Genomic Alterations and Outcomes With Fixed-Duration Ibrutinib + Venetoclax: Results From the Phase 3 GLOW Study in Patients With Previously Untreated Chronic Lymphocytic Leukemia

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INTRODUCTION

- Genomic alterations, including immunoglobulin heavy-chain variable (IGHV) mutation status, are prognostic for chemoimmunotherapy outcomes in chronic lymphocytic leukemia (CLL).[1,2] We explored the prognostic impact of baseline genomic aberrations and IGHV status on efficacy outcomes with fixed-duration ibrutinib + venetoclax (Ibr + Ven) and chlorambucil + obinutuzumab (Clb + O) in the phase 3 GLOW study (NCT03462719)

OBJECTIVES

- To evaluate the impact of baseline genomic alterations on response, undetectable minimal residual disease (uMRD), and progression-free survival (PFS) of Ibr + Ven and Clb + O
- To report PFS and overall survival (OS) outcomes at 46 months of median follow-up

METHODS

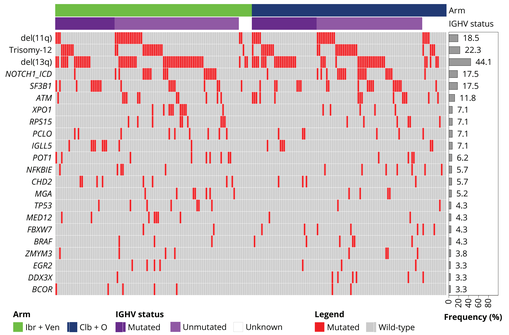
- GLOW evaluated efficacy and safety of Ibr + Ven and Clb + O in patients with previously untreated CLL. Patients aged ≥ 65 or 18 to 64 years with Cumulative Illness Rating Scale score of > 6 or creatinine clearance of < 70 mL/min were randomized 1:1 and stratified by del(11q) and IGHV status. Patients with del(17p) or known *TP53* mutation were excluded. Del(11q), trisomy-12 (+12), and del(13q) were assessed by fluorescence *in situ* hybridization (FISH), IGHV mutation status by DNA-based next-generation sequencing (NGS, 98% cutoff), and exome-scale gene mutation analysis by NGS (Personalis ImmunoID NeXT), with minimal variant allele frequency detection limit of 5%. NGS was also used to assess uMRD (< 10^{-4}) in peripheral blood (PB)
- Cox proportional hazard models, Kaplan-Meier estimates, and log-rank tests were used to analyze time-to-event variables. Fisher's exact test was used for association between binary variables. Reported *P* values are nominal. For statistical comparisons between and within arms, genes with a ≥ 7% frequency, *MGA* and *TP53* were used

B-CELL MALIGNANCIES

RESULTS

- Incidences of baseline genomic alterations across both arms based on Döhner hierarchy were 18.5% for del(11q), 22.3% for +12, and 44.1% for del(13q). IGHV was unmutated (uIGHV) in 58.8% and mutated (mIGHV) in 31.8% of samples. The most frequent gene mutations were *NOTCH1-ICD*, *SF3B1*, *ATM*, *XPO1*, and *RPS15* (**Figure 1**)
  - Baseline genomic alterations were balanced between treatment arms

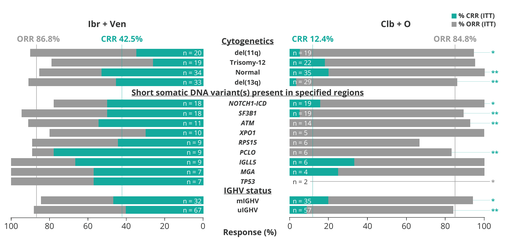
FIGURE 1: Incidence of genomic alterations



ICD, intracellular domain.

- Patients with del(11q), normal karyotype, del(13q), *NOTCH1-ICD*, *SF3B1*, *ATM*, *PCLO*, mIGHV, and uIGHV achieved significantly higher complete response rates (CRRs) in the Ibr + Ven arm versus those in the Clb + O arm (**Figure 2**)

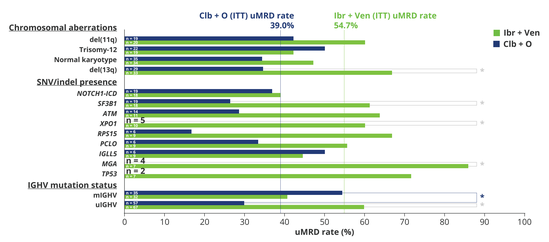
FIGURE 2: Best response by genetic subgroups



CRR, complete response rate; ITT, intent to treat; ORR, overall response rate.
*$P < 0.05$; ** $P < 0.01$. Significant difference between the arms is marked with a teal asterisk for CRR and a gray asterisk for ORR.

- Patients in the Ibr + Ven arm achieved higher uMRD rates at 3 months after end of treatment (EOT + 3) than those in the Clb + O arm, regardless of genetic alterations, except for +12, *IGLL5*, and mIGHV (**Figure 3**)

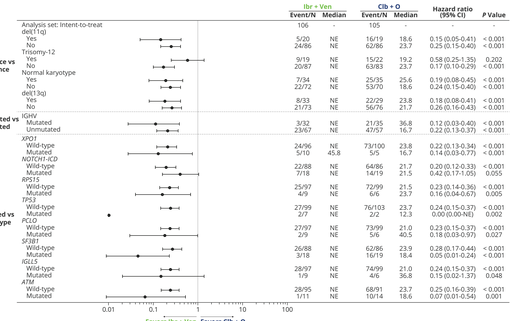
FIGURE 3: uMRD rates in PB at EOT + 3 by genetic alteration



IGHV, immunoglobulin heavy-chain variable; indel, short insertions/deletions; ITT, intent to treat; mIGHV, mutated IGHV; uIGHV, unmutated IGHV SNV, single nucleotide variant; uMRD, undetectable minimal residual disease. Vertical lines refer to rates in the ITT population. *$P < 0.05$. Significant differences in uMRD rates are marked with a blue bracket and an asterisk for Clb + O, and a gray bracket and an asterisk for between-arm comparisons

- Among patients treated with Ibr + Ven, uMRD rates trended higher for del(13q) (presence, 66.7% vs absence, 49.3% and uIGHV, 59.7% vs mIGHV 40.6%), and lower for +12 (42.1% vs absence 57.5%) and *NOTCH1-ICD* (mutated 38.9% vs wild-type 58.0%), however differences were not statistically significant
- For the Clb + O arm, uMRD rates at EOT + 3 in PB trended higher for +12 (50.0% vs absence 36.1%), and lower for *SF3B1* (mutated, 26.3% vs wild-type, 41.9%) and *ATM* (mutated, 28.6% vs wild-type, 40.7%), however differences were not statistically significant. Patients with uIGHV achieved significantly lower uMRD than patients with mIGHV

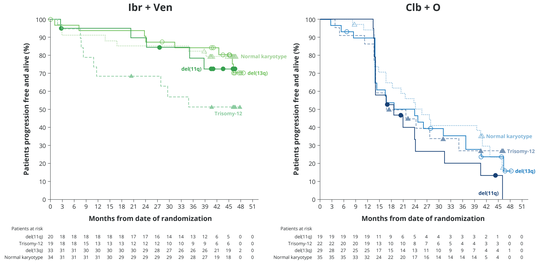
FIGURE 4: PFS of Ibr + Ven versus Clb + O according to chromosomal and genetic alterations



CI, confidence interval; HR, hazard ratio; ICD, intracellular domain; PFS, progression-free survival.
Both +12 and IGHV had imbalances in non–progression-related on-treatment deaths (3/19 [+12] vs 4/87 [absence] and 6/67 [uIGHV] vs 0/32 [mIGHV]) and sample sizes were small, which may limit interpretation of these data

- With median follow-up of 46 months, PFS was significantly improved for patients treated with Ibr + Ven versus Clb + O (HR, 0.214 [95% CI, 0.138-0.334], $P < 0.0001$)
  - PFS was significantly improved for patients in the Ibr + Ven arm versus the Clb + O arm across all chromosomal and genomic subgroups except +12 (HR, 0.58), mutated *NOTCH1-ICD* (HR, 0.42), and mutated *IGLL5* (HR, 0.15), which trended in favor of Ibr + Ven, but were not statistically significant (**Figure 4**)
  - PFS in subgroups with chromosomal aberrations is shown in **Figure 5**

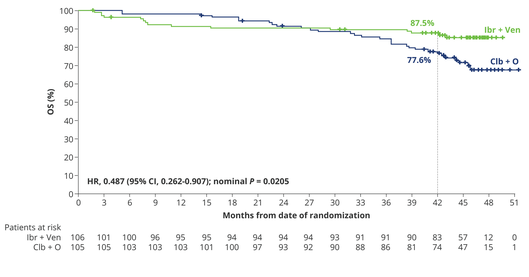
FIGURE 5: PFS in subgroups with chromosomal aberrations



Clb + O, chlorambucil + obinutuzumab; PFS, progression-free survival.

- With median follow-up of 46 months, patients in the Ibr + Ven arm had improved OS versus the Clb + O arm (HR, 0.487 [95% CI, 0.262-0.907]; nominal $P = 0.0205$) (**Figure 6**)

FIGURE 6: OS of Ibr + Ven versus Clb + O



CONCLUSIONS

- Patients in the Ibr + Ven arm achieved higher uMRD rates versus those in the Clb + O arm across most genomic subgroups, except patients with trisomy-12, *IGLL5* mutation, and mIGHV
- Patients in the Ibr + Ven arm achieved significantly improved PFS versus those in the Clb + O arm across most genomic subgroups
- PFS and OS were significantly improved in patients treated with Ibr + Ven versus Clb + O at 46 months of follow-up

ACKNOWLEDGMENTS
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2. Stilgenbauer S, et al. *Blood*. 2014;123:3247-3254.

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