles administered every 21 days. Rituximab will be administered on day 1.
375 mg/m² iv.

Investigational medicinal product name	CYCLOPHOSPHAMIDE
Investigational medicinal product code	PR-3
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Solution for injection

Dosage and administration details:

6 cycles administered every 21 days. Cyclophosphamide will be administered on day 1.
750 mg/m² iv.

Investigational medicinal product name	ADRIAMYCIN
Investigational medicinal product code	PR-8
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

6 treatment cycles administered every 21 days. Adriamycin to be administered on day 1
50 mg/m² iv.

Investigational medicinal product name	PREDNISONE
Investigational medicinal product code	PR-5
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 cycles administered every 21 days. Prednisone will be administered on days 1 to 5.
100 mg oral.

Arm title	CONTROL ARM R-CHOP21X2

Arm description:

Six cycles of treatment with R-CHOP were administered: Rituximab 375 mg/m2 iv on day 1 followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + vincristine 1.4 mg/m2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days.
The administration of rituximab was performed as an iv infusion. The first infusion was started at a rate of 50 mg/hour, and after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions could be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Arm type	Control arm
Investigational medicinal product name	RITUXIMAB
Investigational medicinal product code	PR-6
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Concentrate for solution for infusion

Dosage and administration details:

(Comparator) 6 cycles administered every 21 days. Rituximab will be administered on day 1.
Dose/route of administration: 375 mg/m² iv.

Investigational medicinal product name	CYCLOPHOSPHAMIDE
Investigational medicinal product code	PR-3
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Solution for injection

Dosage and administration details:

6 cycles administered every 21 days. Cyclophosphamide will be administered on day 1.

Dose/route of administration: 750 mg/m² iv.

Investigational medicinal product name	PREDNISONE
Investigational medicinal product code	PR-5
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

6 cycles administered every 21 days. Prednisone will be administered on days 1 to 5.
Dose/route of administration: 100 mg oral.

Investigational medicinal product name	VINCRISTINE
Investigational medicinal product code	PR-10
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Solution for injection

Dosage and administration details:

6 treatment cycles administered every 21 days
1.4 mg/m² iv

Number of subjects in period 1	EXPERIMENTAL ARM BR-CAP21X2	CONTROL ARM R-CHOP21X2
Started	60	61
Completed	60	61

Baseline characteristics

Reporting groups

Reporting group title	OVERALL TRIAL

Reporting group description: -

Reporting group values	OVERALL TRIAL	Total	
Number of subjects	121	121	
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)	100	100	
From 65-84 years	21	21	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	60	60	
Male	61	61	

Subject analysis sets

Subject analysis set title	Inclusion criteria
Subject analysis set type	Full analysis

Subject analysis set description:

- Patients diagnosed with primary diffuse DLBCL who have never received treatment for this condition.
2.- Age between 18 and 70 years.
3.- Age adjusted IPI higher than 1 or equal 1, with high levels of beta-2-microglobulin (above UNL)
4.- Neoplasic B lymphocytes for CD20 positivity.
5.- ECOG 0-3 6.- More than 12 weeks of life expectancy.
7.- Signed Informed Consent.
8.- Nor pregnant women nor breast-feeding women without heterosexual activity during the entire study. Women with
heterosexual activity only if they are willing to use two methods of contraceptive. The two contraceptive methods can
be, two barrier method or a barrier method combinated with an hormonal contraceptive method to prevent
pregnancy, used during the entire study and until 3 months after the study completion.

Subject analysis set title	Exclusion criteria
Subject analysis set type	Full analysis

Subject analysis set description:

. Pregnant women or in breast-feeding period, or adults in childbearing period not using an effective contraception
method. 2. Patients with CNS lymphoma 3. Patients with severe impairment of renal function (creatinine> 2.5 UNL)
or hepatic (bilirubin or ALT / AST> 3 UNL), unless it is suspected to be due to the disease. 4. HIV positive patients 5.
Patient previously treated for the DLBCL 6. Positive determination of chronic hepatitis B (defined as

positive serology
for HBsAg). It will be allowed to enroll patients with hidden or previuos hepatitis (defined as positive antibodies
against the core of the hepatitis B virus [HBcAb] and HBsAg negative) if undetectable HBV DNA. 7. Positive results
for hepatitis C (antibody serology for hepatitis C virus [HCV]). Patients with HCV positive may participate only if the
result of the PCR is negative for HCV RNA. 8.Patients with previous history of cardiac disease: ventricular ejection
fraction < 50%. 9.

Reporting group values	Inclusion criteria	Exclusion criteria	
Number of subjects	121	121	
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)	100	100	
From 65-84 years	21	21	
85 years and over			
Gender categorical Units: Subjects			
Female	60	60	
Male	61	61	

End points

End points reporting groups

Reporting group title	EXPERIMENTAL ARM BR-CAP21X2

Reporting group description:

Six cycles of treatment with bortezomib were administered subcutaneously at a dose of 1.3 mg/m2 on days 1, 8, and 15, followed by rituximab iv at a dose of 375 mg/m2 on day 1 followed by chemotherapy: cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + prednisone 100 mg oral on days 1-5. The cycles were administered every 21 days

Reporting group title	CONTROL ARM R-CHOP21X2

Reporting group description:

Six cycles of treatment with R-CHOP were administered: Rituximab 375 mg/m2 iv on day 1 followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + vincristine 1.4 mg/m2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days.
The administration of rituximab was performed as an iv infusion. The first infusion was started at a rate of 50 mg/hour, and after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions could be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Subject analysis set title	Inclusion criteria
Subject analysis set type	Full analysis

Subject analysis set description:

- Patients diagnosed with primary diffuse DLBCL who have never received treatment for this condition.
2.- Age between 18 and 70 years.
3.- Age adjusted IPI higher than 1 or equal 1, with high levels of beta-2-microglobulin (above UNL)
4.- Neoplasic B lymphocytes for CD20 positivity.
5.- ECOG 0-3 6.- More than 12 weeks of life expectancy.
7.- Signed Informed Consent.
8.- Nor pregnant women nor breast-feeding women without heterosexual activity during the entire study. Women with heterosexual activity only if they are willing to use two methods of contraceptive. The two contraceptive methods can be, two barrier method or a barrier method combinated with an hormonal contraceptive method to prevent pregnancy, used during the entire study and until 3 months after the study completion.

Subject analysis set title	Exclusion criteria
Subject analysis set type	Full analysis

Subject analysis set description:

. Pregnant women or in breast-feeding period, or adults in childbearing period not using an effective contraception method. 2. Patients with CNS lymphoma 3. Patients with severe impairment of renal function (creatinine> 2.5 UNL) or hepatic (bilirubin or ALT / AST> 3 UNL), unless it is suspected to be due to the disease. 4. HIV positive patients 5. Patient previously treated for the DLBCL 6. Positive determination of chronic hepatitis B (defined as positive serology for HBsAg). It will be allowed to enroll patients with hidden or previuos hepatitis (defined as positive antibodies against the core of the hepatitis B virus [HBcAb] and HBsAg negative) if undetectable HBV DNA. 7. Positive results for hepatitis C (antibody serology for hepatitis C virus [HCV]). Patients with HCV positive may participate only if the result of the PCR is negative for HCV RNA. 8.Patients with previous history of cardiac disease: ventricular ejection fraction < 50%. 9.

Primary: Primary

End point title	Primary

End point description:

End point type	Primary

End point timeframe:

Propotion of patients with event -free survival at 2 years.

End point values	EXPERIMENTAL ARM BR-CAP21X2	CONTROL ARM R-CHOP21X2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	61		
Units: .	60	61		

Statistical analyses

Statistical analysis title	Complete analisis
Comparison groups	EXPERIMENTAL ARM BR-CAP21X2 v CONTROL ARM R-CHOP21X2
Number of subjects included in analysis	121
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	< 0.25 [1]
Method	t-test, 1-sided

Notes:

[1] - If the p-value
associated with the test was below 0.25, we considered the test to be positive,
and we declared the combination to be effective.

Secondary: Secondary

End point title	Secondary

End point description:

1. Event -free survival at 2 years in differents biological DLBCL subgroups: CGB vs non-CGB. 2. Overall survival at 2
years in patients diagnosed of DLBCL with aIPI > 1 or aIPI=1 with elevated levels of beta 2-microglobulin (above
UNL). 3. Overall response rate and complete remissions in patients diagnosed of DLBCL with aIPI > 1 or aIPI=1 with
elevated levels of beta 2-mcroglobulin (above UNL). 4. Toxicity according to the CTC criteria (version 3.0) of the
National Cancer Institute (NCI). http://ctep.cancer.gov/reporting/ctcnew.html) 5. To evaluate the predictive value for
EFS of interim PET/CT evaluation after 2 and 4 cycles of chemotherapy. 6. To identify clinical and biological
prognostic factors for response and surviva

End point type	Secondary

End point timeframe:

1. Event -free survival at 2 years in differents biological DLBCL subgroups: CGB vs non-CGB. 2. Overall survival at 2
years in patients diagnosed of DLBCL with aIPI > 1 or aIPI=1 with elevated levels of beta 2-microglobulin (above

End point values	EXPERIMENTAL ARM BR-CAP21X2	CONTROL ARM R-CHOP21X2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	61		
Units: .	60	60		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A total of 121 patients received at least 1 infusion of study treatment and were included in the safety analysis. The analysis was performed considering the worst grade of reported AE per patient and considering a sample size of 121 patients.

Assessment type	Non-systematic

Dictionary used

Dictionary name	NCI-CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	EXPERIMENTAL ARM BR-CAP21X2

Reporting group description:

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Reporting group title	CONTROL ARM R-CHOP21X2

Reporting group description:

Six cycles of treatment with R-CHOP were administered: Rituximab 375 mg/m2 iv on day 1 followed by CHOP-type chemotherapy (cyclophosphamide 750 mg/m2 iv on day 1 + Adriamycin 50 mg/m2 iv on day 1 + vincristine 1.4 mg/m2 iv (maximum 2 mg) on day 1 + prednisone 100 mg oral on days 1-5). The cycles were administered every 21 days.
The administration of rituximab was performed as an iv infusion. The first infusion was started at a rate of 50 mg/hour, and after the first 30 minutes, the dose could be increased in increments of 50 mg/hour every 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions could be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour at intervals of 30 minutes to a maximum of 400 mg/hour.

Serious adverse events	EXPERIMENTAL ARM BR-CAP21X2	CONTROL ARM R-CHOP21X2	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 60 (10.00%)	3 / 61 (4.92%)	
number of deaths (all causes)	33	33	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Infection			
subjects affected / exposed	1 / 60 (1.67%)	2 / 61 (3.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Anaemia			

subjects affected / exposed	3 / 60 (5.00%)	1 / 61 (1.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour lysis syndrome			
subjects affected / exposed	2 / 60 (3.33%)	0 / 61 (0.00%)	
occurrences causally related to treatment / all	0 / 1	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	EXPERIMENTAL ARM BR-CAP21X2	CONTROL ARM R-CHOP21X2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 60 (21.67%)	7 / 61 (11.48%)	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	10 / 60 (16.67%)	5 / 61 (8.20%)	
occurrences (all)	1	1	
Platelet count abnormal			
subjects affected / exposed	3 / 60 (5.00%)	2 / 61 (3.28%)	
occurrences (all)	1	1	

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