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# Results of a phase I/II study of ocrelizumab, a fully humanized anti-CD20 mAb, in patients with relapsed/refractory follicular lymphoma

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**Background:** Ocrelizumab is a humanized anti-CD20 antibody with increased antibody-dependent cellular cytotoxicity compared with rituximab. This phase I/II study evaluated its safety and efficacy in patients with relapsed/refractory follicular lymphoma (FL) after prior rituximab therapy.

**Design and methods:** Forty-seven patients were treated in three dose cohorts and received eight infusions every 3 weeks: cohort A, 200 mg/m$^2$ ($n$ = 15); cohort B, 375 mg/m$^2$ ($n$ = 16); cohort C, first dose 375 mg/m$^2$, seven subsequent doses of 750 mg/m$^2$ ($n$ = 16). Patients were assessed for safety, efficacy, pharmacodynamics and pharmacokinetics.

**Results:** The median patient age was 58 years, the majority had Ann Arbor stage III/IV disease and had received a median of 2 (range 1–6) prior regimens. Ocrelizumab was well tolerated with grade 3/4 toxicity occurring in 9% of patients. The most common toxicity was infusion-related reactions (74% patients), all grade 1/2 except one grade 3 event. The objective response rate was 38% and was similar in patients with low-affinity and high-affinity variants of the Fcγ receptor IIIa (FcγRIIIa). With follow-up of ∼28 months, the median progression-free survival was 11.4 months.

**Conclusion:** Ocrelizumab demonstrated activity in patients with relapsed/refractory FL following prior rituximab treatment, with safety similar to rituximab although adverse events appeared milder.

**Key words:** ADCC, anti-CD20 antibody, CDC, follicular lymphoma, ocrelizumab



## introduction

Rituximab is one of the most significant advances in the last decade in the treatment of B-cell lymphomas. In patients with relapsed/refractory follicular lymphoma (FL), rituximab has shown substantial efficacy as monotherapy [1] or combined with chemotherapy [2–7]. Several studies have demonstrated a benefit in progression-free survival (PFS) and overall survival when rituximab is combined with chemotherapy in frontline treatment [2–4, 8] or in patients with relapsed/refractory disease, when it is given as maintenance treatment [6, 7]. Still, most patients relapse after successful initial response to a rituximab-containing regimen and improved treatments with better outcomes are needed. Further development of immunotherapy with anti-CD20 mAbs, to improve efficacy and safety, is one important avenue of investigation.

Ocrelizumab is a humanized IgG1 anti-CD20 mAb that differs from rituximab at several positions within the complementarity-determining regions of the light chain and heavy chain variable regions. It is also derived from a different allotype of human Fc than rituximab. Ocrelizumab mediates lysis of CD20-expressing B cells by antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC) and apoptosis. Compared with rituximab *in vitro*, ocrelizumab demonstrated increased ADCC (two- to fivefold) against CD20-expressing cells, lower CDC (three- to fivefold) and superior binding to the low-affinity variants of the Fcγ receptor IIIa (FcγRIIIa, CD16) expressing the FF/FV phenotype at position 158 (data on file). Data from two clinical studies indicate that patients homozygous for the high-affinity variant of FcγRIIIa (VV phenotype) have a superior disease outcome following single-agent rituximab treatment compared with patients carrying the low-affinity variant (FV or FF phenotype) [9, 10]. Given these properties, it was postulated that ocrelizumab may have greater clinical efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the

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low-affinity FcγRIIIa variants. The humanized nature of the antibody as well as the lower CDC activity could provide additional benefits such as reduced immunogenicity and milder infusion-related reactions (IRR).

We present here the results from a phase I/II dose-escalation trial (BO18414) of ocrelizumab, as a single agent, in patients with relapsed/refractory FL following prior treatment with a rituximab-containing regimen.

## design and methods

### objectives

The purpose of this open-label multicenter trial was to assess the safety and tolerability of escalating i.v. doses of ocrelizumab in patients with CD20+ FL with relapsed/refractory disease after a prior rituximab-containing regimen. A secondary objective was to evaluate the antitumor efficacy of ocrelizumab [objective response rate (ORR) and PFS].

### patients

Eligible patients were aged ≥18 years with histologically confirmed CD20+ FL (any grade) [11] and either objective response or stable disease (SD) to the last rituximab-containing regimen provided time to progression (TTP) was at least 6 months. Patients with SD (i.e. no response to prior rituximab) were defined as rituximab refractory. In addition, patients had to have at least one bi-dimensionally measurable lesion ≥1.5 cm by computerized tomography, an Eastern Cooperative Oncology Group (ECOG) performance status of zero or one and an estimated life expectancy of at least 6 months.

The main exclusion criteria were prior exposure or severe allergic reaction to any mAb other than rituximab, histological transformation to diffuse large B-cell lymphoma, central nervous system involvement, known active infections (including hepatitis B and C) and impaired renal, hepatic or hematopoietic function unrelated to lymphoma.

Approval was obtained from the independent/research ethics committees of each participating site before trial initiation. All patients provided written informed consent.

### trial design

Patients were assigned to one of the three treatment cohorts in a partly sequential partly randomized fashion in a 1 : 1 : 1 ratio. The treatment schedule consisted of eight cycles (maximum) of ocrelizumab given 3-weekly. Three dose levels were evaluated: cohort A, 200 mg/m$^2$; cohort B, 375 mg/m$^2$; cohort C, one dose of 375 mg/m$^2$ and seven doses of 750 mg/m$^2$. Enrollment started in cohort A until the third consecutive patient had completed one cycle without dose-limiting toxicity (DLT); at this time point, cohort B was opened and assignment to cohort A or B was on the basis of a predefined two-arm randomization list. Cohort C opened after four patients in cohort B had completed one cycle without DLT; assignment to a cohort was then on the basis of a predefined three-arm randomization list (A, B or C).

DLT was defined as all grade 3/4 toxic effects occurring in cycle 1 with the exception of the following: grade 3/4 lymphopenia; grade 3/4 neutropenia not resulting in febrile neutropenia and resolving without growth factor support; grade 4 thrombocytopenia resolving within 5 days or grade 3 thrombocytopenia, both not requiring platelet transfusion; and reversible grade 3 IRR.

### ocrelizumab administration

Ocrelizumab was administered i.v. at an initial rate of 50 mg/h up to 400 mg/h after dilution in 0.9% sodium chloride to a concentration of 1–4 mg/ml. Premedication was with oral acetaminophen and an antihistamine; corticosteroids were only allowed in exceptional circumstances.

### trial assessments

Safety and tolerability were assessed by monitoring laboratory parameters as well as the incidence, severity and type of adverse events (AEs). AEs were graded according to the common toxicity criteria.

Titers of human anti-human antibodies were analyzed at baseline and 28 days after the last dose using an antibody electrochemiluminescent assay.

Tumor response and progression were assessed by the investigator using standard criteria [12] at weeks 12 and 24 after study entry, at 3-month intervals during the first year and at 6-month intervals until 2 years after enrollment.

Assessment of FcγRIIIa genotypes in baseline blood samples was carried out at Roche (Basel, Switzerland) using a nested PCR technique followed by direct sequencing [13].

Serum samples for pharmacokinetic analysis of ocrelizumab were taken before and after infusion at each cycle throughout the study and for an extended period after cycle 1 (cohorts A and B), cycle 2 (cohort C) and cycle 8 (all cohorts). Ocrelizumab levels were analyzed using an enzyme-linked immunoassay method.

Samples for the quantification of T lymphocytes, B lymphocytes and natural killer (NK) cell subsets in peripheral blood by flow cytometry were collected at screening, end of treatment and 1, 3 and 12 months after the last infusion.

For detection of minimal residual disease, *Bcl2-IgH* rearrangement was assessed in peripheral blood at weeks 12 and 24 using a real-time quantitative PCR technique [14] (Laboratory of Cellular and Gene Therapy, Bergamo, Italy).

### statistical analysis

Three cohorts, each including 15 patients, were considered sufficient to estimate the incidence of DLTs and other toxic effects since extensive experience with rituximab meant the relative safety profile of ocrelizumab could be predicted with some confidence.

The safety and efficacy analyses were carried out on all treated patients. The efficacy end points were ORR (last and best) and PFS (defined as the time from randomization to disease progression, relapse or death). Two-sided 95% confidence intervals (CIs) for ORR were calculated using Clopper–Pearson methodology. Kaplan–Meier analyses, including estimations of medians, were carried out for PFS. No statistical comparison was carried out between the study arms since there was no formal statistical hypothesis testing.

## results

### patients

A total of 58 patients were screened, and 47 were treated in this study (15 in cohort A and 16 each in cohorts B and C).

The treatment cohorts were generally comparable with respect to baseline demographic, clinical and pathological characteristics (Table 1). The median age was 58 years (range 38–83 years) and most patients (72%) had Ann Arbor stage III/IV disease at study entry. On the basis of the Follicular Lymphoma Prognostic Index (FLIPI) [15], 15%, 29% and 45% of patients had high-, intermediate-, and low-risk disease, respectively, at study entry; for the remaining 11% of patients, FLIPI was missing. The median number of previous treatment regimens received before study entry was 2 (range 1–6). All patients received rituximab as the last treatment before study entry either as monotherapy (53%) or with chemotherapy (47%). Sixty-six percent of patients had achieved complete response (CR)/complete response unconfirmed (CRu) after

**Table 1.** Baseline demographic and disease characteristics of the study population

| | Cohort A, 200 mg/m$^2$ ($N$ = 15) | Cohort B, 375 mg/m$^2$ ($N$ = 16) | Cohort C, 750 mg/m$^2$ ($N$ = 16) |
|---|---|---|---|
| Age, years | | | |
| Median (range) | 59 (38–83) | 57 (39–71) | 60 (40–75) |
| Gender, *n* (%) | | | |
| Male | 10 (67) | 8 (50) | 10 (63) |
| Female | 5 (33) | 8 (50) | 6 (38) |
| Stage (Ann Arbor), *n* (%) | | | |
| I–II | 3 (20) | 1 (6) | 4 (25) |
| III–IV | 10 (67) | 13 (81) | 11 (69) |
| Missing | 2 (13) | 2 (13) | 1 (6) |
| WHO histological grade, *n* (%) | | | |
| 1 | 7 (47) | 5 (31) | 9 (56) |
| 2 | 4 (27) | 7 (44) | 5 (31) |
| 3 | 0 (0) | 1 (6) | 0 (0) |
| 3a | 3 (20) | 1 (6) | 0 (0) |
| 3b | 0 (0) | 0 (0) | 1 (6) |
| Missing | 1 (7) | 2 (13) | 1 (6) |
| FLIPI, *n* (%) | | | |
| 0–1 (good prognosis) | 9 (60) | 7 (44) | 5 (31) |
| 2 (intermediate prognosis) | 2 (13) | 5 (31) | 7 (44) |
| 3–5 (poor prognosis) | 2 (13) | 2 (13) | 3 (19) |
| Missing | 2 (13) | 2 (13) | 1 (6) |
| Bulky disease (>5 cm), *n* (%) | 9 (60) | 6 (38) | 6 (38) |
| No. of previous regimens | | | |
| Median (range) | 2 (1–5) | 3 (1–6) | 2 (1–4) |
| No. of previous rituximab-containing regimens | | | |
| Median (range) | 1 (1–3) | 1 (1–3) | 1 (1–4) |
| Type of rituximab regimen, *n* (%) | | | |
| Rituximab single agent | 9 (60) | 9 (56) | 7 (44) |
| Rituximab plus chemotherapy or immunotherapy | 6 (40) | 7 (44) | 9 (56) |
| Response to last rituximab-containing regimen, *n* (%) | | | |
| CR/CRu | 12 (80) | 9 (56) | 10 (63) |
| PR | 1 (7) | 4 (25) | 5 (31) |
| SD | 2 (13) | 3 (19) | 1 (6) |
| Treatment-free interval (months), *n* (%) | | | |
| 6–12 | 5 (33) | 4 (25) | 6 (38) |
| 12–24 | 5 (33) | 7 (44) | 6 (28) |
| 24–36 | 4 (27) | 2 (13) | 2 (13) |
| >36 | 1 (7) | 3 (19) | 2 (13) |
| ECOG PS, *n* (%) | | | |
| 0 | 13 (87) | 13 (81) | 10 (63) |
| 1 | 2 (13) | 3 (19) | 6 (38) |

WHO, World Health Organization; FLIPI, Follicular Lymphoma International Prognostic Index; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; ECOG PS, performance status according to the European Cooperative Oncology Group scale.

their last rituximab-containing regimen and six patients (13%) were rituximab refractory. Most patients (68%) had a treatment-free interval of at least 12 months.

## treatment

The scheduled eight cycles of ocrelizumab therapy were administered to 70% of patients. More patients in cohort B (94%) compared with cohorts A and C (53% and 63%, respectively) received all eight doses; hence the total number of ocrelizumab infusions administered was higher in cohort B (123 versus 91 and 103 in A and C, respectively). This was because fewer patients in cohort B (one) compared with cohorts A and C (six and four, respectively) withdrew due to insufficient therapeutic response, mainly after cycle 4.

## safety

Overall, treatment with ocrelizumab was well tolerated. Although the majority of patients (91%) experienced at least

one AE during the study, most events (93%) were of grade 1 or 2 severity occurring predominantly with the first dose. The most common toxicity associated with treatment was IRRs (74% of patients); all were grade 1 or 2 with the exception of one grade 3 event. In cycle 1, 23% of patients received corticosteroids and 40% had the infusion interrupted due to IRR (in subsequent cycles, fewer patients required interruptions—13% and 2% patients in cycles 2 and 8, respectively). Very few patients required decreases in the infusion rate during ocrelizumab administration (4%, 1% and 0% in cycles 1, 2 and 8 respectively). Other less frequent AEs (≥10% incidence) reported during the study included nasopharyngitis (15% of patients) and asthenia (13% of patients). Approximately half (78 of 153) of the reported AEs were considered by the investigator as treatment related.

Six patients (one patient each in cohorts A and B; four patients in cohort C) experienced a total of nine grade 3 AEs and one grade 4 AE. The grade 3 AEs were neutropenia and bone pain in one patient in cohort B and pleural effusion, pleuritic pain, lymphopenia, constipation, non-small-cell lung cancer, IRR and paresthesia in cohort C. Only the events of lymphopenia and IRR were considered by the investigator to be treatment related. One grade 4 AE occurred in cohort A, in a patient with dyspnea at baseline which worsened on ocrelizumab treatment and was attributed to obliterative bronchiolitis exacerbated by the study drug.

Three patients discontinued ocrelizumab treatment; the reasons were IRR (grade 2), non-small-cell lung cancer and obliterative bronchiolitis.

Two deaths were reported. One was due to disease progression and occurred 5 months after last ocrelizumab administration. The second death, considered by the investigator as remotely treatment related, was due to a pulmonary embolism (in the patient with obliterative bronchiolitis) and occurred ∼10 months after last ocrelizumab administration.

Grade 1 or 2 infections during therapy were reported in approximately one-third (17 of 47) of all patients; there were no grade 3 or 4 infections. The most common infection was nasopharyngitis. Most patients (12) with infections received treatment, mainly with broad-spectrum antibiotics, and all resolved without complications.

The only grade 3 or 4 hematologic toxicity of relevance was neutropenia which occurred at a low frequency (three patients, cohort B; one, cohort C) and was not associated with grade 3 or 4 infections. There were no late-occurring (beyond 4 weeks post-treatment termination) or prolonged neutropenic events reported.

There were no clinically relevant changes observed in serum chemistry parameters and T lymphocytes/NK cell subsets and no patient developed human anti-human antibodies up to 12 months after the last dose of ocrelizumab.

On the basis of observed toxicity and laboratory data, the maximum tolerated dose (MTD; i.e. dose at which at least 33% of patients experienced DLT) for ocrelizumab was not identified in this study.

## efficacy

In the overall population, the ORR at the end of treatment was 38% (27%, 50% and 38% in cohorts A, B and C, respectively) (Table 2). Of 18 who achieved a response, 7 (15%) were in CR/CRu and 11 (23%) were in partial response (PR). Seventeen

**Table 2.** Response to ocrelizumab treatment: ORR (last and best) and progression-free survival

| | Cohort A, 200 mg/m$^2$ ($N$ = 15) | Cohort B, 375 mg/m$^2$ ($N$ = 16) | Cohort C, 750 mg/m$^2$ ($N$ = 16) | Total ($N$ = 47) |
|---|---|---|---|---|
| Last ORR, *n* (%) | 4 (27) | 8 (50) | 6 (38) | 18 (38) |
| 95% CI (%) | 8–55 | 25–75 | 15–65 | 25–54 |
| CR, *n* | 0 | 2 | 0 | 2 |
| CRu, *n* | 2 | 2 | 1 | 5 |
| PR, *n* | 2 | 4 | 5 | 11 |
| SD, *n* | 6 | 6 | 5 | 17 |
| PD, *n* | 5 | 2 | 4 | 11 |
| Missing[a], *n* | 0 | 0 | 1 | 1 |
| Best ORR, *n* (%) | 6 (40) | 9 (56) | 6 (38) | 21 (45) |
| 95% CI (%) | 16–68 | 30–80 | 15–65 | (30–60) |
| CR, *n* | 1 | 3 | 2 | 6 |
| CRu, *n* | 1 | 1 | 0 | 2 |
| PR, *n* | 4 | 5 | 4 | 13 |
| SD, *n* | 5 | 7 | 6 | 18 |
| PD, *n* | 4 | 0 | 3 | 7 |
| Missing[a], *n* | 0 | 0 | 1 | 1 |
| Median progression-free survival, months (95%CI) | 9.4 (4.7–12.0) | 17.2 (8.6–23.5) | 17.2 (5.8–N.E.) | 11.4 (8.3–17.4) |
| 1-year event-free rates | 0.22 | 0.60 | 0.53 | 0.45 |

ORR, objective response rate; CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; PR, partial response; SD, stable disease; PD, progressive disease; N.E., not estimable; IRR, infusion-related reactions.

[a]Patient withdrew after the first dose of ocrelizumab due to an IRR and had no post-treatment tumor assessments.

patients (36%) had SD and 11 (23%) patients progressed during treatment. The best ORR during the study period (during treatment and follow-up) was 45% (21 of 47).

In the subgroup of 38 assessable patients that expressed the FF/FV variants of FcγRIIIa, the end of treatment ORR was 39% (15 of 38) which is comparable with that in the subgroup that expressed the VV variant (43%; 3 of 7 patients). In the subgroup of patients with a previous response to rituximab therapy (CR/CRu or PR), the ORR was 41% (17 of 41; 7 CR/CRu) compared with 17% in those that were rituximab refractory (of 6 patients, 1 achieved PR, 4 achieved SD and 1 progressed).

Five of the 11 (45%) assessable patients who had PCR-detectable *Bcl-2* gene rearrangement in peripheral blood at baseline converted to PCR-negative status after treatment. Radiologically, three of these five patients achieved a CRu, one achieved a PR and one had SD.

After a follow-up time of ∼28 months, 74% (35 of 47) of patients had progressed. The Kaplan–Meier-estimated median PFS was 11.4 months (95% CI 8.3–17.4 months) for the overall population, with a 1-year event-free rate of 45% (Table 2 and Figure 1). Of the 18 responders, 11 (1 CR, 2 CRu and 8 PR) had progressed during follow-up (Table 2).

## pharmacodynamics

Ocrelizumab induced dose-dependent depletion of B cells (CD19+) with profound and prolonged effects being observed in cohorts B and C (Table 3). Recovery to baseline was observed within 3 months following treatment cessation in cohort A, whereas in cohorts B and C, B cells were still notably lower than baseline up to 12 months after the end of treatment.

## pharmacokinetics

Pharmacokinetic results after cycle 1 (cohorts A and B) or 2 (cohort C) and cycle 8 (steady state) are shown in Table 3. On the basis of a limited dataset of 18 patients, ocrelizumab had a mean terminal half-life of 23–28 days and a slow systemic clearance (0.19–0.71 l/day) at steady state. The steady-state volume of distribution was low and ranged between 5.4 and 6.1

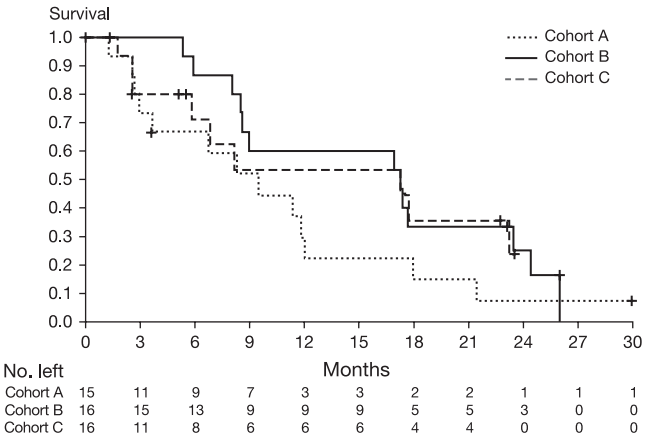


**Figure 1.** Time to progression for cohorts A, B and C.

**Table 3.** Pharmacodynamic and pharmacokinetic characteristics of ocrelizumab

| | Cohort A, 200 mg/m$^2$ | Cohort B, 375 mg/m$^2$ | Cohort C, 750 mg/m$^2$ |
|---|---|---|---|
| Pharmacodynamic parameters: average percentage of CD19 B cells | | | |
| Baseline | 12.8 ($n$ = 12) | 12.8 ($n$ = 13) | 12.5 ($n$ = 12) |
| 6 months | 10.2 ($n$ = 6) | 1.5 ($n$ = 10) | 1.0 ($n$ = 11) |
| 9 months | 18.3 ($n$ = 4) | 3.0 ($n$ = 11) | 2.4 ($n$ = 5) |
| 12 months | 24.4 ($n$ = 5) | 2.5 ($n$ = 6) | 0.6 ($n$ = 5) |
| 18 months | – | 8.0 ($n$ = 3) | 4.5 ($n$ = 4) |
| Pharmacokinetic parameters: mean (±SD) at cycle 1 (cohorts A and B) or cycle 2 (cohort C) | | | |
| No. of patients | 14 | 14 | 7 |
| $C_{max}$ (μg/ml) | 104 ± 40.0 | 202 ± 76.6 | 345 ± 78.1 |
| $AUC_{0–21}$ (μg·day/ml) | 665 ± 395[a] | 1648 ± 430[a] | 2800 ± 1220 |
| $AUC_{0–inf}$ (μg·day/ml) | 845 ± 585[a] | 2202 ± 603[a] | 4061 ± 2325 |
| Pharmacokinetic parameters: average (±SD) at steady state (cycle 8) | | | |
| No. of patients | 3 | 5 | 4 |
| $C_{max}$ (μg/ml) | 125 ± 57.0 | 335 ± 76.2 | 455 ± 66.5 |
| $AUC_{0–tau}$ (μg·day/ml) | 1402 ± 1075 | 3807 ± 977 | 5827 ± 1797 |
| $t_{1/2}$ (day) | 22.9 ± 12.5[b] | 27.6 ± 4.09[c] | 25.9 ± 8.91[d] |
| CL (l/day) | 0.710 ± 0.858 | 0.194 ± 0.066 | 0.242 ± 0.104 |
| Vss (l) | 5.37 ± 3.08 | 6.11 ± 2.21 | 6.14 ± 1.97 |

Pharmacokinetic parameters were estimated by noncompartmental methods using the software WinNonlin Version 5.2 (Pharsight).
SD, standard deviation; $C_{max}$, maximum serum concentration; AUC, area under the serum concentration–time curve; $t_{1/2}$, half-life; CL, clearance; Vss, volume of distribution at steady state; $AUC_{0-21}$, area under the serum concentration-time curve from time 0 to day 21; $AUC_{0-inf}$, area under the serum concentration-time curve from time 0 to infinity; $AUC_{0-tau}$, total area under the serum concentration time curve for the dosing interval at steady-state.
[a]$n$ = 13.
[b]$n$ = 5.
[c]$n$ = 7.
[d]$n$ = 6.

l across the cohorts. Maximum serum concentration ($C_{max}$) and $AUC_{0-tau}$ (total area under the serum concentration time curve for the dosing interval at steady-state) increased with increasing doses, being more than dose proportional from 200 to 375 mg/m$^2$ and less than dose proportional from 375 to 750 mg/m$^2$. Steady-state values for half-life, clearance and volume of distribution for ocrelizumab were generally comparable across dose levels. Due to the limited number of patients assessable for pharmacokinetic analysis, it was not possible to correlate exposure with efficacy.

## discussion

The results from this phase I/II study demonstrated that the fully humanized anti-CD20 mAb, ocrelizumab, was safely administered at doses up to 750 mg/m$^2$ in patients with relapsed/refractory FL. Overall, i.v. administration of ocrelizumab was well tolerated; no DLTs were observed and the MTD was not defined in this trial. On the basis of the known safety profile of rituximab, a chimeric anti-CD20 mAb, there were no unexpected AEs or new safety findings in this trial with ocrelizumab. The majority of AEs were grade 1 or 2 and mainly associated with the first infusion. In this study, only one grade 3 IRR was reported (i.e. a rate of 2%); this compares favorably with a rate of 9% reported for rituximab [3]. IRR were manageable mainly by interrupting the infusion, and in a few cases, the rate of infusion had to be reduced. Premedication with acetaminophen and an antihistamine was sufficient to manage most reactions. The frequency, severity and type of AEs did not appear to be dose related; although more grade 3 or 4 AEs were reported in cohort C, only two events (lymphopenia and IRR) were considered by the investigator as treatment related. Clinically relevant hematologic toxicity occurred rarely. Late-onset neutropenia, which is a rare complication of rituximab therapy [1], was not observed with ocrelizumab within the period of observation (~28 months). There were no serious infections observed with ocrelizumab compared with a rate of up to 4% reported for rituximab [16]. No patient developed human anti-human antibodies following ocrelizumab therapy. The safety profile of ocrelizumab is consistent with that previously reported for rituximab monotherapy, although AEs appeared to be generally milder, especially with respect to IRRs [1, 17, 18].

With the doses and schedule employed in this trial, ocrelizumab achieved an ORR, at the end of treatment, of 38% (95% CI 25% to 54%), with an estimated median PFS of 11.4 months (95% CI 8.3–17.4 months). No dose–response relationship was evident in this small phase I/II trial. The numerically higher ORR seen with the 375 mg/m$^2$ dose could not be explained by an imbalance in baseline prognostic factors.

These efficacy data for ocrelizumab are within the range reported with rituximab re-treatment [17, 18] or other second-generation anti-CD20 mAbs [19, 20]. In a study conducted in patients relapsing after single-agent rituximab, an ORR of 38% was reported following rituximab re-treatment, with an estimated median TTP of 16.3 months in responders [17]. Hainsworth et al. [18] reported an ORR of 35% after rituximab re-treatment of patients relapsing after rituximab monotherapy and a median PFS of 7.4 months. More recent data in the relapsed setting with the second-generation mAbs ofatumumab and veltuzumab demonstrated ORR of 42% and 44%, respectively, with estimated median TTP and PFS of 8.8 and 6.2 months, respectively [19, 20]. In the present trial, the patient population had received a median of 2 prior regimens for FL, 47% had relapsed/progressed following combination therapy with rituximab chemotherapy and a small proportion (13%) were rituximab refractory. Further, the present trial used a 3-weekly dosing regimen (eight cycles) with the view that further development would be in combination with chemotherapy compared with the other trials, where a weekly schedule (four cycles) was employed [17, 18, 19, 20]. Hence, although the total cumulative dose of ocrelizumab may have been higher than in the other trials, the dose intensity was substantially lower, especially when comparing the time point at which clinical assessments were carried out. Since ocrelizumab has a long terminal half-life (23–28 days), steady-state levels would only have been reached some 3 months after initial dosing. Failure to achieve and maintain therapeutic levels of ocrelizumab early during the course of treatment may have contributed to the high-drop out rate at cycle 4 and probably influenced treatment outcome.

In the subgroup of patients refractory to rituximab, the ORR with ocrelizumab was 17%. This response rate is within the range reported for ofatumumab (7%–22%) in the same setting [21], indicating that structural changes in second-generation anti-CD20 mAb may be not sufficient to overcome resistance to rituximab.

Ocrelizumab induced potent depletion of B cells from peripheral blood at doses of 375 and 750 mg/m$^2$. At both doses, B cells were still depleted 12 months after the end of treatment indicating a more prolonged depletion than previously seen with rituximab [1]. Whether this effect is related to the longer duration of ocrelizumab treatment, greater potency or higher total cumulative dose is presently unclear.

A relationship between Fc$\gamma$RIIIa genotype versus clinical (ORR and PFS) and molecular response to rituximab monotherapy has been reported in patients with non-Hodgkin's lymphoma [9, 16]. Since ocrelizumab demonstrates superior *in vitro* binding activity to the low-affinity variants of Fc$\gamma$RIIIa and increased ADCC compared with rituximab, we were interested to explore whether this effect correlated with clinical outcome. Despite the small number of patients in the subgroups, the results indicate comparable efficacy of ocrelizumab in both the high- and low-affinity subgroups (43% and 39% for VV versus VF/FF, respectively). While the ORRs reported with ocrelizumab are lower than previously reported for rituximab [9], this could be accounted for by difference in the patient population (first line versus relapsed setting) and dosing schedule (weekly rituximab versus 3-weekly ocrelizumab).

In conclusion, ocrelizumab was safely administered to patients with relapsed/refractory FL. Despite the lack of a head-to-head trial, the data would indicate a more favorable safety profile than seen with rituximab and efficacy that is at least comparable with other second-generation anti-CD20 mAbs. It is possible that further increase of ADCC might lead to better results as is the case for the third-generation anti-CD20 antibody, GA101, which has shown promising early clinical results [22–24].

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