Ibrutinib Versus Ofatumumab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL): Results From the Randomized Phase III RESONATE™ (PCYC-1112) Trial

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Context: Ibrutinib, a first-in-class, once-daily oral, covalent inhibitor of Bruton's tyrosine kinase, demonstrated single-agent activity and an acceptable safety profile in a phase II relapsed/refractory (R/R) CLL/SLL study (Byrd et al. NEJM 2013). Ibrutinib is FDA approved for CLL patients who have received ≥1 prior therapy, and for patients with del(17p) CLL.

Objective: Interim safety and efficacy results from an international, multicenter, open-label, randomized phase III study of single-agent ibrutinib vs ofatumumab in R/R CLL/SLL

Patients: Patients with R/R CLL/SLL who received ≥1 previous therapy considered inappropriate for purine analogs

Main Outcome Measures: Independent Review Committee-assessed PFS (primary); overall survival (OS), ORR, safety (secondary)

Intervention: 420 mg oral ibrutinib daily or IV ofatumumab 300/2000 mg (12 doses)

Results: 391 patients (median age 67 years, 40% ≥70 years, 30% del17p); 195 randomized to ibrutinib, 196 to ofatumumab. Ibrutinib patients had median 3 prior therapies vs 2 for ofatumumab. Ibrutinib significantly improved PFS (median not reached vs 8.1 months; HR 0.215, 95% CI 0.146-0.317, P<0.0001; 78.5% risk reduction), and OS (median not reached; HR 0.434, 95% CI 0.238-0.789, P=0.0049; 57% risk reduction) vs ofatumumab. Ofatumumab patients (n=57) with confirmed progressive disease crossed over to the ibrutinib arm. ORR by IRC, including partial response with lymphocytosis: 62.6% for ibrutinib vs 4.1% for ofatumumab. Major hemorrhage rates: 1% for ibrutinib vs 1.6% for ofatumumab. Drug discontinuation due to AEs: 4.1% for ibrutinib vs 3.6% for ofatumumab. At median time on study of 9.6 months, 86% of ibrutinib patients were continuing treatment.

Conclusions: Single-agent ibrutinib significantly improved PFS, OS, and ORR in patients with previously treated CLL/SLL compared with ofatumumab. The effect of ibrutinib on PFS was observed irrespective of baseline features, including del(17p) or purine analog-refractory disease. The safety profile was comparable with that reported previously. These results support ibrutinib as an effective therapy for patients with previously treated CLL.