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First-Line Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab in Elderly or Comorbid Patients With Chronic Lymphocytic Leukemia: GLOW Study 67-Month Follow-up and Adverse Event-Free Progression-Free Survival Analysis

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Key Takeaway

Ibr+Ven continues to deliver superior clinical responses versus Clb+O at an extended follow-up of 67 months in the phase 3 GLOW study in older or comorbid patients with previously untreated CLL

Conclusions

At 67-month median follow-up, Ibr+Ven continues to show superior PFS, reduced risk of requiring 2L treatment, and sustained OS advantage versus Clb+O in patients with previously untreated CLL

Fixed-duration Ibr+Ven achieves longer grade 3/4 TEAE-free PFS by more than 21 months compared with Clb+O, without ongoing toxicity associated with continuous treatment

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Poster

Supplementary material

https://www.congresshub.com/ASH2024/Oncology/Ibrutinib/Niemann

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Acknowledgments
Writing assistance was provided by Jennifer Venzie, PhD, of Parexel. This study is sponsored by Janssen Research & Development, LLC, a Johnson & Johnson company.

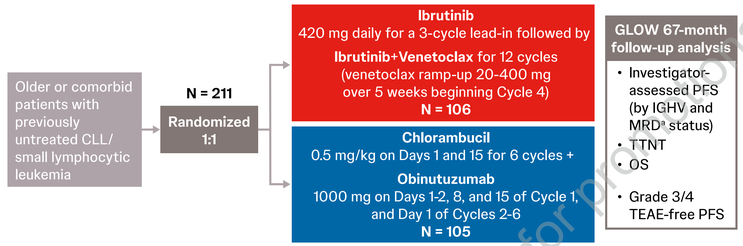
Disclosures
CU Niemann: Research funding from AbbVie, AstraZeneca, Janssen, Novo Nordisk Foundation, and Octopharma; consultant for AbbVie, AstraZeneca, Beigene, CSL Behring, Eli Lilly, Genmab, Janssen, MSD, Octopharma, Synaptics Therapeutics, and Takeda.

Introduction

- The GLOW primary analysis (27.7-month median follow-up) showed superior progression-free survival (PFS) and deeper, more durable responses with Ibrutinib+Venetoclax (Ibr+Ven) versus Chlorambucil+Obinutuzumab (Clb+O) in patients with previously untreated chronic lymphocytic leukemia (CLL)[1]
- This analysis of the GLOW study presents:
  - PFS, overall survival (OS), and time to next treatment (TTNT), including subgroup analysis by IGHV and minimal residual disease (MRD) status, at 67-month median follow-up
  - Assessment of grade 3/4 treatment-emergent adverse event (TEAE)-free PFS

Methods

GLOW (NCT03462719) phase 3 clinical study design



[a]MRD in peripheral blood was measured by next-generation sequencing 3 months post end of treatment (EOT+3), with undetectable MRD (uMRD) defined as < 1 CLL cell per 10,000 leukocytes (< 10^{-4}); patients with ≥ 1 CLL cell per 10,000 leukocytes (≥ 10^{-4}) were considered to have detectable MRD.

Grade 3/4 TEAE-free PFS analysis

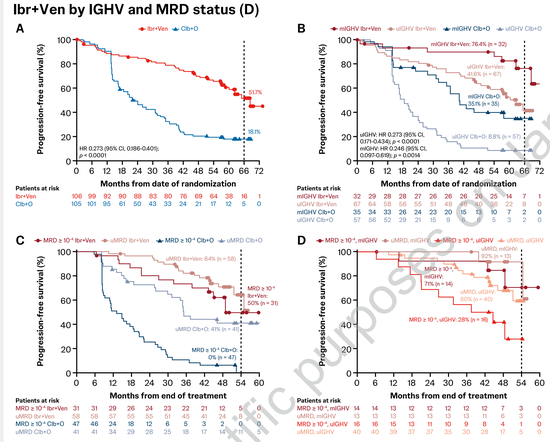
- Median (range) treatment duration was 13.8 months (0.7-19.5) for Ibr+Ven versus 5.1 months (1.8-7.9) for Clb+O, resulting in a > 2.5-fold longer AE collection for Ibr+Ven versus Clb+O (AEs collected ≤ 30 days post final dose)
  - AEs occurring after this period were not considered treatment emergent unless specifically considered treatment related by the investigator
- 3 distinct health states were defined: time with grade 3/4 TEAEs before progression (TOX time), time without grade 3/4 TEAEs before progression (grade 3/4 TEAE-free PFS time), time after progression (post-progression survival time)
  - Health states were estimated using Kaplan-Meier curves, and the mean durations for each state were estimated by calculating the area under the curve using restricted mean survival time (RMST) for grade 3/4 TEAE TOX, PFS, and OS
  - Mean duration of grade 3/4 TEAE-free PFS and post-progression survival time were computed as the difference in RMST between PFS and TOX and between PFS and OS, respectively

Results

Progression-free survival (Figure 1 and Supplementary Material)

- PFS was improved with Ibr+Ven versus Clb+O (hazard ratio [HR] 0.273 [95% confidence interval (CI), 0.186-0.401]; nominal $p < 0.0001$) (**Figure 1A**)
- PFS was prolonged with Ibr+Ven over Clb+O regardless of IGHV (**Figure 1B**) or MRD status at EOT+3 (**Figure 1C**)
- uMRD at EOT+3 was more critical for long-term PFS in patients with unmutated IGHV (uIGHV) versus those with mutated IGHV (mIGHV) treated with Ibr+Ven (**Figure 1D**)

Figure 1: PFS for all patients (A) by IGHV status (B), by MRD status (C), and for Ibr+Ven by IGHV and MRD status (D)

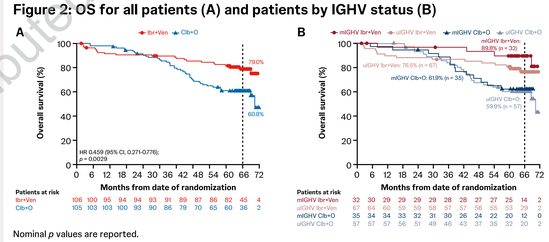


Nominal p values are reported.

Overall survival (Figure 2 and Supplementary Material)

- OS was improved with Ibr+Ven versus Clb+O (HR 0.459 [95% CI, 0.271-0.776]; nominal $p = 0.0029$) (**Figure 2A**)
- There was a trend toward improved OS observed for Ibr+Ven over Clb+O for both mIGHV and uIGHV groups (**Figure 2B**)

Figure 2: OS for all patients (A) and patients by IGHV status (B)

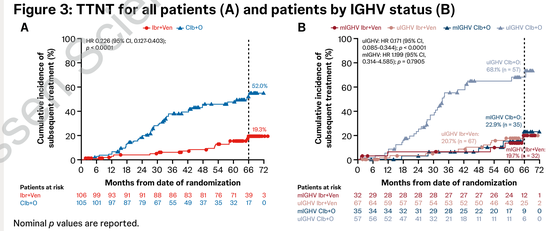


Nominal p values are reported.

Time to next treatment and treatment-free survival (Figures 3 and 4 and Supplementary Material)

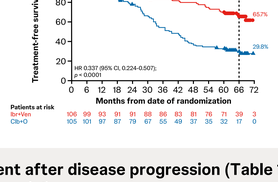
- Ibr+Ven reduced the risk of need for second-line (2L) therapy by 77% versus Clb+O in all patients (**Figure 3A**), and by 83% in patients with uIGHV (**Figure 3B**)
- Few patients with mIGHV required 2L therapy at 67-month follow-up; no difference in TTNT was observed between Ibr+Ven and Clb+O (**Figure 3B**)
- Ibr+Ven prolonged treatment-free survival time by 66% versus Clb+O (**Figure 4**)

Figure 3: TTNT for all patients (A) and patients by IGHV status (B)



Nominal p values are reported.

Figure 4: Treatment-free survival for all patients



Nominal p values are reported.

Patient management after disease progression (Table 1 and Supplementary Material)

- 8 patients in the Ibr+Ven group and 31 patients in the Clb+O group received single-agent ibrutinib
- Best responses for patients in the Ibr+Ven group who received single-agent ibrutinib: 1 complete response, 3 partial responses; 4 did not have disease assessment at clinical cutoff

Table 1: Subsequent treatments following disease progression

Subsequent treatment in patients with PD, n (%)	Ibr+Ven (n = 28)	Clb+O (n = 76)
Patients with subsequent therapy	16 (57.1)	46 (60.5)
Bruton's tyrosine kinase inhibitors		
Single-agent ibrutinib	8 (28.6)	31 (40.8)
Zanubrutinib	1 (3.6)	0
Acalabrutinib	0	7 (9.2)
Other targeted agents		
Venetoclax	3 (10.7)	12 (15.8)
Idelalisib	1 (3.6)	1 (1.3)
Monoclonal antibodies	6 (21.4)	13 (17.1)

PD, disease progression.

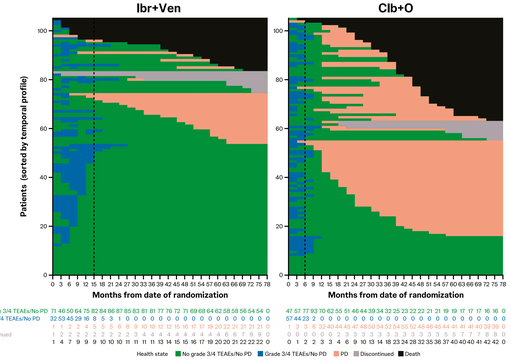
Second primary malignancies (Supplementary Material)

- 14 patients (13.2%) who received Ibr+Ven and 18 (17.1%) who received Clb+O had second primary malignancies

Grade 3/4 TEAE-free PFS (Figures 5 and 6 and Supplementary Material)

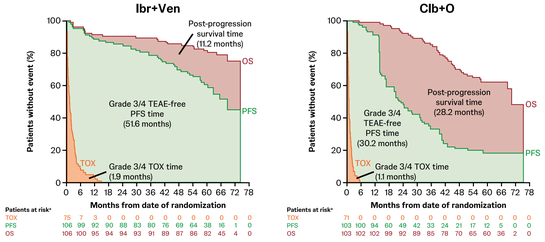
- Compared with Clb+O, patients in the Ibr+Ven group spent more time in the no grade 3/4 TEAEs, no progressive disease health state (**Figure 5**)
- Areas under the curve for grade 3/4 TEAE TOX time, grade 3/4 TEAE-free PFS, and alive post progression are generated from partition curves for Ibr+Ven and Clb+O (**Figure 6**)
  - Patients treated with Ibr+Ven spent longer time in the grade 3/4 TEAE TOX time state versus Clb+O (1.9 versus 1.1 months, nominal $p = 0.004$)
  - Patients in the Ibr+Ven group spent more than 21 months longer in grade 3/4 TEAE-free PFS compared with Clb+O (51.6 versus 30.2 months, nominal $p = 0.0052$)

Figure 5: Patients in the Ibr+Ven group spent more time in the no grade 3/4 TEAEs/no disease progression health state



In each figure, each row represents the temporal pattern of an individual patient's health state. Patients are sorted by temporal profile.[2] Dashed lines represent the treatment time frames plus the grade 3/4 TEAE collection period (AEs were collected ≤ 30 days post dose).

Figure 6: Patients in the Ibr+Ven group spent more time in grade 3/4 TEAE-free PFS versus patients in the Clb+O group



*For TOX only patients with grade 3/4 events in the at-risk population.

Please see our ASH 2024 poster on the comparison of OS estimates between patients receiving fixed-duration Ibrutinib+Venetoclax to an age-matched general European population (Poster 3254)

References
1. Kater AP, et al. *NEJM Evidence*; 2022:1(7):EVIDoa2200006. 2. Norton JD. *Drug Inf J*. 2011;45:741-747.

B-cell Malignancies