First Prospective Data on Minimal Residual Disease (MRD) Outcomes After Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O) for First-Line Treatment of CLL in Elderly or Unfit Patients: The GLOW Study

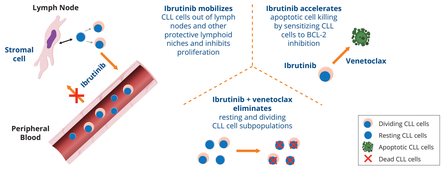
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BACKGROUND

- Ibr+Ven is an all-oral, once-daily, fixed-duration treatment with complementary mechanisms of action that work synergistically to eliminate chronic lymphocytic leukemia (CLL) subpopulations in distinct tumor compartments (**Figure 1**).[1-9]
- In the primary analysis of the phase 3 international GLOW trial, independent review committee (IRC)-assessed PFS for Ibr+Ven was superior to Clb+O (hazard ratio, 0.216; $p < 0.0001$).
- MRD status is a predictor of PFS in CLL following CIT and FDT with venetoclax + an anti-CD20 antibody, but the relationship has not been explored for Ibr+Ven.[10,11]

Figure 1 Ibrutinib + venetoclax: distinct and complementary modes of action that work synergistically

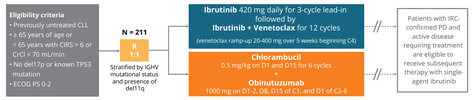


OBJECTIVES

- To investigate MRD outcomes and correlation with PFS in the phase 3 GLOW study (NCT03462719)

METHODS

Figure 2 Phase 3 GLOW Study Design (NCT03462719)



BM, bone marrow; C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; EOT, end of treatment; EOT+3, 3 months after EOT; EOT+12, 12 months after EOT; IRC, independent review committee; NGS, next-generation sequencing; PB, peripheral blood; PD, progressive disease; R, randomization; uMRD, undetectable minimal residual disease.

- Study primary endpoint: PFS as assessed by IRC
- Current MRD analysis:
  - MRD evaluated via NGS and reported with cutoffs of $< 10^{-4}$ and $< 10^{-5}$ (not all samples had sufficient cell yield to be analyzed at $< 10^{-6}$). NGS analysis not yet available beyond EOT+12 time point
  - PB/BM concordance calculated for patients with uMRD in PB at EOT+3 who had a paired BM sample
  - PFS results updated with 34.1 months of follow-up

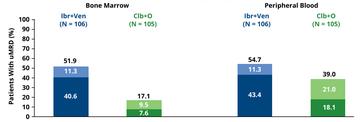
B-CELL MALIGNANCIES

RESULTS

MRD results by NGS at 3 months after end of treatment (EOT+3)

- Rate of uMRD $< 10^{-4}$ was significantly higher with Ibr+Ven vs Clb+O in BM and PB (**Figure 3**)
  - uMRD concordance in PB/BM: 92.9% for Ibr+Ven vs 43.6% for Clb+O
- uMRD rate $< 10^{-5}$ was higher with Ibr+Ven vs Clb+O in both compartments (**Figure 3**)
  - In the Ibr+Ven arm, but not the Clb+O arm, most patients with uMRD $< 10^{-4}$ had deep responses of uMRD $< 10^{-5}$
  - uMRD concordance at $< 10^{-5}$ in PB/BM: 90.9% for Ibr+Ven vs 36.8% for Clb+O

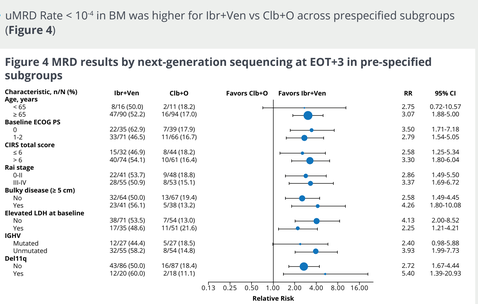
Figure 3 MRD results by next-generation sequencing at EOT+3



EOT, end of treatment; PB, peripheral blood.

- uMRD Rate $< 10^{-4}$ in BM was higher for Ibr+Ven vs Clb+O across prespecified subgroups (**Figure 4**)

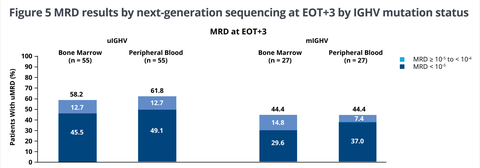
Figure 4 MRD results by next-generation sequencing at EOT+3 in pre-specified subgroups



Size of the blue dot represents relative sample size of each subgroup. CIRS, Cumulative Illness Rating Scale score; EOT, end of treatment; LDH, lactate dehydrogenase; RR, relative risk.

- Ibr+Ven: uMRD rates were high in BM and PB for patients with uIGHV CLL (**Figure 5**)
  - With Ibr+Ven, depth of MRD response was similar in BM and PB for patients with uIGHV CLL
  - Among patients with mutated *TP53*, 5 of 7 achieved uMRD $< 10^{-5}$ in both BM and PB with Ibr+Ven

Figure 5 MRD results by next-generation sequencing at EOT+3 by IGHV mutation status

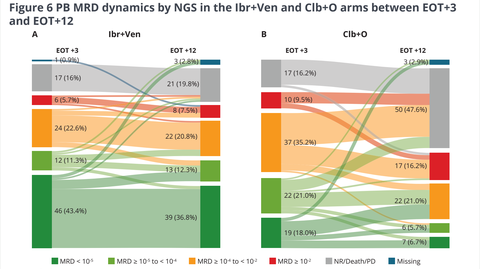


Patients with IGHV status not available (n = 24): 45.8% (BM) and 50.0% (PB) had uMRD $< 10^{-4}$. BM, bone marrow; EOT, end of treatment; mIGHV, mutated IGHV; PB, peripheral blood; uIGHV, unmutated IGHV.

MRD dynamics post-treatment

- uMRD in PB was better sustained with Ibr+Ven from EOT+3 to EOT+12 (**Figure 6A**)
  - 84.5% (49/58) of patients had sustained uMRD $< 10^{-4}$ and 80.4% (37/46) had sustained uMRD $< 10^{-5}$ with Ibr+Ven (sustained uMRD rate is calculated on a per-patient basis, not using intent-to-treat MRD rates at EOT+3 and EOT+12)
    - 29.3% (12/41) and 26.3% (5/19) with Clb+O
  - uMRD $< 10^{-4}$ rate decreased 6% with Ibr+Ven vs 27% with Clb+O
- Patients with detectable MRD ≥ 10^{-4} in the Ibr+Ven arm (**Figure 6B**) were less likely to:
  - Convert to PD vs those in the Clb+O arm
  - Have worsening of detectable MRD levels

Figure 6 PB MRD dynamics by NGS in the Ibr+Ven and Clb+O arms between EOT+3 and EOT+12

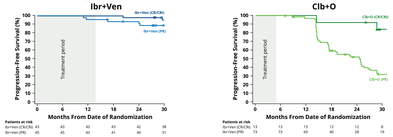


EOT, end of treatment; NR, nonresponder; PB, peripheral blood; PD, progressive disease.

Correlation of MRD with PFS

- Impact of CR/CRi (best response) vs PR on PFS was less pronounced with Ibr+Ven vs Clb+O (**Figure 7**)
  - 30-month PFS remained > 85% for patients with CR/CRi or PR with Ibr+Ven, while most patients with PR had progressed in Clb+O arm (median follow-up 34.1 months)

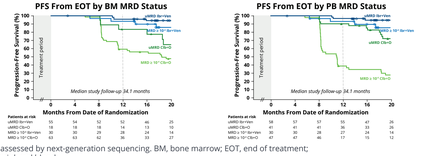
Figure 7 PFS according to response



CR, complete response; CRi, CR with incomplete bone marrow recovery; PR, partial response.

- In patients with uMRD $< 10^{-4}$ in BM, PFS rate was better sustained post-treatment with Ibr+Ven vs Clb+O (**Figure 8**)
- In patients with detectable MRD ≥ 10^{-4} in BM or PB (**Figure 8**):
  - PFS rate > 90% was sustained during the first year post-treatment with Ibr+Ven
  - Early relapse was common with Clb+O
- PFS rate was sustained in the first year post-treatment with Ibr+Ven, independent of BM or PB MRD status (**Figure 8**)

Figure 8 PFS according to BM or PB MRD status at EOT+3

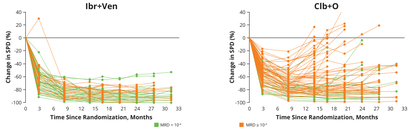


MRD assessed by next-generation sequencing. BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

Correlation of MRD with lymph node responses

- Among patients with uMRD $< 10^{-4}$ in bone marrow at EOT+3, lymph node responses were largely maintained (**Figure 9**)
- Lymph node responses were better maintained over time with Ibr+Ven vs Clb+O in patients with detectable BM MRD (≥ 10^{-4} at EOT+3) (**Figure 9**)

Figure 9 Lymph node responses



EOT, end of treatment; SPD, sum of the product of perpendicular dimensions.

CONCLUSIONS

- All-oral, once-daily, fixed-duration Ibr+Ven achieved deeper ($< 10^{-5}$) and better sustained uMRD responses vs Clb+O as assessed by NGS
  - Deep responses were mirrored in BM and PB in patients with uIGHV
  - Though small numbers, deep responses were seen in patients with *TP53* mutations
- Molecular and clinical relapses were less frequent during the first year post-treatment with Ibr+Ven
- Patients who did not achieve uMRD at the end of Ibr+Ven treatment had PFS > 90% at 1-year post-treatment, and lymph node responses were well maintained
  - Trends were similar to those seen in patients achieving uMRD
- Unique relationship between MRD status and PFS may be explained by broader clearance of multiple disease compartments resulting from complementary mechanisms of Ibr and Ven
  - Additional follow-up is warranted to confirm the longer-term impact of MRD status on PFS

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REFERENCES:
1. Lu P, et al. *Blood Cancer J*. 2021;11:39; 2. Deng J, et al. *Leukemia*. 2017;31:2075-2084; 3. Herman ES, et al. *Clin Cancer Res*. 2015;21:4642-4651; 4. Burger JA, et al. *Leukemia*. 2020;34:787-798; 5. Shanafelt T, et al. *N Engl J Med*. 2019;381:432-443; 6. Cervantes-Gomez F, et al. *Clin Cancer Res*. 2015;21:3705-3715; 7. Kater AP, et al. *Blood Adv* 2021; 5 (23): 5410–5414; 8. Haselager MV, et al. *Blood*. 2020;136:2918-2926; 9. Slinger E, et al. *Leukemia*. 2017;31:2601-2607; 10. Wierda WG, et al. *Leukemia*. 2021;35: 3059–3072; 11. Kater AP, et al. *J Clin Oncol*. 2019;37:269-277.

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