Study Synopsis

Ofatumumab versus Rituximab Salvage Chemoimmunotherapy followed by ASCT in Relapsed or Refractory DLBCL (OMB110928)

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequent subtype of non-Hodgkin’s lymphoma (NHL) comprising approximately 30% of new cases (Armitage and Weisenburger, 1998) but approximately 60% of all lymphomas in older patients in whom prognosis is poorer (Thieblemont & Coiffier, 2007). There are an estimated 22,000 new cases per annum in Europe (Ferlay et al., 2004) and 20,000 in the US (Cancer Facts and Figures 2008).

DLBCL is considered very responsive to chemotherapy. For decades, CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) was the standard first-line treatment. Rituximab, an IgG1 monoclonal antibody, binds to CD20 which occurs almost exclusively on B cells. Treatment results of DLBCL have improved dramatically after the introduction of rituximab (R) into CHOP-like, anthracyclin-based, treatment schedules (Feugier et al., 2005; Sehn et al., 2005; Habermann et al., 2006; Pfreundschuh et al., 2006; Pfreundschuh et al., 2008), and it is now the standard of care. Nevertheless, even with current R-CHOP-like treatment, approximately 30-40% of patients will ultimately relapse or progress.

Patients failing first-line treatment may be offered salvage chemotherapy followed by high-dose therapy with autologous stem cell transplantation (ASCT) if the disease is still chemo-sensitive. It is a potentially curative treatment, significantly improving disease free survival and overall survival in primary refractory DLBCL (Philip et al., 1995). Different salvage regimens have been used including DHAP (cisplatin, cytarabine, dexamethasone), VIM (etoposide, ifosfamide, methotrexate), ICE (ifosfomide, carboplatin, etoposide), or combinations (Philip et al., 1987; Vose et al., 2001; Velasquez et al., 1988; Girouard et al., 1997; Kewalramani et al., 2004; Vellenga et al 2001).

However, a substantial percentage of patients will either fail to respond to salvage therapy and subsequently not be eligible for ASCT, or progress after ASCT. Major risk factors determining response to salvage treatment, event free and overall survival are: a) duration of first remission; b) secondary age adjusted IPI at relapse or progression; c) metabolic response during salvage treatment as determined by early PET; d) prior treatment with rituximab (Guglielmi et al., 1998; Hamlin et al., 2003; Schot et al., 2007; Gisselbrecht et al., 2007). HOVON, a Dutch/Belgian collaborative group, recently completed a prospective randomized study in 239 DLBCL patients failing first-line CHOP-like treatment (HOVON 44 study). All patients were scheduled to receive 3 cycles of the DHAP salvage chemotherapy regimen, modified by replacing the second cycle with VIM. Patients were randomized to receive rituximab combined with DHAP (R-DHAP) or DHAP alone. Responding patients in both study arms were subsequently treated with high-dose BEAM chemotherapy followed by ASCT. R-DHAP proved to be significantly superior to DHAP salvage treatment, with failure-free survival (FFS) at 2 years of 54% for R-DHAP versus 24% for DHAP. However, even in the R-DHAP arm the percentage of patients not responding to salvage
treatment was 30% (Vellenga et al., 2008). Moreover, most patients in the HOVON 44 study were rituximab naive.

Recently reported interim results of the first 200 patients randomized between rituximab-ICE (R-ICE) versus rituximab-DHAP (R-DHAP) salvage therapy followed by BEAM and ASCT, in the ongoing CORAL 50-03B study show that patients who have received prior rituximab treatment have much inferior response rates than rituximab naïve patients (Gisselbrecht et al., 2007). Rituximab naïve patients had a 82% response rate and 66% 2-year FFS compared with a 54% response rate and 34% FFS for patients who had received prior rituximab treatment. Thus, as R-CHOP-like regimens have become standard first-line treatment in DLBCL and patients who have received prior rituximab may be less likely to respond to rituximab salvage treatment, there is a need for new therapies in patients failing first-line R-CHOP-like therapy.

**Ofatumumab**

Ofatumumab is a fully human monoclonal IgG1κ-antibody targeting a novel CD20-epitope. Preclinical data show that ofatumumab is active against B-cell lymphoma/chronic lymphocytic leukemia cell-lines with low CD20-antigen density and an increased expression of complement inhibitory molecules. Ofatumumab was superior to rituximab in its ability to induce lysis in B-cell lines and also killed fresh B-chronic lymphocytic leukemia cells that were resistant to rituximab. Ofatumumab has a slower off-rate and more stable CD20 binding in comparison with rituximab and targets a different epitope than rituximab of the CD20 antigen (Teeling et al., 2004; Teeling et al., 2006). In cynomologus monkeys, the duration of B-cell depletion from peripheral blood and lymph nodes induced by ofatumumab was longer than that of rituximab (Dechant et al., 2003).

Safety and efficacy of ofatumumab, has been analyzed in multicenter dose-escalating phase I/II studies in chronic lymphocytic leukemia and follicular lymphoma. Three cohorts of patients including 33 patients with relapsed or refractory chronic lymphocytic leukemia received weekly infusions of ofatumumab for four weeks as follows: cohort A, the first infusion was 100 mg and three subsequent infusions of 500 mg; cohort B, the first infusion was 300 mg and three subsequent infusions of 1000 mg; cohort C, the first infusion was 500 mg and three subsequent infusions of 2000 mg. The maximum tolerated dose was not reached. The majority of related adverse events occurred at first infusion, and the number of adverse events decreased at each subsequent infusion. Seventeen (51%) of 33 patients experienced infections, 88% of them of grade 1-2. One event of interstitial pneumonia was fatal; all other cases resolved within one month. The response rate in cohort C was 50% (13/26 patients) (Coiffier et al., 2008).

Recent data from a single arm Phase III trial in refractory CLL will be presented at ASH 2008. The activity of ofatumumab was evaluated in 138 patients with refractory CLL. About half of the patients (59) were refractory to both fludarabine and alemtuzumab and 79 were refractory to fludarabine and considered inappropriate candidates for alemtuzumab due to bulky tumor in their lymph nodes. An objective response rate of 51% consisting of 30 partial responses (PR) was achieved in the group of patients refractory to fludarabine and alemtuzumab. In the fludarabine refractory, alemtuzumab inappropriate patient group, an objective response rate of 44% was achieved, including 1 complete response (CR), and 34 PRs. Ofatumumab was generally well tolerated with the most frequently reported adverse events being pyrexia, diarrhea, fatigue, cough, neutropenia, anemia and pneumonia.
In a phase I/II trial evaluating safety and efficacy of ofatumumab in relapsed or refractory follicular non-Hodgkin’s lymphoma (FL) grade 1-2, 4 dose-groups of 10 patients received 4 weekly infusions of 300, 500, 700, or 1000 mg (Hagenbeek et al., 2008). Patients had a median of two prior FL therapies and 13% had elevated LDH. No safety concerns or maximum tolerated dose were identified. Most adverse events occurred on the first infusion day and were CTC grade 1-2. Eight related events were grade 3. Treatment caused immediate and profound B-cell depletion. Clinical response rates ranged from 20–63%. Median time to progression (TTP) for all patients was 8.8 months. Median TTP for responders, duration of response, and time to next anti-FL therapy has not been reached at a median follow-up of 9.2 months. Ofatumumab was able to induce responses in 9 of 14 patients relapsing following rituximab, including 3 of 4 rituximab refractory patients. Ofatumumab is currently being evaluated in patients with rituximab-refractory FL. The safety of combining ofatumumab with chemotherapy is being evaluated in other trials.

**Study Objectives**

**Primary objective:**
- To evaluate the progression-free survival (PFS) in patients receiving ofatumumab combined with salvage chemotherapy (O-chemo) compared to patients receiving rituximab combined with salvage chemotherapy (R-chemo).

**Secondary objectives.** To evaluate the following in patients receiving ofatumumab combined with salvage chemotherapy (O-chemo) compared to patients receiving rituximab combined with salvage chemotherapy (R-chemo):

- Overall response rate after R-chemo or O-chemo as determined by positron emission tomography (PET)/CT
- Overall response rate three months after ASCT
- Complete response rate
- Event-free survival
- Overall survival
- Incidence and type of grade 3 & 4 (CTCAE v3) non-hematological toxicities
- Time to neutrophil and platelet recovery after each cycle of therapy including BEAM/ASCT
- Adequate number of autologous stem cells (≥2 million CD34+ cells/kg) mobilized prior to administration of BEAM.
- Exploratory prognostic markers
- Pharmacogenetics profile associated with response to ofatumumab.

**Study Design**

This is a Phase III, parallel group, open label, active comparator, randomised (1:1), registration trial. Subjects must be refractory to, or have relapsed following, first-line treatment with rituximab in combination with an anthracycline containing regimen, and be eligible for ASCT. Subjects with the following disease responses will be deemed refractory: 1) progressive disease during first-line treatment, 2) stable disease after at least 3 cycles of first-line treatment, and 3) PR after at least 6 cycles of first-line treatment. CD20 positive DLBCL must be re-confirmed after
completion of first-line treatment. Subjects will be randomised to receive either rituximab or ofatumumab in combination with three cycles of salvage chemotherapy. Depending upon feedback from investigators, the salvage chemotherapy may be limited to DHAP-VIM-DHAP (DVD), alternatively ICE may also be included. If both regimens are included, centres must prospectively elect to use one of these regimens for all of their patients until the CORAL trial reports. Based on data indicating that increasing the number of rituximab infusions in combination with first-line CHOP may improve efficacy in poor prognosis patients (Pfreundschuh et al., 2007), and depending upon feedback from investigators, a total of six doses of ofatumumab or rituximab will be dosed (schedule to be discussed, dosing on Day 1 and Day 8 of each cycle has been proposed). Disease assessments, including CT and PET scans, will be performed at screening. After the second cycle of salvage therapy a CT scan will be performed and subjects not achieving CR or PR will be considered treatment failures and will not receive any further protocol therapy. CT and PET scans will be performed after the third cycle of salvage therapy and, provided that there is continuing response, subjects will continue with treatment as per protocol. Recognised disease response criteria will be used (Cheson et al., 2007). According to local policy, during the second and/or third cycle of salvage therapy, stem cells will be mobilized with GCSF and harvested. Responding patients will receive high dose chemotherapy with BEAM followed by autologous stem cell transplantation. Success of engraftment will be assessed.

Following completion of treatment, patients will be followed every 3 months for the first two years, every 6 months for the next 2 years, and annually to year 5. The first follow-up assessment at 3 months post treatment will include CT and PET scans, thereafter CT scans will be performed annually or if clinically indicated to exclude disease relapse.

Hematology and biochemistry analysis will be performed by a central laboratory. Paraffin blocks of the original diagnostic lymph node biopsy and the lymph node biopsy after termination of first-line treatment will be submitted to a central lab for producing TMAs for subsequent prognostic analysis.

The trial will be composed of Part A and Part B. The first 100 patients will be recruited to Part A and analysed for futility of efficacy based on response at conclusion of salvage chemotherapy, adequacy of stem cell mobilization and safety. With the agreement of the IDMC, the trial will then recruit the remaining 170 patients in Part B. Recruitment will not be interrupted while the Part A cohort are analysed.
Study Schema

- **Screening**
  - DLBCL
  - R-anthracyline refractory or relapsed

- **Stratification**
  - Chemo regimen
  - R-anthracycline response duration
  - saaIPI
  - centre

- **Response**
  - R-Chemo
  - O-Chemo

- **Follow-up**
  - Cycle 1
  - Cycle 2
  - Cycle 3
  - BEAM ASCT

- **CT-PET**

- **No further protocol treatment**

R=Rituximab
O=Ofatumumab
Chemo=DVD alone, or DVD or ICE
Cycle=21 days
Study Assessments

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</table>

1. Only if initially positive & required to determine response.
2. CT required at 3 months post BEAM/ASCT, thereafter, required annually and when clinically indicated to exclude disease relapse.
3. Assessments to be performed predose during the treatment phase.
4. Salvage therapy related toxicity. All SAEs should be reported during follow-up regardless of causality.
5. LDH only.
6. Flow cytometry for CD19+ will be performed until values are normal, or values are ≥baseline, or until initiation of other therapy for DLBCL.
8. Stem cell mobilisation will take place in cycle 2 and/or 3 according to local policy.
**Inclusion Criteria**

1. CD20 positive DLBCL. Biopsies performed after first-line treatment must confirm CD20 positive DLBCL.

2. Refractory to, or relapsed following, first-line treatment with rituximab combined with anthracycline-based chemotherapy. Relapse is defined as biopsy confirmed CD20 positive DLBCL after a complete response. Refractory disease must fulfill one of the following:
   - persistent lymphoma after at least 6 cycles of rituximab combined with anthracycline-based chemotherapy. Subjects with stage I/II disease will also be eligible if treated with at least 3 cycles of rituximab combined with anthracycline-based chemotherapy and definitive involved-field radiation therapy. Biopsy confirmation of CD20 positive DLBCL is preferred but not required.
   - persistent lymphoma and stable disease (SD) after at least 3 cycles of rituximab combined with anthracycline-based chemotherapy. Biopsy confirmation of CD20 positive DLBCL is preferred but not required.
   - primary progressive disease (PD) despite treatment with rituximab combined with anthracycline-based chemotherapy. Progression is defined as any of the following:
     - New lesion >1.5 cm
     - ≥50% increase in the sum of the product of diameters (SPD) of nodes/lesions

3. CT scan showing at least:
   - 2 or more clearly demarcated lesions with a largest diameter ≥ 1.5 cm
   - OR
   - 1 clearly demarcated lesion with a largest diameter ≥ 2.0 cm.

4. Baseline FDG-PET scans must demonstrate positive lesions compatible with CT defined anatomical tumor sites.

5. Age ≥18

6. ECOG performance status 0, 1, or 2.

7. Eligible for high dose chemotherapy and ASCT.

8. Resolution of toxicities from first-line therapy to grade ≤1.

9. Written informed consent.

**Exclusion Criteria**

1. Any previous cancer therapy for DLBCL, with the exception of:
   - rituximab in combination with an anthracycline-based chemotherapy.
   - radiotherapy as part of the first-line treatment plan or to a limited field at a maximum dose of ≤10Gy (dose for discussion) to control life-threatening symptoms.

2. Known CNS involvement of DLBCL.
3. Received any of the following treatments within 4 weeks prior to start of trial treatment:
   a. Anti-cancer therapy (e.g. alkylating agents, anti-metabolites, purine analogues)
   b. Radiotherapy unless to a limited field at a maximum dose of $\leq 10\text{ Gy}$ (dose for discussion) to control life-threatening symptoms.
   c. Glucocorticoid unless given in doses equivalent to $\leq 1\text{ mg/kg of prednisolone/day}$ for a total duration of $\leq 7$ days.

4. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to randomisation, congestive heart failure (NYHA III-IV), and arrhythmia unless controlled by therapy, with the exception of extra systoles or minor conduction abnormalities.

5. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease.

6. History of significant cerebrovascular disease.

7. Known or suspected hypersensitivity to trial treatments.

8. Known HIV positivity.

9. Hepatitis B: Positive serology for hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBeAb positive and HBsAb negative, a HB DNA test will be performed and if positive the subject will be excluded. Note: If HBeAb positive and HBsAb positive, which is indicative of a past infection, the subject can be included.

10. Hepatitis C: Positive serology for hepatitis C (HC) defined as a positive test for HCAb, in which case reflexively perform a HC RIBA immunoblot assay on the same sample to confirm the result.

11. Active infections requiring systemic therapy.

12. Past or current malignancy with the exception of DLBCL, basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, and tumors successfully treated with curative intent at least 5 years prior to trial entry.

13. Use of investigational therapy in the 4 weeks prior to start of trial therapy.

14. Prior treatment with anti-CD20 monoclonal antibodies, except rituximab, at any time, or treated with other monoclonal antibodies within 3 months prior to start of trial therapy.

15. Screening laboratory values:
   a. platelets $< 50 \times 10^9/L$ (unless due to DLBCL involvement of the bone marrow)
   b. neutrophils $< 1.0 \times 10^9/L$ (unless due to DLBCL involvement of the bone marrow)
   c. creatinine $> 2.0$ times upper normal limit (unless normal creatinine clearance)
   d. total bilirubin $> 1.5$ times upper normal limit (unless due to liver involvement with DLBCL)
   e. ALT $> 2.5$ times upper normal limit (unless due to liver involvement with DLBCL when the limit is $> 5$ times upper limit of normal)
f. alkaline phosphatase > 2.5 times upper normal limit (unless due to liver involvement with DLBCL)

16. Patients known or suspected of being unable to comply with the trial protocol.

17. Pregnant or lactating women. Women of childbearing potential must have a negative pregnancy test prior at screening.

18. Women of childbearing potential, including women whose last menstrual period was less than one year prior to screening, unable or unwilling to use adequate contraception during trial treatment and one year after the last dose of anti-CD20 therapy. Adequate contraception is defined as hormonal birth control, intrauterine device, double barrier method or total abstinence.

19. Male subjects unable or unwilling to use adequate contraception methods from the time of first dose of study medication until one year after the last dose of ofatumumab.

Endpoints

Primary
- Progression-free survival.

Secondary
- Overall response rate.
- Complete response rate.
- Event-free survival.
- Overall survival.

Other(s)
- Mobilisation of \( \geq 2 \) million CD34+ cells/kg prior to BEAM.
- Successful neutrophil engraftment following stem cell transplantation.
- Exploratory prognostic markers in lymph nodes biopsied at original diagnosis and relapse after first-line treatment.
- Exploratory pharmacogenetic biomarkers.

Safety
- Grade 3 & 4 (CTCAE v3) non-hematological toxicity.
- Neutrophil and platelet counts.
Dose Information

Ofatumumab or rituximab will be combined with three cycles DHAP-VIM-DHAP. If ICE is also allowed then centres must elect to use one of these regimens for all of their subjects until the results of the CORAL trial are reported.

There will be six infusions of ofatumumab or rituximab (schedule to be discussed, dosing on Day 1 and Day 8 of each cycle has been proposed). To minimise infusion reactions the first dose of ofatumumab will be 300mg, thereafter, 1000mg of ofatumumab will be administered. Ofatumumab will administered intravenously in 1000mL of 0.9% saline. Rituximab will be administered at a dose of 375mg/m$^2$, and at a concentration of 1-4mg/mL in either 0.9% saline or 5% dextrose in water.

Salvage Chemotherapy

The duration of each cycle of DHAP-VIM-DHAP is 3 weeks and will be dosed as follows:

DHAP cycle 1 & 3:

<table>
<thead>
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<th>Dose/day</th>
<th>Route</th>
<th>Dosing days</th>
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</thead>
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<tr>
<td>Dexamethasone</td>
<td>40mg</td>
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<tr>
<td>Cisplatin</td>
<td>100mg/m$^2$</td>
<td>24 hrs continuous infusion i.v.</td>
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<tr>
<td>Cytarabine</td>
<td>2g/m$^2$ q12 hrs</td>
<td>3 hrs for each infusion i.v.</td>
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VIM cycle 2:

<table>
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<tr>
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<td>2 hrs infusion i.v</td>
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<tr>
<td>Ifosfamide</td>
<td>1200 mg/m²</td>
<td>1 hr infusion i.v.</td>
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<tr>
<td>Mesnum</td>
<td>10 mg/kg</td>
<td>1 hr infusion i.v. combined with ifosfamide 8 hrs infusion i.v. after ifosfamide</td>
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<tr>
<td>Methotrexate</td>
<td>30 mg/m²</td>
<td>Bolus i.v.</td>
<td>1, 5</td>
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If ICE is included in the trial, the duration of each cycle is 3 weeks and will be dosed as follows:

- Ifosfamide and mesna both at 5g/m²/24h on day 2 of each cycle
- Carboplatin: [AUC 5] on day 2 of each cycle
- Etoposide: 100mg on days 1-3 of each cycle

**Stem cell mobilization**

In cycle 2 and/or 3 of salvage therapy, stem cells will be mobilised by 5 microgram/kg/day G-CSF starting at Day 5 and stem cells will be harvested at approximately Day 15.

**High-dose chemotherapy & ASCT**

All responsive patients with adequate stem cell collection will receive BEAM regimen 4-6 weeks after the last cycle of salvage therapy.

High dose chemotherapy will be BEAM. The dose and schedule is for discussion but the following is proposed (Vellenga et al., 2008):

- BCNU (Carmustine): 300 mg/m² i.v. day -6
- Etoposide: 200 mg/m² i.v. day -5, -4, -3, -2
- ARA-C (cytarabine): 200 mg/m² i.v. day -5, -4, -3, -2
- Melphalan: 140 mg/m² i.v. day -1
- Stem cell reinfusion: at least 2x10⁶ CD34⁺ cells/kg day 0

Patients will receive premedication with antiemetics, paracetamol and antihistamine, and supportive care during treatment with irradiated blood products, oral antibiotics and antifungal prophylaxis.
Ofatumumab will be centrally supplied, where possible other trial treatments will be sourced locally.

**Randomization Criteria**

Randomisation will be stratified using a minimisation procedure by the following criteria:


2. Time to failure after first-line rituximab+anthracycline-based therapy: >12 months versus ≤12 months. This is still under discussion and the criteria for failure are still to be defined but will probably be PD, SD, relapse, PR with positive histology and/or unequivocal PET positivity.

3. Centre.

4. Salvage chemotherapy regimen, if more than one is allowed.

**Sample Size Calculations & Statistical Analyses**

The primary objective is to evaluate the progression-free survival (PFS) in patients receiving ofatumumab combined with salvage chemotherapy compared to patients receiving rituximab combined with salvage chemotherapy. PFS is defined as the time from entry onto study until lymphoma progression or death from any cause. If failure to respond is considered an indication for another therapy according to local policy, such patients will be censored for progression at the start of the new therapy (Cheson et al., 2007).

A 15% improvement in 2 year PFS is considered clinically significant and achievable. This will require 122 evaluable patients per group to demonstrate superiority in PFS of the O-Chemo group compared to the R-Chemo group with 80% power and alpha=0.05. It is planned to enrol a total of 270 patients in the study allowing for 10% protocol violations and patients lost to follow-up. PFS will be estimated using Kaplan-Meier plots and the comparison will be made using the stratified log-rank test between the two treatment arms. Analysis will be done using the ‘intent to treat’ population. Recruitment will take 3 years and the final analysis will take place when all patients have completed 2 years of follow-up.

There will be an interim analysis with stopping criteria for futility of efficacy, adequacy of stem cell mobilisation and safety. The interim analysis will be conducted using overall response at the conclusion of salvage therapy when the data on the first 100 patients is available (Part A of protocol). The trial will be stopped if the overall response for O-chemo is not superior to R-chemo (odds ratio ≤1.0). Stopping criteria for adequacy of stem cell mobilisation and safety are being developed. An independent data monitoring committee (IDMC) will be established to review the data. With the recommendation of the IDMC, the trial will then recruit the remaining 170 patients (Part B of protocol).
References


