Clinical trial results:
A phase II study of oral Panobinostat in adult patients with relapsed/refractory diffuse large B-cell lymphoma after high-dose chemotherapy with autologous stem cell transfusion (ASCT) or in adult patients who are not eligible for ASCT

Summary

EudraCT number	2011-000175-13
Trial protocol	IT
Global end of trial date	03 April 2017

Results information

Result version number	v1 (current)
This version publication date	21 August 2022
First version publication date	21 August 2022

Trial information

Trial identification

Sponsor protocol code	FIL_PanAL10

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01523834
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	09 February 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 January 2014
Global end of trial reached?	Yes
Global end of trial date	03 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To explore the antitumor activity of panobinostat in term of overall response (OR) at the end of the induction phase (i.e. month 6 from the beginning of panobinostat)

Protection of trial subjects:

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. These dose adjustments comprise delays in dosing and/or reductions in the dose being administered. Dosing should always be temporarily discontinued if the physician determines it is in the best interest of the patient. All dose modifications must be recorded on the Dosage Administration Record form.
The dose of panobinostat may be modified for a patient during any cycle. The first dose adjustment consists in the modification of panobinostat administration from three times every week (QW) to three times every other week (QOW). Subsequent dose adjustments consist in panobinostat dose reductions. Dosages lower than 30 mg three times QOW are not permitted. When and if it is determined that a patient would require a dose below 30 mg QOW, the patient should be discontinued from study treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 June 2011
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: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	11
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Thirtyfive patients recruited in Italy from 14th June 2011, with date of last completed at 3rd April 2017.

Pre-assignment

Screening details:

Adult patients with R/R DLBCL who previously received at least two lines of treatments including ASCT consolidation or patients with PD after a single first line R-CHOP if not eligible for ASCT because of age or co-morbidities.
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 receive panobinostat. The treatment is divided in three phases: induction phase (course 1 to 6), consolidation phase (courses 7 to 12), maintenance phase (from course 13 until the end of therapy for any reason). The duration of a treatment course will be 28 days.
The first dose of panobinostat in course 1 defines day 1 of the treatment cycle, and each cycle thereafter will begin 28 days later.

Arm type	Single arm study
Investigational medicinal product name	Panobinostat
Investigational medicinal product code	
Other name	LBH589
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Panobinostat should be taken p.o. at the dose of 40mg/day three-times every week (QW),as part of 28 days treatment cycle.
Induction phase
Patients will receive panobinostat for 6 courses.Response assessment will be performed every 2 courses until the end of the induction phase.Patients with responsive (CR/PR) or stable disease during each assessment will complete the induction phase.
Consolidation phase
Response assessment will be performed every 3 courses until course 12.Patients with responsive or stable disease will continue with maintenance.
Maintenance phase
Patients will continue therapy until disease progression, intolerability, withdrawal of consent and/or if the investigator determines that further therapy is not in the patient’s best interest. Response assessment will be performed every three courses until course 36.For patients still in therapy after course 36,the subsequents response assessments will be performed according to each institutional policy.

Number of subjects in period 1	Single arm
Started	35
Completed	4
Not completed	31
Adverse Event	6
Death	1
Progression	24

Baseline characteristics

Reporting groups

Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	35	35	
Age categorical Units: Subjects			
Adults (18-64 years)	11	11	
From 65-84 years	24	24	
Age continuous Units: years			
median	73		
inter-quartile range (Q1-Q3)	65 to 75.5	-	
Gender categorical Units: Subjects			
Female	14	14	
Male	21	21	
Previous lines of therapy Units: Subjects			
Previous lines 1	9	9	
Previous lines 2	12	12	
Previous lines 3	9	9	
Previous lines 4	5	5	
Patients with previous autologous stem cell transplant Units: Subjects			
Yes	12	12	
No	23	23	
Patients with previous allogeneic stem cell transplant Units: Subjects			
Yes	1	1	
No	34	34	
Refractory patients to the last line of therapy before panobinostat Units: Subjects			
Yes	16	16	
No	19	19	
ECOG performance status Units: Subjects			
ECOG 0-1	28	28	
ECOG 2	7	7	
Ann Arbor stage Units: Subjects			
I-II	6	6	
III	9	9	

IV	18	18	
NA	2	2	
Systemic Symptoms Units: Subjects			
Yes	9	9	
No	26	26	
Increased LDH Units: Subjects			
Yes	24	24	
No	11	11	
International prognostic index Units: Subjects			
0–2	11	11	
3–5	20	20	
NA	4	4	
Median lines of previous therapy Units: Lines			
median	2		
full range (min-max)	1 to 4	-	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

Patients will receive panobinostat. The treatment is divided in three phases: induction phase (course 1 to 6), consolidation phase (courses 7 to 12), maintenance phase (from course 13 until the end of therapy for any reason). The duration of a treatment course will be 28 days.
The first dose of panobinostat in course 1 defines day 1 of the treatment cycle, and each cycle thereafter will begin 28 days later.

Subject analysis set title	Subject analyzed
Subject analysis set type	Full analysis

Subject analysis set description:

Thirtyfive patients recruited in Italy from 14th June 2011, with date of last completed at 3rd April 2017.

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

ORR is defined as the proportion of patients achieving a Complete Response (CR) or Partial Response (PR) according to the Cheson 1999 response criteria

End point type	Primary

End point timeframe:

At the end of the induction phase (i.e. month 6 from the beginning of panobinostat)

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35	35		
Units: Number of patients				
ORR (CR+PR)	6	6		

Statistical analyses

Statistical analysis title	Overall Response Rate (ORR)
Comparison groups	Single arm v Subject analyzed
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Frequency percent (%)
Point estimate	17.1
Confidence interval	
level	95 %
sides	1-sided
lower limit	7.8

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)

End point description:

TTR is defined as the time from enrolment to Overall Response

End point type	Secondary

End point timeframe:

36 months

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	6[1]	6[2]		
Units: Months				
median (full range (min-max))	2.6 (1.8 to 12)	2.6 (1.8 to 12)		

Notes:

[1] - Only 6 responders

[2] - Only 6 responders

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

The Progression Free Survival (PFS) is defined as the time from enrolment to disease progression or death from any cause.

End point type	Secondary

End point timeframe:

50% of survival

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35	35		
Units: Months				
median (confidence interval 95%)	2.4 (1.4 to 7.0)	2.4 (1.4 to 7.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

The Overall Survival (OS) is defined as the time from enrolment to death from any case

End point type	Secondary

End point timeframe:

50% survival

End point values	Single arm	Subject analyzed		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	35	35		
Units: Months				
median (confidence interval 95%)	7.6 (3.0 to 12.7)	7.6 (3.0 to 12.7)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 years

Adverse event reporting additional description:

Common Terminology Criteria for Adverse Events (CTCAE Version 4.0). For non-serious adverse events all grade.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Single arm

Reporting group description:

Patients will receive panobinostat. The treatment is divided in three phases: induction phase (course 1 to 6), consolidation phase (courses 7 to 12), maintenance phase (from course 13 until the end of therapy for any reason). The duration of a treatment course will be 28 days.
The first dose of panobinostat in course 1 defines day 1 of the treatment cycle, and each cycle thereafter will begin 28 days later.

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 35 (48.57%)		
number of deaths (all causes)	29		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic aneurysm rupture			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Deep vein thrombosis			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cerebral ischaemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Parossistic atrial fibrillation			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Congestive heart failure			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Paralysis of arms			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	6 / 35 (17.14%)		
occurrences causally related to treatment / all	2 / 6		
deaths causally related to treatment / all	0 / 4		
Gastrointestinal disorders			
Subocclusive syndrome			

subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract pain			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute renal injury			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Nausea, diarrhoea, hypokaliemia			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences causally related to treatment / all	1 / 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	34 / 35 (97.14%)		
Vascular disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 35 (2.86%)		
occurrences (all)	1		
Other bleeding			
subjects affected / exposed	4 / 35 (11.43%)		
occurrences (all)	5		

Cerebral ischaemia subjects affected / exposed occurrences (all) Thrombosis subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1 1 / 35 (2.86%) 1		
Cardiac disorders Supraventricular arrhythmia subjects affected / exposed occurrences (all) Ischemia heart attack subjects affected / exposed occurrences (all) Hypertension subjects affected / exposed occurrences (all) Hypotension subjects affected / exposed occurrences (all)	5 / 35 (14.29%) 5 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1 1 / 35 (2.86%) 1		
Nervous system disorders Motor neuropathy subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
Blood and lymphatic system disorders Leucocytes subjects affected / exposed occurrences (all) Platelets subjects affected / exposed occurrences (all) Haemoglobin subjects affected / exposed occurrences (all) Granulocytes subjects affected / exposed occurrences (all) Febrile neutropenia	20 / 35 (57.14%) 60 32 / 35 (91.43%) 109 22 / 35 (62.86%) 60 20 / 35 (57.14%) 73		

subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1		
General disorders and administration site conditions Other toxicities subjects affected / exposed occurrences (all)	 17 / 35 (48.57%) 56		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Mucositis subjects affected / exposed occurrences (all)	 6 / 35 (17.14%) 13 17 / 35 (48.57%) 60 4 / 35 (11.43%) 4		
Hepatobiliary disorders Liver dysfunction subjects affected / exposed occurrences (all)	 1 / 35 (2.86%) 1		
Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all)	 1 / 35 (2.86%) 1		
Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all)	 4 / 35 (11.43%) 4		
Infections and infestations Viral infection subjects affected / exposed occurrences (all) Bacterial infection subjects affected / exposed occurrences (all)	 6 / 35 (17.14%) 9 6 / 35 (17.14%) 9		
Metabolism and nutrition disorders			

Hyperglycemia subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 4		
Hyperbilirubinemia subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 2		
Hyperuricemia subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2012	Change in the legal representative of the Fondazione Italiana Linfomi Onlus
29 August 2016	Changes to the protocol and synopsis: clarification on the definition of the conclusion of the study, updating of contact details, correction of typos. In addition, with this amendment proceeds to: - Update of the Investigator Brochure: new version no. 12.1 of 06/28/2016; - Change of PI hematology center of IRCCS A.O.U. San Martino-IST di Genova (updated list of centers v. 3 of 25 July 2016). The amendment is intended only for the centers still open in Alessandria (coordinator) and in Genova Dott.ssa Congiu.

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/29616865