TRIAL SUMMARY: Obinutuzumab vs rituximab in patients with comorbidities

BACKGROUND
CLL11 is a large randomized phase III trial investigating first-line chemoimmunotherapy in CLL patients with comorbidities. The final stage 1 analysis recently showed that GA101 plus Clb (GClb) or rituximab plus Clb (RClb) has superior efficacy to chemotherapy with Clb alone. This abstract presents the final stage 2 analysis with efficacy and safety results of the head-to-head comparison between GClb and RClb; at the pre-planned interim analysis, the primary endpoint was met early and the results were released by the independent data monitoring board (see Table 1).

Treatment-naive CLL patients with a Cumulative Illness Rating Scale (CIRS) total score >6 and/or an estimated creatinine clearance (CrCl) <70 mL/min were eligible. Patients received Clb alone (0.5 mg/kg po d1; d15 q28 days, 6 cycles), GClb (100 mg iv d1, 900 mg d2, 1000 mg d8, d15 of cycle 1; 1000 mg d1 cycles 2–6), or RClb (375 mg/m² IV d1 cycle 1, 500 mg/m² d1 cycles 2–6). Primary endpoint was investigator-assessed progression-free survival (PFS). Response rates, minimal residual disease (MRD), and overall survival (OS) were key secondary efficacy endpoints.

FINDINGS
The number of patients with MRD-negative blood samples at end-of-treatment was more than 10-fold higher with GClb compared with RClb (63/214 [29.4%] vs 6/243 [2.5%]). Grade 3–4 infusion-related reactions (IRRs) with GClb occurred at first infusion only.

COMMENTS:
Obinutuzumab is a novel type II anti-CD20 monoclonal antibody (MAb) derived from humanization of a mouse antibody and glycoengineered to enhance antibody-dependent cell-mediated cytotoxicity (ADCC) and direct cell death. Like many novel anti-CD20 antibodies, the early preclinical studies of obinutuzumab were very encouraging and suggested increased efficacy over rituximab, an agent that has already revolutionized the treatment of CD20+ lymphoproliferative disorders. Based on encouraging early studies, several phase III trials have been undertaken to assess the efficacy and safety of obinutuzumab in different CD20+ malignancies. The first of these phase III trials to have closed to accrual and have results presented is the CLL11 study of the German CLL Study Group (GCLLSG).

The CLL11 study was a multicentre, open-label, randomised, 3-arm study investigating the efficacy and safety of obinutuzumab (GA101) plus chlorambucil (GClb) versus rituximab plus chlorambucil (RClb) versus chlorambucil monotherapy in previously untreated patients with CLL and
comorbidities. Stage 1 results from this study, comparing both antibody combination arms to Clb monotherapy, were presented at the ASCO annual meeting in June 2013. The final stage 2 results comparing the GCib to RClb arms were presented in December 2013 at the ASH annual meeting.

The study and its results are important for two reasons. Firstly, the impressive results are practice-changing and will likely be implemented across Canada very quickly. Secondly, the study specifically targeted a population that has previously been excluded from most oncology chemotherapy trials, namely elderly patients and patients with comorbidities. This population was not expected to tolerate intensive chemotherapy with fludarabine, cyclophosphamide and rituximab (which, until recently, was the only therapy proven to improve OS in previously untreated CLL patients). These inclusion criteria resulted in a population with a median age of 72–74 years, reflective of the average age at treatment onset for CLL patients. All patients also had either reduced renal function (30–70mL/min creatinine clearance) and/or a number of comorbidities. Because of the frailty of this population, it was previously unclear whether anti-CD20 MAb therapy would result in significant improvements in survival, due to concerns that toxicities would negate any benefit. Successful accrual to this study documents that such elderly or frail patients are appropriate populations to specifically evaluate in cancer trials.

The stage 1 results presented at ASCO clearly demonstrated that the addition of an anti-CD20 MAb to Clb resulted in clinically significant improvements in PFS in this population. More importantly, the lengthier followup of this analysis at ASH enabled to detection of an OS advantage in the G-Clb patients compared to Clb monotherapy. No OS advantage has yet been demonstrated with RClb over Clb monotherapy, nor with GCib compared to RClb. Based on these results, it is now confirmed that all patients with CLL should receive chemoimmunotherapy with an anti-CD20 MAb, at least as a part of frontline therapy.

The stage 2 analysis directly compared GCib to RClb and demonstrated improved PFS with GCib compared to RClb (26.7 months vs 15.2 months, p<0.0001). Impressively, a sizable minority of patients in the GCib arm also achieved MRD negativity, a surprising finding given the expected lack of potency of the Clb chemotherapy backbone. The number of patients with MRD negativity was over 10-fold higher in the GCib group compared to the RClb group, further clarifying the superiority of obinutuzumab over rituximab in these CLL patients. A

The toxicity profiles were similar between the two antibodies, except that obinutuzumab resulted in a significantly higher rate of grade 3–4 IRRs, which nearly all occurred during the first infusion only. Unfortunately, a number of patients were removed from treatment on the GCib arm after these IRRs, which may have reduced the observed difference between the GCib and RClb arms. To date, the investigators have not been able to clearly identify any risk factors for severe IRRs, so all patients should be monitored closely with a first obinutuzumab infusion and should receive this as a divided dose for cycle 1. It is also important to note that the incidence of severe infections or treatment-related deaths was not higher with obinutuzumab compared to the other groups.

Some criticism has been leveled about the unequal dosing between rituximab and obinutuzumab in this and other studies. While it is possible that improved responses and survival may be observed if rituximab were provided at a higher dose-intensity, it would seem unlikely that such a change would lead to results as impressive as those observed with GCib in this study (particularly in reference to the frequency of MRD negativity).

The data provided from the CLL11 study should have implications for CLL patients across Canada. Until now, many elderly or frail CLL patients were not offered anti-CD20 MAb-based therapy for their disease, a practice that should now change to result in all patients receiving chemoimmunotherapy for frontline treatment of CLL. The demonstrated superiority of obinutuzumab over rituximab in terms of a clinically valuable PFS advantage (11.5 months) and the OS advantage demonstrated against Clb monotherapy suggest that obinutuzumab should be the MAb of choice in CLL. Ultimately, the availability of obinutuzumab in Canada will be based on cost-benefit analyses that are likely already being undertaken. The very impressive efficacy of obinutuzumab warrants further evaluation of this MAb for other CD20+ lymphoproliferative malignancies in combination with conventional chemotherapy, as well as novel agents, such as the new tyrosine kinase inhibitors targeting the B-cell-receptor signaling pathway.

References


