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ORAL ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 55-Month Follow-up from the Glow Study

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Introduction **:** In the GLOW trial (NCT03462719), fixed-duration Ibr+Ven treatment has shown superiority to Clb+O in progression-free survival (PFS), better sustained undetectable minimal residual disease (uMRD) responses, and overall survival (OS) benefit in patients with previously untreated chronic lymphocytic leukemia (CLL) who are older and/or have comorbidities (CU Niemann, et al. *Blood*. 2022;140[suppl 1]:228-230). In this analysis, we report clinical outcomes, including PFS, OS, and MRD analysis, from the Ibr+Ven combination in GLOW with a median follow-up of 55 months, including subgroup analyses by IGHV and MRD.

Methods **:** Patients aged ≥ 65 years or 18 to 64 years with a Cumulative Illness Rating Scale score > 6 or creatinine clearance < 70 mL/min were randomized 1:1 to Ibr+Ven (3 cycles of Ibr lead-in, followed by 12 cycles of Ibr+Ven; N = 106) or 6 cycles of Clb+O (N = 105). Each cycle was 28 days. Patients were excluded if they had del17p or known *TP53* mutations at screening. End points included investigator-assessed PFS, uMRD rates, time to next treatment (TTNT), and OS. MRD was assessed sequentially over time in peripheral blood by next-generation sequencing for patients with partial response (PR) or better. Patients with < 1 CLL cell per 10,000 leukocytes (< 10^{-4}) were considered to have uMRD, whereas patients with ≥ 1 CLL cell per 10,000 leukocytes (≥ 10^{-4}) were considered to have detectable MRD (dMRD). All *p* values reported were nominal. Safety was not further assessed, as all patients were already past the treatment period in previous analyses.

Results of updated analyses **:** With a median follow-up of 55 months, PFS remained superior for Ibr+Ven (hazard ratio [HR] 0.239 [95% confidence interval (CI), 0.159-0.359]; $p < 0.0001$); 54-month PFS rates were 65.8% for Ibr+Ven and 19.1% for Clb+O. In the Ibr+Ven arm, for patients with unmutated IGHV (uIGHV; n = 67) and mutated IGHV (mIGHV; n = 32), 54-month PFS rates were 58% and 90%, respectively. Also in the Ibr+Ven arm, PFS rates at 3 years post-treatment were 82% in patients who achieved uMRD at 3 months after end of treatment (EOT+3; n = 58) and 73% for patients with dMRD (n = 31). Among patients with uIGHV, PFS rates at 3 years post-treatment were 81% for those achieving uMRD at EOT+3 (n = 40) and 56% for those with dMRD (n = 16). In patients with mIGHV, PFS rates at 3 years post-treatment were ≥ 92% regardless of MRD status at EOT+3. Overall, at 38 months after end of treatment (EOT+38), 32.1% of patients had uMRD in the Ibr+Ven arm. Of the patients who achieved uMRD at EOT+3 (n = 58), 53.4% sustained uMRD status at EOT+38 in the Ibr+Ven arm. In addition, TTNT was prolonged for patients receiving Ibr+Ven versus Clb+O. The risk of needing second-line therapy was significantly reduced by 83% with first-line Ibr+Ven versus Clb+O (HR 0.174 [95% CI, 0.088-0.342]; $p < 0.0001$), and by 85% among patients with uIGHV (HR 0.146 [95% CI, 0.069-0.310]) compared with a 29% risk reduction in those with mIGHV (HR 0.708 [95% CI, 0.118-4.256]). In the Ibr+Ven arm, 4 patients received single-agent ibrutinib as subsequent therapy as part of the study; while 1 patient had not yet had a disease assessment, the best response for the other 3 patients were complete response (n = 1) and PR (n = 2). Finally, Ibr+Ven continues to demonstrate improved OS versus Clb+O, reducing the risk of death by 58% (HR 0.421 [95% CI, 0.237-0.747]; $p = 0.0023$). Estimated 54-month OS rates were 84.5% for the Ibr+Ven arm and 63.1% for the Clb+O arm.
Conclusion **:** With prolonged follow-up of 55 months in the GLOW study, all-oral, once-daily, fixed-duration Ibr+Ven continues to show superior PFS versus Clb+O. Among patients treated with Ibr+Ven, benefit in PFS was particularly observed in patients with uIGHV who achieved uMRD at EOT+3 and in patients with mIGHV regardless of MRD status at EOT+3. Moreover, Ibr+Ven fixed-duration combination treatment continues to demonstrate an OS advantage versus chemoimmunotherapy in patients with previously untreated CLL.

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