Obinutuzumab (GA101) in relapsed/refractory chronic lymphocytic leukemia: final data from the phase 1/2 GAUGUIN study

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Online supplementary material

Pharmacokinetic and pharmacodynamic assessments

Obinutuzumab pharmacokinetics (maximum plasma concentration \( [C_{\text{max}}] \), trough plasma concentration \( [C_{\text{trough}}] \)) and pharmacodynamics (peripheral CD19+ B-cell depletion/recovery) were secondary objectives. The threshold for B-cell depletion was CD19+ lymphocyte counts <0.07 \( \times 10^9 \)/L. Complement (C3, C3a, C4, C5a) was measured pre-infusion, immediately post-infusion and 2-5 hours post-infusion on days 1, 8, and 15, cycle 1, day 1, cycles 2 and 5, and 28 days after last obinutuzumab dose. IFN-\( \alpha/\beta \), TNF-\( \alpha \), IL-6, IL-8, and IL-10 were measured pre-infusion, mid-infusion, immediately post-infusion, and 2-5 hours post-infusion on days 1, 8, and 15, cycle 1 and day 1, cycle 2.

Pharmacodynamics results

In phase 1, all patients achieved a rapid (within days) and sustained elimination of CLL cells, with 12/13 patients (92%) exhibiting B-cell depletion (CD19+ cell counts <0.07 \( \times 10^9 \)/L) (Figure 5B). One patient (1000/1000 mg cohort) did not become B-cell depleted. In phase 2, 16/18 patients (89%) became B-cell depleted. Two patients were B-cell depleted at screening and were included based on prior CLL diagnoses and lymph node progression. Peripheral B-cell counts had not yet returned, presumably due to prior
treatment with B-cell-depleting agents (alemtuzumab, rituximab). There was no bone marrow involvement in the patient previously treated with alemtuzumab; bone marrow status was unknown for the other patient.

At the end of the treatment period, 10 phase 1 participants were B-cell depleted. Of these, 8 experienced B-cell recovery (CD19+ cell counts >0.07 x 10⁹/L after depletion), 3 within 6 months of follow-up, 3 within 9 months of follow-up, 1 within 18 months of follow-up, and one after >24 months of follow-up. Five recovered in the absence of PD. Ten phase 2 participants exhibited B-cell recovery. Of these, 3 recovered within 6 months of follow-up, 3 within 12 months of follow-up, 2 within 18 months of follow-up, and 2 within 24 months of follow-up. Seven experienced PD either before or within 45 days after B-lymphocyte recovery; 3 recovered in the absence of PD.