Clinical trial results:
Randomized phase III study of a treatment driven by early PET response compared to a treatment not monitored by early PET in patients with Ann Arbor Stage III-IV or high risk IIB Hodgkin lymphoma

Summary

EudraCT number	2010-022844-19
Trial protocol	FR BE
Global end of trial date	30 September 2019

Results information

Result version number	v1 (current)
This version publication date	07 February 2023
First version publication date	07 February 2023

Trial information

Trial identification

Sponsor protocol code	AHL2011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01358747
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Hospitalier Universitaire de Dijon
Sponsor organisation address	1 boulevard Jeanne d'Arc, DIJON CEDEX, France, 21079
Public contact	Project Management, LYSARC, contact@lysarc.org
Scientific contact	Project Management, Pr Olivier Casasnovas, olivier.casasnovas@chu-dijon.fr

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	19 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 September 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the non inferiority in term of progression free survival (PFS) of a therapeutic strategy driven by PET with a ABVD conventional dose chemotherapy for patients reaching a negative PET after 2 cycles of BEACOPPesc, compared to a treatment not monitored by early PET delivering 6 cycles of BEACOPPesc.

Protection of trial subjects:

DSMC periodically reviewed the safety and efficacy data from the trial prepared by the independent statistician. All data presented at the meeting were confidential. Following each meeting the DMSC prepared a report and may recommended changes in the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 May 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 765
Country: Number of subjects enrolled	France: 58
Worldwide total number of subjects	823
EEA total number of subjects	823

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)	16
Adults (18-64 years)	807
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

88 study centers in France and Belgium.
Date first subject first visit: 19 May 2011
Date last subject completed: 29 April 2019

Pre-assignment

Screening details:

Male or female adult (aged 16 to 60 years old) subjects with histologically proven HL not previously treated, with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2, and life expectancy ≥ 90 days were eligible for participation in the study

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard Arm

Arm description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 4 cycles. A PET was performed after 2 cycles of chemotherapy (PET2) with no decisional value, and after 4 cycles with decisional value.
In case of PET4 negative result, patient received 2 additional cycles of BEACOPPesc delivered every 3 weeks
In case of PET4 positive result, patient received a salvage therapy

Arm type	Active comparator
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

10 mg/m2 at Day 8

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

200 mg/m2 at days 1, 2and 3

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

35 mg/ m2 on day 1

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

1250 mg/m2 on day 1

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:

1.4 mg/m2 on day 1

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage: 100 mg/m2
Administration: Daily from Day 1 of each cycle to day 7

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Dosage: 40mg/m2
Administration: Daily from Day 1 of each cycle to day 8 and day 9 to day 14

Investigational medicinal product name	Lenograstim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Cutaneous use

Dosage and administration details:

5 microgr/kg/day start on day 9

Arm title	Experiimental arm

Arm description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 2 cycles followed by a PET scan (PET2).

After PET2 central review:
- In case of positive PET2, the treatment was completed by 2 additional cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)
- In case of negative PET2, the treatment was completed by 2 cycles of ABVD delivered every 4 weeks (induction treatment = 2 x BEACOPPesc + 2 x ABVD).

After PET4 central review:
- In case of positive PET4, a salvage therapy was decided by the investigator
- In case of negative PET4 :
  - if PET2 was negative, treatment was completed by 2 cycles of ABVD (induction treatment = 2 x BEACOPPesc + 4 x ABVD).
  - if PET2 was positive, treatment was completed by 2 cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)

Arm type	Experimental

Investigational medicinal product name	Bleomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:
10 mg/m2 at Day 8

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:
200 mg/m2 at days 1, 2and 3

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:
35 mg/ m2 on day 1

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:
1250 mg/m2 on day 1

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Intravenous use

Dosage and administration details:
1.4 mg/m2 on day 1

Investigational medicinal product name	Procarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
Dosage: 100 mg/m2
Administration: Daily from Day 1 of each cycle to day 7

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
Dosage: 40mg/m2
Administration: Daily from Day 1 of each cycle to day 8 and day 9 to day 14

Investigational medicinal product name	Lenograstim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Cutaneous use
Dosage and administration details: 5 microgr/kg/day start on day 9	
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use
Dosage and administration details: 25 mg/ m2 on day 1 and day 15	
Investigational medicinal product name	Bleomycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use
Dosage and administration details: 10 mg/m2 on day 1 and day 15	
Investigational medicinal product name	Vinblastine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 6 mg/m2 on day 1 and day 15	
Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use
Dosage and administration details: 375 mg/m2 on day 1 and day 15	

Number of subjects in period 1	Standard Arm	Experiimental arm
Started	413	410
Completed	342	359
Not completed	71	51
Consent withdrawn by subject	4	3
Physician decision	2	3
death	4	2
Adverse event, non-fatal	28	4
other	4	3
Lack of efficacy	26	19

Protocol deviation	3	17

Baseline characteristics

Reporting groups

Reporting group title	Overall

Reporting group description: -

Reporting group values	Overall	Total	
Number of subjects	823	823	
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)		0	
From 65-84 years		0	
85 years and over		0	
Subjects		0	
Age continuous Units: years			
arithmetic mean	32.9		
full range (min-max)	16 to 60	-	
Gender categorical Units: Subjects			
Female	307	307	
Male	516	516	

Subject analysis sets

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set contains all patients who were formally randomized regardless whether they have received treatment or not (following an intent-to-treat principle).
Patients are analyzed according to the treatment arm they were randomized to receive.
The ITT set is used for the efficacy analysis.

Reporting group values	ITT		
Number of subjects	823		
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) From 65-84 years 85 years and over Subjects			
Age continuous Units: years			
arithmetic mean	32.9		
full range (min-max)	16 to 60		
Gender categorical Units: Subjects			
Female	307		
Male	516		

End points

End points reporting groups

Reporting group title	Standard Arm

Reporting group description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 4 cycles. A PET was performed after 2 cycles of chemotherapy (PET2) with no decisional value, and after 4 cycles with decisional value.
In case of PET4 negative result, patient received 2 additional cycles of BEACOPPesc delivered every 3 weeks
In case of PET4 positive result, patient received a salvage therapy

Reporting group title	Experiimental arm

Reporting group description:

Patients were treated by a BEACOPPesc regimen every 3 weeks for 2 cycles followed by a PET scan (PET2).

After PET2 central review:
- In case of positive PET2, the treatment was completed by 2 additional cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)
- In case of negative PET2, the treatment was completed by 2 cycles of ABVD delivered every 4 weeks (induction treatment = 2 x BEACOPPesc + 2 x ABVD).

After PET4 central review:
- In case of positive PET4, a salvage therapy was decided by the investigator
- In case of negative PET4 :
  - if PET2 was negative, treatment was completed by 2 cycles of ABVD (induction treatment = 2 x BEACOPPesc + 4 x ABVD).
  - if PET2 was positive, treatment was completed by 2 cycles of BEACOPPesc (induction treatment = 4 x BEACOPPesc)

Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT set contains all patients who were formally randomized regardless whether they have received treatment or not (following an intent-to-treat principle).
Patients are analyzed according to the treatment arm they were randomized to receive.
The ITT set is used for the efficacy analysis.

Primary: PFS

End point title	PFS

End point description:

The primary endpoint was progression-free survival. PFS was measured from the date of randomization to the date of first documented progression of the lymphoma in non-responding patients, relapse for CR patients or death from any cause without progression, whichever occurs first

End point type	Primary

End point timeframe:

5-year progression-free survival

End point values	Standard Arm	Experiimental arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	413	410		
Units: percent				
arithmetic mean (confidence interval 95%)	87.5 (83.9 to 90.4)	86.7 (83.0 to 89.7)		

Attachments (see zip file)	PFS.png

Statistical analyses

Statistical analysis title	Comparison according to treatment arm

Statistical analysis description:

Based on a Cox model, the Hazard Ratio (HR) of patients in experimental treatment are compared to patients in standard arm.

Comparison groups	Standard Arm v Experiimental arm
Number of subjects included in analysis	823
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.64
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.071
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.738
upper limit	1.554

Notes:

[1] - The Com-Nougue non-inferiority test for PFS gave a similar conclusion in the ITT population by rejecting the null hypothesis (p=0.0037).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any episode of any grade of toxicities, related to a Serious Adverse Event must be reported as "Serious Adverse Event"
· Non-serious adverse events not to be reported.
· The following events are not to be reported as SAE if require hospitalization le

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	BEACOPP only

Reporting group description:

patients who received BEACOPP only and who performed cycle 1

Reporting group title	BEACOPP + ABVD

Reporting group description: -

Serious adverse events	BEACOPP only	BEACOPP + ABVD	
Total subjects affected by serious adverse events			
subjects affected / exposed	160 / 458 (34.93%)	97 / 361 (26.87%)	
number of deaths (all causes)	19	10	
number of deaths resulting from adverse events	6	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
subjects affected / exposed	7 / 458 (1.53%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	8 / 8	3 / 3	
deaths causally related to treatment / all	2 / 3	1 / 2	
Vascular disorders			
VASCULAR DISORDERS			
subjects affected / exposed	11 / 458 (2.40%)	9 / 361 (2.49%)	
occurrences causally related to treatment / all	3 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

subjects affected / exposed	30 / 458 (6.55%)	16 / 361 (4.43%)	
occurrences causally related to treatment / all	13 / 37	10 / 18	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
IMMUNE SYSTEM DISORDERS			
subjects affected / exposed	4 / 458 (0.87%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	2 / 4	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
REPRODUCTIVE SYSTEM AND BREAST DISORDERS			
subjects affected / exposed	2 / 458 (0.44%)	0 / 361 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
subjects affected / exposed	19 / 458 (4.15%)	15 / 361 (4.16%)	
occurrences causally related to treatment / all	14 / 21	11 / 18	
deaths causally related to treatment / all	1 / 2	0 / 0	
Injury, poisoning and procedural complications			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
subjects affected / exposed	2 / 458 (0.44%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	2 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC DISORDERS			
subjects affected / exposed	8 / 458 (1.75%)	10 / 361 (2.77%)	
occurrences causally related to treatment / all	3 / 8	3 / 11	
deaths causally related to treatment / all	1 / 1	0 / 1	
Nervous system disorders			
NERVOUS SYSTEM DISORDERS			
subjects affected / exposed	3 / 458 (0.66%)	3 / 361 (0.83%)	
occurrences causally related to treatment / all	2 / 3	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
subjects affected / exposed	29 / 458 (6.33%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	30 / 33	13 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
EYE DISORDERS			
subjects affected / exposed	0 / 458 (0.00%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
GASTROINTESTINAL DISORDERS			
subjects affected / exposed	20 / 458 (4.37%)	8 / 361 (2.22%)	
occurrences causally related to treatment / all	21 / 26	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATOBILIARY DISORDERS			
subjects affected / exposed	5 / 458 (1.09%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	4 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
subjects affected / exposed	3 / 458 (0.66%)	5 / 361 (1.39%)	
occurrences causally related to treatment / all	3 / 3	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
RENAL AND URINARY DISORDERS			
subjects affected / exposed	6 / 458 (1.31%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	1 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			

subjects affected / exposed	7 / 458 (1.53%)	4 / 361 (1.11%)	
occurrences causally related to treatment / all	7 / 10	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
INFECTIONS AND INFESTATIONS			
subjects affected / exposed	90 / 458 (19.65%)	42 / 361 (11.63%)	
occurrences causally related to treatment / all	91 / 121	43 / 56	
deaths causally related to treatment / all	2 / 2	1 / 1	
Metabolism and nutrition disorders			
METABOLISM AND NUTRITION DISORDERS			
subjects affected / exposed	2 / 458 (0.44%)	1 / 361 (0.28%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BEACOPP only	BEACOPP + ABVD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	458 / 458 (100.00%)	361 / 361 (100.00%)	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	68 / 458 (14.85%)	59 / 361 (16.34%)	
occurrences (all)	68	59	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	354 / 458 (77.29%)	275 / 361 (76.18%)	
occurrences (all)	354	275	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	8 / 458 (1.75%)	11 / 361 (3.05%)	
occurrences (all)	8	11	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			

subjects affected / exposed	146 / 458 (31.88%)	104 / 361 (28.81%)	
occurrences (all)	146	104	
Investigations			
Investigations			
subjects affected / exposed	199 / 458 (43.45%)	152 / 361 (42.11%)	
occurrences (all)	199	152	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	40 / 458 (8.73%)	28 / 361 (7.76%)	
occurrences (all)	40	28	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	157 / 458 (34.28%)	123 / 361 (34.07%)	
occurrences (all)	157	123	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	458 / 458 (100.00%)	358 / 361 (99.17%)	
occurrences (all)	458	358	
Gastrointestinal disorders			
Gastro-intestinal disorders			
subjects affected / exposed	365 / 458 (79.69%)	305 / 361 (84.49%)	
occurrences (all)	365	305	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	9 / 458 (1.97%)	4 / 361 (1.11%)	
occurrences (all)	9	4	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	138 / 458 (30.13%)	115 / 361 (31.86%)	
occurrences (all)	138	115	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	31 / 458 (6.77%)	16 / 361 (4.43%)	
occurrences (all)	31	16	
Infections and infestations			
Infections and infestations			

subjects affected / exposed occurrences (all)	198 / 458 (43.23%) 198	145 / 361 (40.17%) 145	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 70 / 458 (15.28%) 70	 35 / 361 (9.70%) 35	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2011	Version 2.0 (20 October 2011) Removal of LH dosage in men under the age of 45 and participating in the fertility study.

Notes:

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/30658935