Cirmtuzumab is a specific inhibitor of ROR1 signaling. It is a broad-spectrum high-affinity, nonmonoclonal antibody that binds the extracellular domain of human ROR1 and is distinct from other anti-ROR1 antibodies. It does not recognize normal adult tissues. An earlier phase 1 trial in relapsed/refractory CLL showed it to safely inhibit ROR1 signaling, reverse stem-lineage gene expression signatures of leukemic cells, and to prolong PFS with anti-CLL effects (Cho et al. Cell Stem Cell 2019).

Cirmtuzumab, in combination with ibritinib, exerted potent synergistic effects in both MCL and CLL (Yu et al. 2017, 2018).

This is a Phase 1/2 study of safety, pharmacokinetics, pharmacodynamics, and antitumor activity of the combination of cirmtuzumab and ibritinib (I+1).

Part 1: Dose-finding in MCL and CLL

Cirmtuzumab: Weight-based fixed dosing cohorts (N=12/8 cohort)
- 2, 4, and 8 mg/kg per dose
- 300 mg and 600 mg per dose

Single agent cirmtuzumab in the first month to assess biomarkers, including receptor occupancy, followed by combination treatment of I+1.

Cirmtuzumab is administered iv. GVHD is followed by monthly administration for a total duration of one year. Ibritinib administered using FDA-approved dosing for 48 weeks. CLL results reported here. Full results of Part 1 for MCL will be reported separately.

ROR1-Related Receptor Occupancy and Pharmacokinetics

(A) Percent receptor occupancy (RO) for ROR1 was evaluated by flow cytometry of PBMCs, using competitive or non-competitive binding for ROR1 on CLL cells. Good RO was observed across all doses, with less variability in the first 4 weeks of treatment in the higher dose groups (8 mg/kg and 16 mg/kg). No RO was observed across all doses, with less variability in the first 4 weeks of treatment in the higher dose group (8 mg/kg and 16 mg/kg).

So patients with MCL have also been treated in the CRLL study, and their part I data will be reported separately. One patient treated in a complete response after 3 months of cirmtuzumab (2 mg/kg) + ibritinib treatment, including complete resolution of a large hepatic lesion. The CR is confirmed for 6 months.