EXPERT OPINION

1. Introduction
2. Preclinical studies
3. Clinical studies
4. Conclusion
5. Expert opinion

Obinutuzumab for B-cell malignancies

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Introduction: We analyse data for the use of obinutuzumab in the treatment of CD20$^+$ lymphoproliferative disorders with a focus on chronic lymphocytic leukaemia (CLL). Targeted therapy against CD20 with the mAb rituximab led to significant improvements in survival for patients with B-cell non-Hodgkin lymphoma (NHL) and is the current mainstay of treatment for CD20$^+$ malignancies. Despite this, many patients relapse or become refractory after rituximab-containing therapies, so efforts have been made to develop better anti-CD20 mAbs. Obinutuzumab recently demonstrated superiority over rituximab in the only published Phase III study comparing the two antibodies.
Areas covered: Obinutuzumab is a humanised, anti-CD20 mAb being compared to rituximab in several Phase III studies. An overview of obinutuzumab, its mechanisms of action and results of Phase I–III studies are presented.
Expert opinion: The demonstration of superiority of obinutuzumab over rituximab in the CLL11 Phase III study is potentially practice-changing. Obinutuzumab has also proven safe and efficacious in CD20$^+$ NHL in Phase I/II studies and results of Phase III studies in NHL are eagerly awaited. The potential implications of improved outcomes for CLL and NHL with the introduction of this more potent anti-CD20 antibody are tremendous given the impressive results obtained after the introduction of rituximab over a decade ago.

Keywords: antibody, CD20, chronic lymphocytic leukaemia, non-Hodgkin lymphoma

Expert Opin. Biol. Ther. (2014) 14(8):1197-1205

1. Introduction

The development of the anti-CD20 mAb rituximab provided one of the first examples of successful targeted therapy for cancer and has revolutionised the treatment of CD20$^+$ lymphoproliferative disorders. Over 90% of B-cell non-Hodgkin lymphomas (NHLs) and the majority of chronic lymphocytic leukaemias (CLLs) express CD20 and are thus amenable to targeted therapy directed against CD20. CD20 is an ideal target for directed therapy, being highly expressed on most B cells [1] but not expressed on stem cells, precursor cells or the majority of plasma cells. As such, B-cell development and mature antibody production are not impaired by anti-CD20 therapy [2].

Immuno-chemotherapy, comprising chemotherapeutics and rituximab, has resulted in progression-free (PFS) and overall survival (OS) advantages in NHL and CLL [3-6]. However, despite the notable impact of rituximab in the treatment of NHL, its single-agent efficacy is only modest, especially in CLL [7], and many patients either fail to respond or relapse after rituximab-containing therapies making it clear that better treatment options are required for many patients with CD20$^+$ lymphoproliferative disorders.

One avenue of research and drug development has focused on the development of improved anti-CD20 antibodies that can provide superior responses to rituximab. Several such mAbs have been developed and are currently being investigated. Similar to rituximab, the majority of these novel anti-CD20 mAbs are termed Type I

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Box 1. Drug summary.

Drug name	Obinutuzumab
Phase	III
Indication	Treatment of chronic lymphocytic leukaemia [and being investigated in $CD20^+$ (B cell) non-Hodgkin lymphoma]
Pharmacology description/mechanism of action	Anti-CD20 mAb resulting in high levels of antibody-dependent cellular cytotoxicity and direct cell death induction
Route of administration	Intravenous
Pivotal trials(s)	Chronic lymphocytic leukaemia 11 and other ongoing studies

antibodies. These antibodies function via stabilisation of CD20 on lipid rafts, resulting in strong complement (C1q) binding in vitro and potent induction of complement-dependent cellular cytotoxicity (CDCC) [8]. The exact mechanisms of in vivo activity of rituximab and other Type 1 molecules remain controversial with most studies suggesting primarily CDCC activity [9-15] and others demonstrating more antibody-dependent cellular cytotoxicity (ADCC) [16,17]. A second class of mAbs, the Type II antibodies, do not require lipid rafts and thus leave CD20 distributed across the surface of the B cell. They have much lower in vitro complement binding and CDCC, but result in significantly greater ADCC and direct cell death (DCD) compared to Type I mAbs [18]. Obinutuzumab (GA101, RO5072759) is such a Type II mAb, recognises overlapping CD20 epitopes to rituximab, has shown efficacy in preclinical and early-phase clinical trials and is currently being investigated in Phase III trials (**Box 1**). The first Phase III study to be reported demonstrated superiority of obinutuzumab over rituximab in terms of PFS in CLL patients with co-morbidities, and represents the first head-to-head comparison of a novel anti-CD20 mAb to show superiority to rituximab in an advanced-phase clinical trial [19].

Obinutuzumab is a humanised anti-CD20 mAb that has a glyco-engineered Fc portion, selected to increase its affinity for Fcγ RIIIa receptors on immune effector cells, intended to elicit enhanced ADCC. Glycoengineered antibodies are less inhibited by complement activation or excess-free IgG than their non-glycoengineered parental antibodies [20]. Obinutuzumab also contains a modified elbow hinge region to provide superior antigen binding [18,21]. The elbow hinge modification is reported to increase DCD but at the expense of reduced CDCC activity. Both antibody modifications were designed to induce much greater cell killing by obinutuzumab compared to rituximab [22].

Several groups have worked to clarify the differing mechanisms of action of obinutuzumab and rituximab. Golay *et al.* demonstrated that obinutuzumab activates neutrophils and mediates phagocytosis through CD16B on neutrophils better than rituximab. The same group looked at the effect of the glycoengineered antibody and the parental antibody and demonstrated that neutrophil-induced phagocytosis was more effective with the glycoengineered antibody. In whole blood, no significant phagocytosis was observed with rituximab but efficient induction of phagocytosis was elicited by obinutuzumab [23].

Several other in vitro studies have also been performed to further clarify the mechanism of cell death induced by obinutuzumab. Alduaij *et al.* determined that the DCD induced by obinutuzumab occurs by a non-apoptotic process involving actin reorganisation and lysosomes. Significantly higher DCD was noted in response to obinutuzumab compared to rituximab [22]. The importance of lysosomes in the induction of cell death was highlighted in these experiments and is a novel mechanism that appears unique to Type II antibodies [24]. As this mechanism of cell killing is independent of classic apoptosis pathways, it was postulated that obinutuzumab may be able to overcome resistance to chemotherapy-induced apoptosis, an important resistance mechanism in multiply treated NHL or CLL [22,25,26].

Several different mechanisms of resistance to rituximab have been described and are summarised in our previous review including, importantly, CD20 modulation and CD20 'shaving' in which rituximab/CD20 complexes are removed from the B-cell surface by monocytes through an endocytic reaction called trogocytosis. These mechanisms appear to be less for Type II mAbs such as obinutuzumab and may explain some of the increased potency of Type II antibodies [27].

More information has also recently emerged regarding the mechanism of action of obinutuzumab versus rituximab. Reslan *et al.* examined mechanisms of induction of apoptosis of the two antibodies by evaluating the change in mitochondrial membrane potential and expression of apoptosis-related proteins produced by both mAbs. These studies were performed using CLL cells. Obinutuzumab but not rituximab exhibited a significant induction of apoptosis in a caspase-dependent manner. Additional investigations confirmed that mitochondria are involved in the early caspase activity during apoptosis induced by obinutuzumab [28]. The results of this study were very interesting in that they failed to demonstrate a role for reactive oxygen species (ROS) in obinutuzumab-induced cell death. These data conflict with another recent study that showed that ROS were critical for programmed cell death induced by several mAbs, including obinutuzumab, observations made in human B-cell lymphoma cell lines and primary CLL cells [29]. Thus, the exact mechanism of cell killing by obinutuzumab remains to be conclusively demonstrated but is clearly multifaceted.

Additionally, studies have demonstrated that obinutuzumab and other Type II mAbs induce less internalisation of CD20 than Type 1 antibodies like rituximab. The studies demonstrated that Type I mAbs induced significant internalisation of CD20 from the surface of B cells, whereas Type II antibodies remained largely cell-surface localised and thus more effective at cell killing. The rate of internalisation was directly correlated with expression of the inhibitory FCγRIIb. Interestingly, this also explained the reduced efficacy of

rituximab in mantle cell lymphoma (MCL) and CLL in which there is higher expression of FcγRIIb than in other NHLs [30,31]. These results are particularly relevant to the recent data comparing rituximab and obinutuzumab in CLL.

2. Preclinical studies

Several in vitro studies of obinutuzumab were performed and demonstrated superior efficacy over rituximab. Details of these studies including B-cell depletion assays in whole blood, binding and cell death assays in NHL cell lines and tumour killing in xenograft models were described in a previous review [27].

3. Clinical studies

3.1 Pharmacokinetic studies in early-phase clinical trials

Pharmacokinetic data were analysed in two Phase I/II studies of obinutuzumab monotherapy with results used to determine the dose for all subsequent Phase III studies. Plasma concentrations of obinutuzumab were obtained pre- and post-infusion in the GAUGUIN study (in which obinutuzumab was dosed every 3 weeks for 8 cycles) and GAUSS study (in which obinutuzumab was provided weekly for 4 weeks) [27]. Higher levels of obinutuzumab were obtained more quickly with the weekly infusion schedule and higher plasma concentrations were also noted in the higher dose (1600 mg/800 mg) than the lower dose (400 mg/400 mg) groups in the GAUGUIN study. This information and additional modelling and simulation were used to select an optimal dose of 1000 mg provided on Days 1, 8 and 15 of cycle 1 then on Day 1 of subsequent cycles [32].

3.2 Chronic lymphocytic leukaemia

Table 1 demonstrates the reported clinical studies of obinutuzumab. Small numbers of relapsed/refractory CLL patients were included in early Phase I studies of obinutuzumab with some reports of less responses than observed in NHL patients [33]. Despite these findings, safety signals did not appear different between CLL and NHL patients, justifying progression to Phase II/III studies in CLL. The details of the Phase I/II studies of obinutuzumab have been previously reviewed [27] except for the GALTON Phase Ib study of obinutuzumab in combination with FC (fludarabine and cyclophosphamide) or B (bendamustine) using investigator choice of chemotherapy backbone in patients with previously untreated CLL [34]. In the monotherapy Phase I studies for CLL patients, toxicities were mild though there were frequent Grade 1 – 2 infusion-related reactions (IRRs). The end of treatment response was 20% with four partial remissions. The conclusion from the study was that obinutuzumab was safe in patients with advanced CLL but that the single-agent activity was modest and combination chemo-immunotherapy was likely to be necessary for most CLL patients, especially those with higher tumour burdens [35]. These results are similar to early results reported with the use of rituximab, which also has very modest single-agent activity in CLL. The results of the GALTON study were reported recently and revealed high levels of Grade 3 – 4 haematological toxicities as expected with these chemotherapy regimens, as well as high rates of IRRs, which were not dose-limiting. The overall response rate (ORR) was 62% in the FC-containing arm and 90% in the B arm though several patients had treatment discontinued for AEs. The conclusion of the authors was that obinutuzumab could safely be administered with intensive chemotherapy to previously untreated CLL patients [34].

Despite the concern that CLL patients may exhibit less responsiveness to obinutuzumab than NHL patients, Phase III studies were initiated in all $CD20^+$ lymphoproliferative disorders, including frontline therapy in elderly CLL patients (German CLL Study Group (GCLLSG) CLL11 study), frontline therapy in indolent NHL (iNHL) (the GALLIUM study), frontline therapy in diffuse large B cell lymphoma (DLBCL) (the GOYA study) and salvage therapy in relapsed/refractory iNHL (the GADOLIN study). The first of these studies to be completed and published is the GCLLSG CLL11 study, which has reported impressive results of obinutuzumab.

The GCLLSG CLL11 study was a multicenter, open-label, randomised, three-arm study investigating the efficacy and safety of obinutuzumab plus chlorambucil (CLB) versus rituximab plus CLB versus CLB monotherapy in previously untreated CLL patients of advanced age with co-morbidities [19]. Prior to the publication of the final results, the authors reported data from the safety run-in in six patients to ensure that the combination of obinutuzumab and CLB was safe and feasible in an older, frailer CLL population [36]. Adverse events were noted but were not dose-limiting and were treatable with a high incidence of IRRs (five of six patients) that were generally limited to the first infusion as well as Grade 3 – 4 neutropenia events that were not associated with fever, infection or requirement for antibiotics. No late Grade 3 – 4 neutropenic episodes were observed in the 6 months following completion of therapy. Some treatment delays occurred but all patients completed the planned therapy.

The CLL11 study focuses on a patient population that has previously been neglected in clinical trials with most CLL studies focusing on young, fit patients who are better able to tolerate novel or intensive therapies. The study design included two stages of analysis, the first examining the comparison of both antibody arms against CLB monotherapy to determine if anti-CD20 mAbs were valuable in this elderly, unfit population and the second stage investigating a comparison between the obinutuzumab-CLB and rituximab-CLB arms. The final results of the study were recently reported and demonstrate an advantage in terms of ORR with more complete remissions (CRs) and PFS with the addition of an anti-CD20 mAb (obinutuzumab or rituximab) to CLB monotherapy. More importantly, an OS advantage was noted in the obinutuzumab-CLB arm compared to the CLB

Table 1. Summary of clinical trials examining the efficacy and safety of obinutuzumab in B-cell malignancies.

Trial	Study design	Number of subjects		Patient population	Obinutuzumab dose/combination
GAUGUIN	Phase I	34		Relapsed/refractory NHL (iNHL or aNHL and CLL)	Single agent, dose escalation (400 – 2000 mg)
	Phase II	100	40	Relapsed/refractory iNHL	LD cohorts: 400 mg D1 + D8 Cycle 1, 400 mg
			40	Relapsed/refractory aNHL	D1 Cycles 2 – 6
			20	Relapsed/refractory CLL	HD cohorts: 1600 mg D1 + D8 Cycle1, 800 mg D1 Cycles 2 – 6
GAUSS	Phase I	22		Relapsed/refractory NHL	200 – 2000 mg D1, D8, D22 repeated q4 weeks × 6 cycles (D1 50% dose) Responding patients receive maintenance q3 months × 24 months
	Phase II	175	87	Relapsed/refractory iNHL	Obinutuzumab 1000 mg weekly × 4 then q2 months × 24 months in responders
			88		Rituximab 375 mg/m^2 weekly × 4 then q2 months × 24 in responders
GAUDI	Phase Ib	56	28	Relapsed/refractory FL	LD cohort: 400 mg D1, D8 Cycle 1, 400 mg D1 Cycles 2 – 6 + CHOP or FC
			28		HD cohort: 1600 mg D1, D8 Cycle 1, 800 mg D1 Cycles 2 – 6 + CHOP or FC
GALTON	Phase Ib	41	21	Relapsed/refractory CLL	Obinutuzumab 100 mg D1, 900 mg D2, 1000 mg D8, 1000 mg D15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + FC
			20		Obinutuzumab 100 mg D1, 900 mg D2, 1000 mg D8, 1000 mg D15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + B
CLL11	Phase III	781		Previously untreated CLL with co-morbidities	Obinutuzumab 1000 mg D1, 8, 15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + CLB
GOYA	Phase III	Not yet reported		Previously untreated DLBCL	Obinutuzumab 1000 mg D1, 8, 15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + CHOP
GALLIUM	Phase III	Not yet reported		Previously untreated FL or MZL	Obinutuzumab 1000 mg D1, 8, 15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + chemotherapy followed by 1000 mg q2 months × 24 months in responders
GADOLIN	Phase III	Not yet reported		Rituximab-refractory iNHL	Obinutuzumab 1000 mg D1, 8, 15 Cycle 1, 1000 mg D1 Cycles 2 – 6 + B

aNHL: Aggressive non-Hodgkin lymphoma; B: Bendamustine; CHOP: Cyclophosphamide, doxorubicin, vincristine, prednisone; CLB: Chlorambucil; CLL: Chronic lymphocytic leukaemia; DLBCL: Diffuse large B cell lymphoma; FC: Fludarabine, cyclophosphamide; FL: Follicular lymphoma; HD: High dose; iNHL: Indolent non-Hodgkin lymphoma; LD: Low dose; MZL: Marginal zone lymphoma.

monotherapy arm (p = 0.002) while no such difference was yet demonstrated with the addition of rituximab to CLB (p = 0.11). Obinutuzumab was also superior to rituximab with a statistically significant and clinically important improvement in PFS and a trend to an OS advantage (p = 0.08) [19]. As the follow-up time is still relatively short, it remains possible that R-CLB may prove statistically superior to CLB in terms of OS and that obinutuzumab-CLB may prove superior to R-CLB if later analyses are performed.

Minimal residual disease (MRD) analysis was also performed as a secondary outcome in the study and surprisingly demonstrated high rates of MRD negativity in the obinutuzumab-CLB group, with more than a 10-fold higher incidence in the peripheral blood than that observed with rituximab. MRD eradication has been correlated with improvements in OS in CLL [37]; but until now, such deep responses were not thought possible in frailer or older patients. Many centres, particularly in America, do not consider CLB to be a sufficiently active agent to justify its use as the primary chemotherapy backbone in CLL even in elderly patients. The ability to elicit high CR and MRD negative rates in combination with a weak chemotherapy agent supports the marked potency of obinutuzumab observed in this trial. These results highlight the efficacy of obinutuzumab in CLL in its ability to achieve deep remissions in combination with a chemotherapeutic agent recognised for its limited potency (no MRD eradication was observed in the CLB monotherapy arm). The marked increase in MRD eradication in the obinutuzumab versus rituximab arms also suggests that this may lead to an OS advantage in the obinutuzumab versus rituximab groups with lengthier follow-up.

Toxicity profiles were notable in this study with a high incidence of IRRs with the first infusion. Unfortunately, this led to treatment discontinuation in 7% of patients, despite the fact that IRRs proved exceedingly uncommon with subsequent infusions. Although the rate of IRRs with obinutuzumab in CLL seems higher than that reported or expected with rituximab, the majority were Grade 1 – 2 and could be

managed with usual supportive care techniques. The incidence of severe infections or treatment-related deaths was not increased in the obinutuzumab group compared to the rituximab or CLB monotherapy groups, demonstrating that obinutuzumab is safe even in a frail, older patient population.

3.3 Non-Hodgkin lymphoma

3.3.1 *Indolent NHL*

Two Phase I studies of obinutuzumab were performed in patients with relapsed/refractory CD20$^+$ NHL as previously reviewed [27,33,38]. In the study involving monotherapy with obinutuzumab followed by maintenance therapy in responders, the duration of response in responders ranged from 3.0 to 21.1 months with 4 of 7 responses lasting > 1 year [33]. The Phase II follow-up study was also previously reported as showing efficacy [27,39].

Obinutuzumab was also investigated in a Phase Ib study in combination with conventional cytotoxic chemotherapy in relapsed follicular lymphoma (FL) patients [27,40]. The results of the maintenance portion of this study were recently presented with the observation of an increase in the CR rate with the use of maintenance and the lack of any new safety concerns. The median follow-up was 32 – 37 months with the median PFS not reached in the obinutuzumab-CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) arm and 46.0 months in the obinutuzumab-FC arm. These results suggest safety and potent activity of obinutuzumab in combination with chemotherapy and justify the ongoing studies of chemo-immunotherapy followed by maintenance with obinutuzumab in FL [41].

Finally, a randomised Phase II study (B021003) was performed in relapsed indolent CD20$^+$ NHL, comparing single-agent obinutuzumab at 1000 mg weekly for 4 doses, followed by maintenance therapy every 2 months for 2 years in responding patients, compared to single-agent rituximab at 375 mg/m^2 weekly for 4 doses followed by the same maintenance schedule. Results from this study were presented at the American Society of Hematology Annual Meeting in 2011 but have not yet been published or updated. A total of 175 patients who were not rituximab-refractory were enrolled, of which 149 had FL (87 received obinutuzumab and 88 received rituximab). The median number of prior therapies was 2 and 99 patients had received prior rituximab. The ORR at the end of induction by investigator assessment was 43% for the obinutuzumab-treated patients and 39% for the rituximab-treated patients in the FL group. A greater difference in response rates was reported by central blinded radiology review, reporting an ORR of 43% for obinutuzumab and 28% for rituximab. No new safety signals were noted in the study. The authors' conclusions were that the response rates appeared more favourable for obinutuzumab at this early assessment point and that this justified the ongoing Phase III studies in NHL [42].

3.3.2 *Aggressive NHL*

After safety was demonstrated in a broad group of NHL patients in the Phase I study, 40 patients with relapsed/refractory CD20$^+$ aggressive lymphoma were investigated in the Phase II with encouraging results in both DLBCL and MCL [27]. Twenty percent of rituximab-refractory patients exhibited treatment response. The tolerability and efficacy of obinutuzumab were thought to be encouraging given the high-risk nature of these heavily pretreated patients and the median response duration was 9.8 months with several patients exhibiting responses of > 1 year [43].

4. Conclusion

Obinutuzumab is a novel anti-CD20 mAb that has now proven to be superior to rituximab in a Phase III clinical trial when combined with CLB in older CLL patients with co-morbidities. This Type II mAb has demonstrated improved ADCC and DCD in preclinical studies compared to Type I anti-CD20 mAbs and Phase I/II clinical trials have demonstrated that obinutuzumab is safe and tolerable in several relapsed/refractory patient populations with toxicities similar to those seen with rituximab.

IRRs appear to be more frequent with the first infusion of obinutuzumab but most are Grade 1 – 2 and easily managed and do not recur with subsequent infusions.

Three additional Phase III studies of obinutuzumab are currently underway in NHL and their results are eagerly awaited.

5. Expert opinion

Obinutuzumab is a novel anti-CD20 mAb that has now proven to be superior to rituximab in a Phase III clinical trial of frontline therapy for CLL patients with co-morbidities. Given the marked improvement in survival elicited by the addition of rituximab to the therapy of NHL and CLL, the demonstration of superiority of obinutuzumab over rituximab in the CLL11 study is extremely exciting. As rituximab is less effective as a single agent in CLL than NHL (likely due to the reduced expression of CD20 on CLL cells compared to NHL), it is possible that CLL is the best disease in which to observe clinical improvements related to this more potent anti-CD20 mAb. However, even very small gains in survival in NHL would lead to major clinical impact given the prevalence of CD20$^+$ NHL and the curability of some and, thus, this agent may also one day replace rituximab for the management of NHL.

This is a very exciting time in the management of CLL with the recent introduction of several novel agents in this disease, all demonstrating marked efficacy. Targeted therapy of the B-cell receptor or bcl-2 inhibitors is actively being investigated in Phase III studies after early trials demonstrated impressive efficacy and safety results [44-46]. Some in vitro evidence has

been reported suggesting synergism between Bcl-2 family inhibitors and obinutuzumab (or other mAbs), making the combination of obinutuzumab with novel agents an obvious avenue for future studies [28,47]. ABT-199 (GDC-0199), a bcl-2 inhibitor, looks especially potent in CLL [46] and thus might be an ideal agent to combine with obinutuzumab in the treatment of CLL.

The addition of rituximab to the treatment of NHL and CLL has had a significant and clinically important impact on survival. Since the introduction of rituximab, many pharmaceutical companies have been attempting to develop a better anti-CD20 mAb to outperform rituximab. Until now, none of these novel compounds had proven to be sufficiently 'better' than rituximab in the clinical setting but most of these novel mAbs were Type I antibodies similar to rituximab, and this may explain why they did not result in a marked improvement in efficacy. Obinutuzumab is a Type II mAb, which may explain its increased potency over rituximab in $CD20^+$ NHL and CLL.

However, many investigators have criticised the current comparisons of rituximab and obinutuzumab due to the higher administration dose of obinutuzumab. Early studies of rituximab in CLL demonstrated disappointing response rates, much inferior to those noted in most other subtypes of NHL and this was ascribed to reduced drug levels of rituximab due to altered pharmacokinetics and/or to the low density of CD20 expression on CLL cells [48,49]. In an effort to improve the efficacy of rituximab in CLL, two subsequent studies examined higher doses of rituximab monotherapy and reported improved response rates [50,51]. However, despite these early findings, a follow-up study of dose-dense rituximab in combination with FC did not result in improved outcomes in a study in younger, fit CLL patients, a finding that leads to reduced enthusiasm for this approach to improving outcomes for CLL patients [52]. Currently, the French GOELAMS group is conducting a Phase II clinical trial of intensified prophase rituximab before fludarabine, cyclophosphamide and rituximab (FCR) with MRD negativity as a primary endpoint (NCT01370772). While not a Phase III study, this trial will hopefully answer the question of whether intensifying the dose of rituximab may lead to improved CLL results. Of course, such increased doses of rituximab will increase the cost of the treatment and make a Phase III comparison of dose-dense rituximab compared to obinutuzumab less appealing.

It is feasible that obinutuzumab may one day replace rituximab in all areas of hematological oncology, but it is also possible that the efficacy and/or superiority of obinutuzumab noted in CLL may not be reproduced in NHL, hence the interest in the results of the other active Phase III studies of this agent. It is possible that the superiority of obinutuzumab will be easier to demonstrate in diseases with poor rituximab single-agent efficacy, such as CLL.

Additionally, we must continue to remain vigilant for early and late toxicities that may be associated with the higher potency of this novel mAb. The marked increased incidence of IRRs with first obinutuzumab infusion in the CLL11 study caused concern for some sub-investigators, leading to treatment discontinuations. As this patient population was more frail than that of most clinical trials, this likely explains the higher rate of treatment discontinuation than was observed in the Phase I/II studies. However, the majority of IRRs were Grade 1 – 2 and restricted to the first infusion and those patients who experienced Grade 3 – 4 IRRs generally did not experience problems with subsequent infusions. Unfortunately, the CLL11 investigators were not able to identify clinical features that would predict which patients will experience more profound IRRs with first infusion and thus caution should be applied in the treatment of all CLL patients. However, physicians experienced in the use of rituximab should have little troubles managing the anticipated IRRs with obinutuzumab, particularly if the initial dose is divided to allow for a smaller, slowly infused first dose.

To date, no clear explanation has been obtained for the increase in IRRs with obinutuzumab compared to rituximab. In vitro studies have revealed levels of cytokines induced by glycoengineered obinutuzumab that were similar to those reported for alemtuzumab and OKT3, two antibodies recognised for their incidence of severe IRRs [23,53-55]. Significant amounts of TNF, IL-6 and IL-8 cytokines were released in CLL whole blood after stimulation with obinutuzumab, levels much higher than those observed after rituximab [23]. Thus, the increased incidence of IRRs may not prove as significant for NHL patients as for CLL.

Therefore, the data published so far for obinutuzumab in the treatment of $CD20^+$ lymphoproliferative disorders are extremely encouraging. The CLL11 study justifies the replacement of rituximab by obinutuzumab in the treatment of CLL, at least in previously untreated patients. The promising efficacy in CLL warrants further evaluation of this agent with other novel agents in CLL and in NHL, studies that will hopefully be soon to commence. The results of the Phase III studies in NHL are eagerly awaited.

Declaration of interest

The authors were supported by honoraria from Hoffman la Roche not related to this manuscript. The authors have no other relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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• **A review of novel anti-CD20 antibodies in B cell malignancies.**

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