Clinical trial results:
A CLINICO-PATHOLOGIC STUDY OF PRIMARY MEDIASTINAL B-CELL LYMPHOMA

Summary

EudraCT number	2006-005794-22
Trial protocol	IT
Global end of trial date	27 February 2017

Results information

Result version number	v1 (current)
This version publication date	23 November 2018
First version publication date	06 February 2019
Summary attachment (see zip file)	IELSG26 Synopsis (IELSG26_Synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	IELSG26

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00944567
WHO universal trial number (UTN)	-
Other trial identifiers	Previous Protocol Number: IIL-PMDLBL

Notes:

Sponsors

Sponsor organisation name	International Extranodal Lymphoma Study Group
Sponsor organisation address	Ospedale Regionale di Bellinzona e Valli, Bellinzona, Switzerland, 6500
Public contact	Study Coordination Office, International Extranodal Lymphoma Study Group (IELSG) , 0041 91 811 90 40, ielsg@eoc.ch
Scientific contact	Emanuele Zucca, International Extranodal Lymphoma Study Group (IELSG), 0041 91 811 90 40, ielsg@eoc.ch

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	27 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2017
Global end of trial reached?	Yes
Global end of trial date	27 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the PET response rate following chemo-immunotherapy

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 June 2007
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	Italy: 112
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Chile: 1
Worldwide total number of subjects	125
EEA total number of subjects	118

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)	122
From 65 to 84 years	2

85 years and over	1

Subject disposition

Recruitment

Recruitment details:

From 22 June 2007 to 17 Jun 2009

Pre-assignment

Screening details:

Patients with histopathological proven diagnosis of Primary Mediastinal Large B-Cell Lymphoma (PMBCL) of any stage, previously untreated and eligible for intensive immunochemotherapy were enrolled.

Period 1

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

Arms

Arm title	Enrolled patients

Arm description:

The main aim of the study did not comprise any treatment evaluation. Patient were treated with standard immunochemotherapy (followed by consolidation radiotherapy if this was standard policy at the treating centre)

Arm type	Experimental
Investigational medicinal product name	NOT APPLICABLE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Not Applicable

Number of subjects in period 1	Enrolled patients
Started	125
Completed	119
Not completed	6
Lost to follow-up	2
Tumor progression	4

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial
Reporting group description:	
Treated patients	

Reporting group values	Overall Trial	Total	
Number of subjects	125	125	
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)	122	122	
From 65-84 years	2	2	
85 years and over	1	1	
Age continuous Units: years			
median	33		
inter-quartile range (Q1-Q3)	27 to 41	-	
Gender categorical Units: Subjects			
Female	77	77	
Male	48	48	
Performance Status (ECOG) Units: Subjects			
ECOG = 0	61	61	
ECOG = 1	47	47	
ECOG > 1	17	17	
B Symptoms at presentation Units: Subjects			
Present	45	45	
Absent	80	80	
Anna Arbor Stage Units: Subjects			
I-II	98	98	
III-IV	27	27	
International Prognostic Index (IPI) Units: Subjects			
Low risk	91	91	
Low-intermediate risk	21	21	
Intermediate-high risk	12	12	
High risk	1	1	

End points

End points reporting groups

Reporting group title	Enrolled patients

Reporting group description:

The main aim of the study did not comprise any treatment evaluation. Patient were treated with standard immunochemotherapy (followed by consolidation radiotherapy if this was standard policy at the treating centre)

Primary: Complete Metabolic Response (CMR) on PET scanning after frontline immunochemotherapy and risk stratification

End point title	Complete Metabolic Response (CMR) on PET scanning after frontline immunochemotherapy and risk stratification[1]

End point description:

The main purpose is to evaluate the role of PET as a tool to evaluate treatment results in PMBCL. It was verified if the achievement of complete metabolic response after 1st line chemotherapy is significantly associated with a better prognosis.

End point type	Primary

End point timeframe:

At the completion of chemoimmunotherapy

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: OS and PFS were estimated using the Kaplan-Meier or the life-table method as appropriate. Follow-up was calculated as the median time to censoring using a reverse Kaplan-Meier analysis. Cox regression was used for extimation of hazard ratio and its confidence interval. The exact 95%CI were calculated for incidence percentages. P-values of 0.05 or less (two sides test) were considered to indicate statistical significance. Statistical analysis was conducted using the STATA 5.0 software package.

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	115[2]			
Units: Percentage				
number (confidence interval 95%)				
Complete Metabolic Response (CMR) on PET scanning	47 (38 to 56)			
Overall Survival at 5 years	95 (89 to 98)			
Progression Free Survival at 5 years	90 (82 to 94)			

Notes:

[2] - Per-Protocol (Efficacy Evaluable) Population receiving immunotherapy

Statistical analyses

No statistical analyses for this end point

Primary: CMR on PET scanning defined by cutpoint

End point title	CMR on PET scanning defined by cutpoint[3]

End point description:

The main purpose is to evaluate the role of PET as a tool to evaluate treatment results in PMBCL. The cutpoint for defining the achievement of a metabolic complete response was evaluated. CMR defined

by Deauville Score (DS) 2 - Mediastinal Blood Pool (MBP) and DS 3 - Liver uptake were analyzed. Complete results are shown in Figure 1

End point type	Primary

End point timeframe:

At the end of chemiotherapy

Notes:

[3] - 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 PET CR rate was expected to be approximately 50% in the group undergoing protocol therapy, and with a sample size of a minimum 100 patients the PET CR rate would be estimated with a standard error < 5%, and hence the 95% CI would extend from approximately 40%-60%.
The PET CR rate and its 95% CI were estimated for patients who completed the planned chemotherapy

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	115[4]			
Units: Percentage				
number (not applicable)				
DS 2 - Mediastinal Blood Pool	47			
DS 3 - Liver uptake	80			

Notes:

[4] - Per-Protocol (Efficacy Evaluable) Population receiving immunotherapy

Attachments (see zip file)	Figure 1/Figure 1.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: Complete Metabolic Response (CMR) on PET scanning after consolidation radiotherapy

End point title	Complete Metabolic Response (CMR) on PET scanning after consolidation radiotherapy

End point description:

The post-radiotherapy scans were visually assessed according to the Deauville criteria with 18FDG uptake of any residual lesion scored according to the 5-point scale using Mediastinal Blood Pool and liver uptake as reference settings. The achievement of a CMR was defined, according to the Lugano Classification and the results of the previous analysis, by a completely PET-negative scan or a scan having minimal residual uptake less than/equal to the liver activity (Deauville score ≤3).

End point type	Post-hoc

End point timeframe:

At least two months from the completion of involved-field radiotherapy

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	88[5]			
Units: Percentage				
number (confidence interval 95%)	89 (80 to 94)			

Notes:

[5] - Per-Protocol (Efficacy Evaluable) Population receiving consolidation therapy

Statistical analyses

No statistical analyses for this end point

Post-hoc: PET-CT Response assessment and risk stratification - 5 years Overall Survival

End point title	PET-CT Response assessment and risk stratification - 5 years Overall Survival

End point description:

Metabolic PET-metrics, particularly TLG, were evaluated to establish potential biomarkers.
Correlation between the total lesion glycolysis (TLG) and Overall Survival at 5 years is reported. TLG was calculated as the product of Standardized Uptake Value (SUV) mean and Metabolic Tumor Volume (MTV). TLG was homogenously estimated in all patients during the central review of PET scans to mitigate the risks.
Complete results are shown in Figure 2.

End point type	Post-hoc

End point timeframe:

At baseline and 5 years after treatment start

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	103[6]			
Units: Percentage				
number (not applicable)				
Low TLG (<cut off value)	100			
High TLG (> cut-off value)	80			

Notes:

[6] - Per Protocol (Efficacy-evaluable) Population - prognostic stratification

Attachments (see zip file)	Figure 2/Figure 2.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: PET-CT Response assessment and risk stratification - Progression Free Survival (PFS)

End point title	PET-CT Response assessment and risk stratification - Progression Free Survival (PFS)

End point description:

Metabolic PET-metrics, particularly TLG, were evaluated to establish potential biomarkers.
Correlation between the total lesion glycolysis (TLG) and Progression Free Survival at 5 years is reported.
Complete results are shown in Figure 2.

End point type	Post-hoc

End point timeframe:

At baseline and 5 years from treatment start

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	103[7]			
Units: Percentage				
number (not applicable)				
High TLG (> cut off value)	64			
Low TLG (< cut off value)	99			

Notes:

[7] - Per Protocol (Efficacy Evaluable) Population - Prognostic Stratification Analysis

Attachments (see zip file)	Figure 2/Figure 2.pdf

Statistical analyses

No statistical analyses for this end point

Post-hoc: Combination of quantitative PET-CT parameters in prognostic stratification - Positive Predictive Value (PPV)

End point title	Combination of quantitative PET-CT parameters in prognostic stratification - Positive Predictive Value (PPV)

End point description:

Metabolic heterogenity is a prognostic factor and combined with TLG may allow early identification of poor prognosis patients.
TLG and other clinical and imaging parameters were combined to evaluate if PPV can be improved.
Complete results are shown in Table 1.

End point type	Post-hoc

End point timeframe:

At baseline, after chemoimmunotherapy and 5 years after treatment start

End point values	Enrolled patients			
Subject group type	Reporting group			
Number of subjects analysed	100[8]			
Units: Percentage				
number (not applicable)				
End of therapy TLG	53			
Baseline TLG + end of therapy DS	45			

Notes:

[8] - Per Protocol (Efficacy Evaluable) Population - combination of quantitative parameters

Attachments (see zip file)	Univariate Analysis/Table 1.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From the signature of informed consent, during treatment and follow up

Adverse event reporting additional description:

As per protocol only AEs of grade >/=3 with a suspected relationship to the study drugs and SAEs were collected

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	5.1

Reporting groups

Reporting group title	Safety evaluable population

Reporting group description: -

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: No safety objectives were identified for this clinical-pathologic study. As per protocol, only AEs of Grade ≥3 with a suspected relationship to the study drugs and SAEs were collected. All treatments were well tolerated and no unexpected side effects were recorded.
The most frequent toxicities were myelosuppression, transaminases elevation and mucositis, as expected.

Serious adverse events	Safety evaluable population		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 125 (10.40%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	1		
Investigations			
Alanine aminotransferase increased	Additional description: and Aspartate Aminotransferase increased		
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dehydration			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration			

site conditions			
Pyrexia			
subjects affected / exposed	2 / 125 (1.60%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus paralytic			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			

subjects affected / exposed	3 / 125 (2.40%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Pseudomonal sepsis			
subjects affected / exposed	1 / 125 (0.80%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 125 (0.80%)		
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	Safety evaluable population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 125 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 August 2006	Amendment No. 1: the main purpose of this amendment was to change the days of administration of vincristine and the dose of bleomycin (R-MACOP-B and R-VACOP-B regimes). In addition, the web link for the CTCAE was updated to version 3.0.
28 January 2008	Amendment No. 2: this amendment was implemented to align the 2 schedules of follow up reported in the protocol.
12 August 2008	Amendment No.3 : the main purpose of this amendment was the correction of a typo present in the Schedule of Events regarding the CT scan of the neck.
24 November 2008	Amendment No. 4: this amendment was implemented to correct a typo in the section 20 - Statistical Considerations (with a standard error of PET CR <5 %, the CI of 95 % extends approximatively 40%-60%).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Not Applicable

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29720487

http://www.ncbi.nlm.nih.gov/pubmed/28485042

http://www.ncbi.nlm.nih.gov/pubmed/27839910

http://www.ncbi.nlm.nih.gov/pubmed/26089397