METHODS (online supplement)

Study design
This study was an open label, single arm multicenter phase II trial. The primary endpoint was the overall response rate after completion of four cycles of treatment (ORR). Calculation of sample size was based on the primary ORR endpoint. We anticipated an ORR rate of 55% and computed that, using a triangular test procedure every 5 consecutive patients, an average sample size of 50 patients would provide 80% power at the overall 5% (2-sided) significance level to detect a complete response rate (CR) above 40% (null hypothesis: 40%, alternative hypothesis: 55%)(2). The secondary endpoints were ORR at the end of treatment (completion of 8 cycles), toxicity, overall survival (OS) and progression-free survival (PFS).

The local ethics committees and the national regulatory agency according to the French regulatory laws approved the protocol. All patients provided written informed consent. Our study complied with all provisions of the Declaration of Helsinki and its current amendments and was done in accordance with good clinical practice guidelines. It was deposited on the US National Institutes of Health website (NCT00169195).

Patient Selection

The multi-center study phase II study of R-GemOx enrolled patients in 10 institutions in France between August 2003 and January 2009. Patients were eligible if they were aged from 18-75 years old and had refractory/relapsed CD20-positive DLBCL that had been diagnosed in accordance to the World Health Organization (WHO) classification at the time of enrollment. Patients were required to be 1) in first or second relapse, 2) previously treated with a chemotherapy regimen containing anthracyclin, with or without rituximab, and 3) not eligible for high dose therapy. Eligibility requirements also included measurable disease and an Eastern Cooperative Oncology Group [ECOG] performance status of 0 to 2, a minimum
life expectancy of 3 months, negative HIV, HBV and HCV serology tests (except after vaccination).

**Chemotherapy and Dose Adjustments**

R-GemOx was administered as previously described (1). Rituximab 375 mg/m$^2$ was administered on day 1 and gemcitabine and oxaliplatin at 1000 mg/m$^2$ and 100 mg/m$^2$ respectively, on day 2. Cycles were repeated every 15 days. Eight cycles were planned if patients reached at least partial response after 4 cycles. After four cycles, patients who failed to achieve at least a partial response were excluded from the trial. Radiotherapy was not permitted. A complete blood count was recommended on days 7, 10, and 14 of each treatment cycle to assess hematologic toxicity. No dose adjustment was planned in the event of hematologic toxicity, but cycles were postponed until the absolute neutrophil count reached $1.0 \times 10^9$/L and the platelet count reached $100 \times 10^9$/L. Dose adjustment of oxaliplatin was carried out in the event of peripheral neuropathy, as previously described (1).

Growth factors support and antibiotics were used according to the decision of the treating physician for the first cycle but in case of treatment delay or febrile neutropenia, Filgrastim (granulocyte colony-stimulating factor [G-CSF]) was administered for subsequent cycles.

**Staging and follow up.**

The extent of the disease was assessed by physical examination; relevant laboratory tests; computed tomography (CT-scan) of the chest, abdomen, and pelvis; cerebrospinal fluid examination; bone marrow biopsy; and other investigational procedures depending on clinical symptoms. Lymphomas were classified in accordance with criteria of the WHO classification(3). Immunohistochemical determination of the Cell of Origin (COO) was centrally performed according to the Hans algorithm(4). Patients who completed their treatment had a complete clinical examination every 3 months for the first year then every 6
months for 5 years. A CT-scan was performed twice a year. No routine molecular biology procedures or functional imaging methods were used.

**Toxicity and Response Assessments**

Hematologic and non-hematologic toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (Version 2.0). Toxicity evaluation was conducted on day 1 of each treatment cycle and included neurologic examination and laboratory assessment with complete blood cell counts and serum chemistry tests. Every adverse event reported by the patient or observed by the investigator was collected in the case report form in predefined categories. An adverse event was defined as any adverse change from the patient’s baseline condition, independent of treatment status. All grade 3 and 4 events and grade 2 infections were recorded in detail.

Thoracic, abdominal, and pelvic CT scans and bone marrow biopsy (in patients with bone marrow involvement at initial diagnosis) were conducted to assess response according to the International Working Group Criteria after 4 and 8 cycles (5). The local radiologist first assessed tumor measurements, and in order to validate the quality of response declared by each investigator, a review of CT scan images (baseline, mid and end treatment) was conducted in consensus by two expert radiologists (PB, AR).

**Statistical Methods**

Patients were analyzed in an intent-to-treat basis. The ORR was defined as the rare of complete responses, unconfirmed complete responses and partial responses (CR+ CRU +PR). Progression-free survival (PFS) was defined as the time interval from the date of enrollment until disease progression, relapse, or death —whichever occurred first. Relative dose intensity (RDI) for gemcitabine and oxaliplatin was calculated according to Hryniuk et al (6). Overall
survival (OS) was calculated from the date of enrollment until death from any cause. Survival curves were estimated using the product-limit method of Kaplan–Meier and compared using the log-rank test. Multivariate analysis was performed by a Cox model regression. All statistical analyses were performed using SAS software (SAS, version 9.2, SAS institute, Cary, NC)

**Biomarkers**

Pathological specimens of 36 out of 49 patients (73%) with histological material available either at diagnosis (n=23) or at relapse (n=26) or in both situations (n=13) were more extensively analyzed in order to classify tumor biopsies according to cell of origin into germinal center B-cell like (GCB) versus non-GCB subtypes using CD10, BCL6 and MUM1 markers as previously published by Hans et al (4). Immunostaining performed either on full slides or on tissue microarrays containing two or three representative 0.6-mm cores of routinely processed tissues, were reviewed “in consensus” by two pathologists (DC, PG), at the LYSA Center of Pathology. One of these 36 cases corresponds to the patient who did not receive treatment.