# 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<br>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<br>Units: years | | | |
| median | 33 | | |
| inter-quartile range (Q1-Q3) | 27 to 41 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 77 | 77 | |
| Male | 48 | 48 | |
| Performance Status (ECOG)<br>Units: Subjects | | | |
| ECOG = 0 | 61 | 61 | |
| ECOG = 1 | 47 | 47 | |
| ECOG > 1 | 17 | 17 | |
| B Symptoms at presentation<br>Units: Subjects | | | |
| Present | 45 | 45 | |
| Absent | 80 | 80 | |
| Anna Arbor Stage<br>Units: Subjects | | | |
| I-II | 98 | 98 | |
| III-IV | 27 | 27 | |
| International Prognostic Index (IPI)<br>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).<br>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