Clinical trial results:
Phase IIa study on the role of Gemcitabine plus Romidepsin (GEMRO regimen) in the treatment of relapsed/refractory peripheral T-cell lymphoma patients.

Summary

EudraCT number	2012-001404-38
Trial protocol	IT
Global end of trial date	02 July 2018

Results information

Result version number	v1 (current)
This version publication date	01 April 2022
First version publication date	01 April 2022

Trial information

Trial identification

Sponsor protocol code	FIL_GEMRO

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01822886
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	24 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2014
Global end of trial reached?	Yes
Global end of trial date	02 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy, as assessed by the CR rate, of GEMRO combination as salvage treatment in PTCL.

Protection of trial subjects:

Safety assessment by a safety committee will be performed after the first three patients have completed at least one cycle, after 6 patients have completed 2 cycles and quarterly thereafter. For hematologic or non-hematologic drug-related toxicity grade 3 or more the administration of the drug(s) will be postponed a maximum of 3 weeks until toxicity returns to < Grade 1.
In case of the following drug-related toxicities the dose of romidepsin will be modified:
- Grade 4 neutropenia and/or thrombocytopenia that last more than 7 days
- Grade 3 neutropenia and/or thrombocytopenia that last more than 14 days
- Grade 3 extra-hematological toxicity lasting for more than week, or Grade 4 extrahematological toxicity
- Grade 4 febrile neutropenia,
- Cardiac toxicity: QTc ≥ 501 msec, VT, including Torsade de Pointes, VF, new occurrence of > Grade >2 atrial fibrillation or flutter
- Inability to initiate cycle 2, day 1 of therapy within 28 days of anticipated start.

If toxicity recurs, the dose will be further reduced.
Patients who experience toxicity may continue in the study. They may resume treatment at the indicated dose level below that at which the toxicity was observed once they have recovered from the event. Appropriate cardiovascular monitoring precautions will be considered, such as the monitoring of electrolytes and ECGs at baseline and every two cycle during treatment with romidepsin.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 January 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	Italy: 20
Worldwide total number of subjects	20
EEA total number of subjects	20

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)	15
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Twenty patients recruited in Italy from 8 January 2013, with date of last completed at 15 December 2014

Pre-assignment

Screening details:

The screening can be up to 28 days prior to first infusion. Bone marrow results obtained 56 day prior to first infusion will be allowed.
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	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description:

The combination of romidepsin and gemcitabine will be evaluated at the following dose: Romidepsin 12 mg/m2 d.1,8, 15 + Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days followed by Romidepsin 14 mg/m2 d. 1, 15 to PD

Arm type	Single arm study
Investigational medicinal product name	Gemcitabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days

Investigational medicinal product name	Romidepsin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Romidepsin 12 mg/m2 d.1,8, 15 for 6 cycles + Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days followed by Romidepsin 14 mg/m2 d. 1, 15 to PD

Number of subjects in period 1	Single arm
Started	20
Completed	5
Not completed	15
Other	1
Lack of efficacy	14

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	20	20	
Age categorical Units: Subjects			
Adults (18-64 years)	15	15	
From 65-84 years	5	5	
Age continuous Units: years			
median	55		
full range (min-max)	22 to 77	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	10	10	
Histology Units: Subjects			
PTCL-NOS	10	10	
AITL	9	9	
ALCL, ALK negative	1	1	
Stage at enrolment Units: Subjects			
I-II	1	1	
III-IV	19	19	
Extranodal involvement Units: Subjects			
Yes	10	10	
No	10	10	
International Prognostic Index Units: Subjects			
<2	4	4	
≥ 2	16	16	
Refractory to most recent therapy Units: Subjects			
Yes	12	12	
No	8	8	
No. of prior regimens Units: Regimens			
median	2		
full range (min-max)	1 to 4	-	

End points

End points reporting groups

Reporting group title	Single arm

Reporting group description:

The combination of romidepsin and gemcitabine will be evaluated at the following dose: Romidepsin 12 mg/m2 d.1,8, 15 + Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days followed by Romidepsin 14 mg/m2 d. 1, 15 to PD

Primary: Complete Remission (CR) Rate

End point title	Complete Remission (CR) Rate[1]

End point description:

The proportion of patients with complete remission (CR) according to the Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007)

End point type	Primary

End point timeframe:

18 months

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: The study is single-arm without comparator.

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Participants	3			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)

End point description:

The Overall Response Rate (ORR=CR+CRu+PR) is defined as the proportion of patients who achieve CR, CRu or PR relative to the per-protocol population. Disease response and progression will be evaluated according to the "Revised Response Criteria" for malignant lymphoma (Cheson et al. 2007)

End point type	Secondary

End point timeframe:

24 months

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Participants	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression Free survival (PFS) is defined as the time from start of study treatment to first documentation of objective tumor progression or to death due to any cause, whichever comes first. PFS data will be censored on the day following the date of the last radiological assessment of measured lesions documenting absence of progressive disease for patients who do not have objective tumor progression and are still on study at the time of an analysis, are given antitumor treatment other than the study treatment or stem cell transplant, or are removed from study prior to documentation of objective tumor progression. Patients lacking an evaluation of tumor response after their first dose will have their event time censored at 1 day.

End point type	Secondary

End point timeframe:

24 months

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Kaplan Meier probability				
number (confidence interval 95%)	11.2 (3 to 25)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

Overall Survival (OS) is measured from the date of study entry to the date of patient’s death. If the patient is alive or his vital status is unknown, the date of death will be censored at the date that the patient is last known to be alive. Time to subsequent anti-lymphoma therapy will be assessed, for all patients, from the initiation of study treatment to the start of alternative therapy. Patients who do not receive alternate therapy will be censored in the analysis at the date of death or the last known date alive.

End point type	Secondary

End point timeframe:

24 months

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Kaplan Meier probability				
number (confidence interval 95%)	50 (28 to 72)			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety

End point title	Safety

End point description:

Frequency of toxicities Grade 3 and 4.
Frequency of toxicities was reported by type and grade according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0)

End point type	Secondary

End point timeframe:

24 months

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: Events				
Anemia	4			
Neutropenia	10			
Thrombocytopenia	12			
Transaminases increase	3			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months

Adverse event reporting additional description:

Any Grade

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Single arm

Reporting group description:

The combination of romidepsin and gemcitabine will be evaluated at the following dose: Romidepsin 12 mg/m2 d.1,8, 15 + Gemcitabine 800 mg/m2 d.1, 15 for 6 cycles by 28 days followed by Romidepsin 14 mg/m2 d. 1, 15 to PD

Serious adverse events	Single arm		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)		
number of deaths (all causes)	10		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Oxygen saturation decreased	Additional description: Fever with shiver, Hypotension, Desaturation This event is not related to the experimental therapy. It happened before the start of treatment.		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory failure	Additional description: Fever and pulmonary insufficiency		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary tract infection	Additional description: Fever, loss of consciousness and urinary infection		
subjects affected / exposed	1 / 20 (5.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)		
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	Single arm		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 20 (100.00%)		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 20 (60.00%)		
occurrences (all)	12		
Febrile neutropenia			
subjects affected / exposed	2 / 20 (10.00%)		
occurrences (all)	2		
Neutropenia			

subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	11 / 20 (55.00%) 11 16 / 20 (80.00%) 16		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	 6 / 20 (30.00%) 6		
Gastrointestinal disorders Nausea and vomiting subjects affected / exposed occurrences (all)	 10 / 20 (50.00%) 10		
Hepatobiliary disorders Transaminases increased subjects affected / exposed occurrences (all)	 4 / 20 (20.00%) 4		

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27071522