First-Line Fixed-Duration Ibrutinib Plus Venetoclax Versus Chlorambucil Plus Obinutuzumab: Up to 5 Years of Follow-Up From the GLOW Study

Talha Munir,[1] Carolyn Owen,[2] George Follows,[3] José-Ángel Hernández-Rivas,[4] Ohad Benjamini,[5] Ann Janssens,[6] Mark-David Levin,[7] Tadeusz Robak,[8] Martin Simkovic,[9] Sergey Voloshin,[10] Vladimir Vorobyev,[11] Munci Yagci,[12] Loic Ysebaert,[13] Qianya Qi,[14] Emma Smith,[14] Srimathi Srinivasan,[15] Natasha Schuier,[14] Kurt Baeten,[16] Donne Bennett Caces,[14] Carsten U. Niemann,[17] Arnon P. Kater[18]

[1]St James's Hospital, Leeds, United Kingdom; [2]Tom Baker Cancer Centre, Calgary, AB, Canada; [3]Addenbrooke's Hospital, Cambridge, United Kingdom; [4]Hospital Universitario Infanta Leonor, Universidad Complutense, Madrid, Spain; [5]Sheba Medical Center, Ramat Gan, Israel; [6]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [7]Albert Schweitzer Hospital, Dordrecht, Netherlands; [8]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [9]4th Department of Internal Medicine – Haematology, Faculty of Medicine in Hradec Králové, University Hospital and Charles University in Prague, Hradec Kralove, Czech Republic; [10]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [11]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [12]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [13]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [14]Janssen Research & Development, Raritan, NJ, USA; [15]Oncology Translational Research, Janssen Research & Development, Lower Gwynedd Township, PA, USA; [16]Janssen Research & Development, Beerse, Belgium; [17]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [18]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Amsterdam, Netherlands

INTRODUCTION

- Ibrutinib and venetoclax have distinct and complementary modes of action that work synergistically[1-9]
- GLOW is a randomized, multicenter phase 3 study evaluating ibrutinib + venetoclax (Ibr+Ven) versus chlorambucil + obinutuzumab (Clb+O) in patients with previously untreated chronic lymphocytic leukemia (CLL) who are older and/or have comorbidities[10]
- Previous analysis at a median follow-up of 46 months showed the following[11]:
  - Ibr+Ven had higher progression-free survival (PFS) per Independent Review Committee (estimated 42-month rates of 75% vs 25%), higher overall survival (OS) (estimated 42-month rates of 88% vs 78%), and longer time to next treatment (TTNT) (hazard ratio [HR], 0.155 [95% CI, 0.072-0.333]) compared with Clb+O
  - Undetectable minimal residual disease (uMRD) responses as assessed by next-generation sequencing (NGS) were maintained from end of treatment (EOT)+3 (55%) through EOT+27 (38%) in the Ibr+Ven arm

OBJECTIVE

- To present updated clinical outcomes at a median follow-up of 57.3 months (range, 1.7-65.2)

METHODS

Study design

- Adults aged ≥65 or 18-64 years with a Cumulative Illness Rating Scale score of >6 or creatinine clearance of <70 mL/min without del(17p)/*TP53* mutations were randomly assigned (1:1) to Ibr+Ven (3 cycles [28 days] of Ibr, 12 cycles of Ibr+Ven) or Clb+O (6 cycles); details of the study have been previously described[10]

Outcomes

- The outcomes of the current analysis were investigator-assessed PFS, uMRD (measured by NGS in peripheral blood), OS, TTNT, and safety (second primary malignancies). All *P* values are nominal

RESULTS

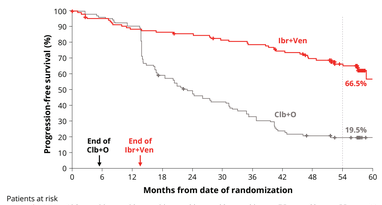
Baseline and clinical characteristics

- Baseline characteristics (previously presented) were generally balanced between arms and reflective of older adults and/or those with comorbidities[11]
- A total of 30% and 63% of patients in the Ibr+Ven arm, and 33% and 54% of patients in the Clb+O arm had mutated immunoglobulin heavy-chain variable (mIGHV) and unmutated IGHV (uIGHV), respectively

PFS

- When compared with Clb+O, Ibr+Ven reduced the risk of progression or death by 74% (HR, 0.256; 95% CI, 0.17-0.38; *P* < 0.0001)
- Estimated 54-month PFS rates at 57 months of follow-up were 67% for Ibr+Ven and 20% for Clb+O (**Figure 1**)

Figure 1: PFS in the ITT population

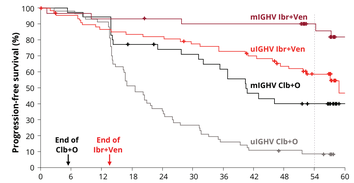


Patients at risk											
Ibr+Ven	106	99	92	90	88	83	80	75	68	55	11
Clb+O	105	101	95	61	50	43	33	24	20	15	2

Investigator-assessed PFS was analyzed.
Clb+O, chlorambucil + obinutuzumab; Ibr+Ven, ibrutinib + venetoclax; ITT, intention to treat; PFS, progression-free survival.

- In patients treated with Ibr+Ven with uIGHV and mIGHV, respectively, 54-month PFS rates were 59% and 90%, versus 8% and 40% for patients in the Clb+O arm (**Figure 2**)

Figure 2: PFS in the ITT population by IGHV status

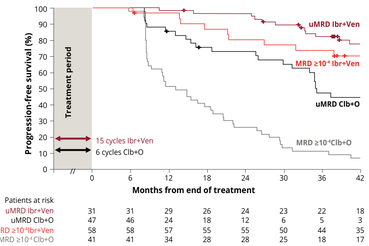


Patients at risk											
mIGHV Ibr+Ven	32	29	28	28	27	26	26	26	26	22	5
uIGHV Ibr+Ven	67	64	58	56	55	51	48	45	39	30	6
mIGHV Clb+O	35	34	33	26	24	23	20	15	13	9	2
uIGHV Clb+O	57	56	52	29	21	15	9	6	5	4	0

Results based on updated IGHV reclassifications. Investigator-assessed PFS was analyzed.
Clb+O, chlorambucil + obinutuzumab; Ibr+Ven, ibrutinib + venetoclax; IGHV, immunoglobulin heavy-chain variable; ITT, intention to treat; mIGHV, mutated IGHV; PFS, progression-free survival; uIGHV, unmutated IGHV.

- PFS rates at 42 months post-treatment were 78% and 70%, respectively, in patients treated with Ibr+Ven with or without uMRD, versus 44% and 6% for patients in the Clb+O arm at EOT+3 (**Figure 3**)

Figure 3: Progression-free survival landmark analysis from EOT[a]

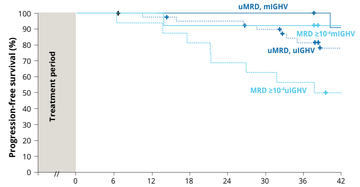


Patients at risk								
uMRD Ibr+Ven	31	31	29	26	24	23	22	18
uMRD Clb+O	47	46	24	18	12	6	5	3
MRD ≥10⁻⁴Ibr+Ven	58	58	57	55	55	50	44	35
MRD ≥10⁻⁴ Clb+O	41	41	34	28	28	25	18	17

[a]Curves generated from EOT (15 cycles for Ibr+Ven, 6 cycles for Clb+O).
All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as <1 CLL cell per 10,000 leukocytes (<10⁻⁴).
Clb+O, chlorambucil + obinutuzumab; CLL, chronic lymphocytic leukemia; EOT, end of treatment; Ibr+Ven, ibrutinib + venetoclax; MRD, minimal residual disease; uMRD, undetectable MRD.

- PFS rates at 42 months post-treatment for patients with or without uMRD at EOT+3 were 78% and 50%, respectively, in patients with uIGHV and were 91% and 92%, respectively, in patients with mIGHV (**Figure 4**)

Figure 4: Ibr+Ven PFS landmark analysis from EOT[a]



Patients at risk								
MRD ≥10⁻⁴mIGHV	14	14	13	12	12	12	12	10
uMRD mIGHV	13	13	13	13	13	13	13	10
MRD ≥10⁻⁴uIGHV	16	16	15	13	11	10	9	7
uMRD uIGHV	40	40	39	37	37	34	29	23

[a]Curves generated from EOT (15 cycles for Ibr+Ven, 6 cycles for Clb+O).
All patients who had MRD outcome at EOT+3 were included in this analysis; uMRD was defined as <1 CLL cell per 10,000 leukocytes (<10⁻⁴). Results based on updated IGHV reclassifications.
Clb+O, chlorambucil + obinutuzumab; CLL, chronic lymphocytic leukemia; EOT, end of treatment; Ibr+Ven, ibrutinib + venetoclax; IGHV, immunoglobulin heavy-chain variable; mIGHV, mutated IGHV; MRD, minimal residual disease; PFS, progression-free survival; uIGHV, unmutated IGHV; uMRD, undetectable MRD.

uMRD

- At EOT+38, 32% of all patients treated with Ibr+Ven and 53% of patients with uMRD at EOT+3 achieved uMRD
- At 3 years post-treatment, uMRD responses in the Ibr+Ven arm had an annual decline of <10%
- uMRD rate remained stable 3 years after treatment completion in patients with mIGHV
- uMRD rate was ~60% after treatment completion in patients with uIGHV and decreased to ~30% at EOT+38

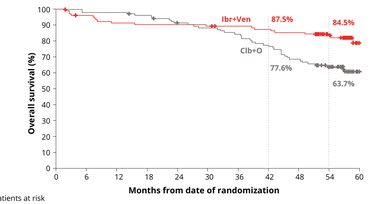
TTNT

- Compared with Clb+O, Ibr+Ven prolonged TTNT and reduced the risk of requiring second-line therapy by 82% (HR, 0.185; 95% CI, 0.096-0.355; *P* < 0.0001)
- At 54 months, in patients with mIGHV or uIGHV, respectively, an estimated 94% and 84% of patients in the Ibr+Ven arm versus 90% and 35% of patients in the Clb+O arm did not require second line-line treatment

OS

- At 57 months of follow-up, OS was better in the Ibr+Ven arm than in the Clb+O arm (HR, 0.453; 95% CI, 0.261-0.785; *P* = 0.0038); 54-month OS rates were 85% and 64%, respectively (**Figure 5**)

Figure 5: Overall survival in the ITTpopulation



Patients at risk											
Ibr+Ven	106	100	95	94	94	93	91	89	87	74	19
Clb+O	105	103	103	100	93	90	86	79	70	57	17

Clb+O, chlorambucil + obinutuzumab; Ibr+Ven, ibrutinib + venetoclax; ITT, intention to treat.

Safety

- At 57 months of follow-up, there were 19 deaths in the Ibr+Ven arm and 39 deaths in the Clb+O arm
- Second primary malignancies occurred in 14 patients in the Ibr+Ven arm and 18 patients in the Clb+O arm

Patient management after disease progression

- After disease progression, 6 patients in the Ibr+Ven arm received single-agent ibrutinib (best responses: 1 complete response, 3 partial responses; 2 did not have disease assessment at time of clinical cutoff)

CONCLUSIONS

- The estimated 54-month PFS rate for Ibr+Ven was 67% versus 20% for Clb+O (HR, 0.256) in previously untreated older adults or patients with comorbidities
  - High PFS rates were observed with Ibr+Ven in patients with mIGHV regardless of MRD at EOT+3
  - A similar high PFS rate was observed with Ibr+Ven in patients with uIGHV who had uMRD at EOT+3, whereas those with MRD ≥10^{-4} had a lower PFS rate
- A relatively slow decline in MRD negativity was observed with Ibr+Ven 3 years after EOT, in particular for patients with mIGHV
- With longer-term follow-up, fixed-duration Ibr+Ven treatment continued to demonstrate an OS advantage (HR, 0.453) versus Clb+O, as observed in the previous analysis
- Fixed-duration Ibr+Ven prolonged TTNT and reduced the risk of needing second-line therapy (HR, 0.185) versus Clb+O, specifically for uIGHV

ACKNOWLEDGMENTS

This study was sponsored by Janssen Scientific Affairs, LLC. Editorial support was provided by Agnieszka Looney, PhD, of ApotheCom, and funded by Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

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;5:5410-5414.
8. Haselager MV et al. *Blood.* 2020;136:2918-2926. 9. Slinger E et al. *Leukemia.* 2017;31:2601-2607. 10. Kater AP et al. *NEJM Evid.* 2022;1:EVIDoa2200006. 11. Niemann CU et al. *Lancet Oncol.* 2023;24:1423-1433.

Poster originally presented at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, California.
Presented at the Society of Hematologic Oncology (SOHO) Annual Meeting; September 4–7, 2024; Houston, Texas