1. TITLE PAGE

Investigational Product:	Gemcitabine-Oxaliplatin plus Rituximab (R-GEMOX)
Protocol No. / Study No.:	**R-GEMOX**
EudraCT No.:	**2005-002344-26**
Study Title:	Gemcitabine-Oxaliplatin plus Rituximab (R-GEMOX) in refractory/relapsed patients with CD 20 positive diffuse large B-cell lymphoma, non eligible for high-dose chemotherapy followed by autotransplantation

Development Phase:	II
Indication:	Relapsed/refractory patients with previously treated diffuse CD20-positive large B-cell lymphoma, not eligible for high-dose chemotherapy followed by autologous transplantation
GCP Statement:	

Date First Patient Enrolled:	12-Aug-2003
Date Last Patient Last Visit:	29-Apr-2011
Report Date:	28-Dec-2012
Report Written by:	APMW – Dr Alain Platel, DSc, PhD, MBA Les Garants 69820 Fleurie - France
Sponsor:	**GELA** : **G**roupe d'**E**tude des **L**ymphomes de l'**A**dulte ✉ : CHU Saint Louis – Centre Hayem 75475 Paris cedex 10 - France ☎: +33(0)1.42.49.98.11 Fax : +33(0)1.42.49.99.72
Sponsor Contact Person:	Christelle Da Cruz ☎: +33 (0)4.72.66.93.33 Fax.: +33 (0)4.72.66.93.71
Sponsor Medical Responsible:	Prof. B. Coiffier Centre Hospitalier Lyon Sud - Secteur Sainte Eugénie Chemin du Grand Revoyet - 69310 Pierre Bénite - France ☎: +33 (0)4 72 66 93 33 Fax: +33 (0)4 72 66 93 71
Coordinating Investigator:	Prof. Corinne HAIOUN Responsable de l'Unité Hémopathies Lymphoïdes Groupe Hospitalier Henri Mondor-Albert Chenevier 94010 Créteil - France ☎:+33 (0)1.49.81.20.51 Fax: +33 (0)1.49.81.20.64 corinne.haioun@hmn.aphp.fr

2. SYNOPSIS

Name of Sponsor/Company: GELA	Individual Study Table Referring to Module x.x.x	*(For National Authority Use only)*
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Title of Study:
Gemcitabine-Oxaliplatin plus Rituximab (R-GEMOX) in refractory/relapsed patients with CD 20 positive diffuse large B-cell lymphoma, non eligible for high-dose chemotherapy followed by autotransplantation.

Coordinating Investigator:
Prof. Corinne Haioun, Service Hématologie, Centre Henri Mondor, F-94010 Créteil, France

Study Centre: Centre Hospitalier Lyon Sud, Secteur Sainte Eugénie, Bât. 41, Chemin du Grand Revoyet, 69310 Pierre Bénite, France

Publication: El Gnaoui T, Tilly H, Mounier N, Gisselbrecht C, Sebban C, Casasnovas O, Delarue R, Petrella T, Canioni D, Haioun C. Rituximab plus gemcitabine and oxaliplatine (R-GemOx) in refractory/relapsed patients with diffuse large B-cell lymphoma (DLBCL) who are not candidates for high-dose therapy (HDT): A GELA study. ASCO 2010 Abstract #8011.

Studied Period (years):		**Phase of Development:**
Date of first patient enrolled:	12-Aug-2003	II
Date of last patient last visit :	29-Apr-2011	

Objectives:
Primary Objective: To determine the **Overall Response Rate** (ORR) (Complete Response, Unconfirmed Complete Response, or Partial Response) **after completion of 4 cycles of R-GEMOX.**

Methodology:
Multicenter, open-label, not randomized, phase II clinical study, evaluating the efficacy and safety of R-GEMOX therapy. The study consisted in two phases:

- Part I: **Induction**: R-GEMOX: 4 cycles
- Part II: **Consolidation**: R-GEMOX: 4 cycles

Number of Patients:
A number of 49 patients were enrolled, 48 received the treatment, 36 completed the induction phase, 28 started the consolidation phase, and 24 completed the treatment phase.

Diagnosis and Main Criteria for Inclusion:
To be eligible for the study, the patients had to have CD20 positive diffuse large B-cell lymphoma, to be not eligible for high-dose chemotherapy followed by auto-transplantation, in relapse after first or second CR, PR or less than PR to first-line treatment for the "rituximab-naïve patients" OR relapse after first or second CR with a minimum delay of 12 months between the last rituximab infusion and the inclusion for the "rituximab-experienced patients", to be aged from 18 to 75 years, , previously treated with chemotherapy regimen containing anthracyclines, with or without rituximab, with ECOG performance status 0 to 2 and a minimum life expectancy of 3 months, and having signed the informed consent.

Patients were not eligible for: Burkitt's, mantle-cell and T-cell lymphomas, CD 20 negative diffuse large B-cell lymphoma, documented HIV or HBV infection, central nervous system or meningeal involvement by the lymphoma, not previously treated with anthracycline, with contraindication to R-GEMOX combination, with

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any radiotherapy during 4 weeks prior to inclusion, with any serious active disease or co-morbid medical condition, poor renal or hepatic function, poor bone marrow reserve, history of cancer during the previous 5 years, treatment with investigational drug within 30 days before planned first Cycle of chemotherapy and during the study. Pregnant or lactating woman and patients unable to provide informed consent due to intellectual impairment were also ineligible.

Test Product:	**Dose and Mode of Administration:**	**Batch Number**
Rituximab (Mabthera®) Gemcitabine (Gemzar®) Oxaliplatin (Eloxatin®)	375 mg/m² i.v. infusion at ≤400 mg/h maximum 1000 mg/m² i.v. infusion over 100 min 100 mg/m² 2 h i.v. infusion in 250 mL 5% glucose	

Duration of Treatment:
Patients were recruited over 5.5 years and followed-up until 29-Apr-2011. Patients were given R-GEMOX regimen every 2 weeks and treated upon completion of treatment (8 cycles) except if disease progression, absence of at least a partial response 5PR) at cycle 4 evaluation, unacceptable toxicity patient refusal of further study treatment or consent withdrawn during treatment.

Criteria for Evaluation:
Efficacy:
Primary efficacy variable:
The primary efficacy variable was the **Overall Response Rate** (ORR) (Complete Response, CR; Unconfirmed Complete Response, CRu and Partial Response, PR) **after completion of 4 cycles of R-GEMOX**.
The secondary efficacy variables were the following:

- **Overall Response Rate** (ORR) (Complete Response, CR; Unconfirmed Complete Response, CRu and Partial Response, PR) **at the end of completion of the planned treatment** (8 cycles of R-GEMOX).
- **Safety** of R-GEMOX in this patient population.
- **Overall survival** (OS), **Progression-Free Survival** (PFS) and **Disease-Free Survival** (DFS) for complete responders.

Statistical Methods:
Quantitative variables were summarized by mean, standard deviation (SD), median, range; quartiles were presented when relevant. Qualitative variables were described in terms of frequencies of each response category and frequencies converted into percentages of the number of patients or adverse events examined.

Censored data were presented as Kaplan-Meier plots of time to first event with 95% confidence intervals (95% CIs). The median time to event was calculated (if reached) with 95% CIs. Estimates of treatment effects were expressed as hazard ratios based on the Cox regression with 95% CI.

Statistical tests were two-sided and performed using a 5% level of significance and 95% CIs were presented where appropriate.

The number and proportion of responders and non-responders, with the two-sided Pearson-Clopper 95%CI were presented, the two-sided exact 95% CI and p-value of exact binomial proportion test comparing the observed complete response rate to the theoretical one.

Primary Efficacy Analysis: The primary efficacy analysis was the comparison of ORR with the theoretical one (40%) at the end of 4 cycles of R-GEMOX, using a two-sided binomial comparison with an overall

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significance level of 5% and a power of 80%. The null hypothesis was the equality of the proportions.

Analysis of Safety: Adverse events were described by individual listings and by summary tables broken by body system, intensity and relation to trial treatment. Laboratory test values were presented by individual listings with flagging of values outside of the normal ranges. Vital signs were listed.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

The median age at inclusion of patients was 69 years (range: 41-77 years), with a majority of men (55%). With date of last contact censored at the stopping date (01-Feb-2011), the median duration of follow-up for the ITT population was 65 months (range: 0-76 months).

In this population, the ORR (CR+CRu+PR) after induction was 60.4% (95% CI: 45.3-74.2%; p=0.0039). The associated probability being < 0.05 and the lower limit of the 95% CI of the ORR being higher than the predefined threshold (40%), it can be concluded that the ORR was significantly different from the predefined threshold of 40%. In this ITT population, the CRR (CR+CRu) after induction was 43.8% (95% CI: 29.5-58.8%). At the end of treatment the ORR was 45.8% (95% CI: 31.4-60.8%), and the CRR was37.5% (95% CI: 24.0-52.6%).

At stopping date (01-Feb-2011), 41 patients (85%) presented with an event: 37 (77%) due to progression/relapse and 4 (8%) due to death without progression. The median duration of PFS was 5 months (95% CI: 4-9 months) and the 5 year-PFS was 12.8% (95% CI: 5.2-23.9%).The median duration of OS was 11 months (95% CI: 7-23 months) and the 5-year OS was 13.9% (95% CI: 5.8-25.6%).

Overall, 24 patients (50%) achieved a CR/CRu before or at the end of treatment and were assessed for Disease-Free Survival (CR/ CRu). The median duration of DFS was 10 months (95% CI: 7-41 months) and the 5-year DFS was 25.0% (95% CI: 10.2-43.1%),

The exploratory analyses performed to evaluate the outcomes to R-GEMOX according to previous treatment with rituximab, to time between the end of last treatment and Cycle 1, to both previous treatment with rituximab and time between the end of last treatment and Cycle 1, to age-adjusted IPI, and to IPI, indicated the following:

- Patients who received a previous treatment with rituximab and/or with < 1 year between the last treatment and Cycle 1 of R-GEMOX had a worst prognosis than those who did not previously receive rituximab and/or with ≥ 1 year between the last treatment and Cycle 1. The worst case was when patients previously received rituximab and had < 1 year between the last treatment and Cycle 1.
- Patients with 0-1 age-adjusted IPI had a better prognosis than those with 2-3 age-adjusted IPI. This difference was not seen with IPI not corrected for age.

At the time of the analysis, 37 patients (77%) in ITT population presented a first progression/ relapse and 22 patients (46%) presented a second progression/ relapse.

The sensitivity analysis conducted in the Per Protocol Population included 45 patients and confirmed the results observed in the ITT population.

SAFETY RESULTS:

The most common toxicities during treatment were hematological toxicities:

- 100% of patients experienced leukocytes toxicities, including 69% with ≥ 1 Grade 3.

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- 98% of patients experienced neutrophils toxicities, including 73% with ≥ 1 Grade 3.
- 98% of patients experienced hemoglobin toxicities, including 23% with ≥ 1 Grade 3.
- 92% of patients experienced platelets toxicities, including 44% with ≥ 1 Grade 3.
- 52% of patients experienced other toxicities (17% with Grade≥3).

Overall during the treatment period, 16 patients (33%) received ≥ 1 RBC transfusion, and 11 patients (23%) received ≥ 1 platelet transfusion, 27 patients (87% of patients with AEs) received ≥ 1 corrective treatment for AE, and 42 out of the 63 AEs (67%) were associated with a corrective treatment.

A total of 26 SAEs were experienced by 19 patients (40%). Overall, 16 (84%) out of the 19 patients who experienced SAEs received at least one corrective treatment, and 20 (77%) out of the 26 SAEs reported were associated with a corrective treatment.

A total of 40 deaths (83% of patients) occurred at the time of the analysis, mainly due to lymphoma (90%).

CONCLUSIONS:
The R-GEMOX regimen shows promising activity with a safe outpatient regimen for relapsed or refractory diffuse large B-cell lymphoma not eligible for high-dose therapy. The R-GEMOX regimen could be considered as a platform for new combinations with targeted treatment in order to improve PFS, especially in refractory and early relapsed patients previously treated with rituximab.

Report Date:
28-Dec-2012