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

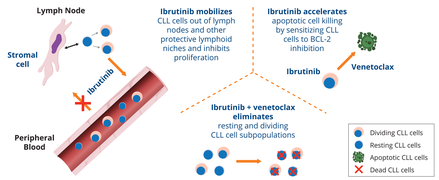
Talha Munir[1], Carol Moreno[2], Carolyn Owen[3], George Follows[4], Ohad Benjamini[5], Ann Janssens[6], Mark-David Levin[7], Anders Osterborg[8], Tadeusz Robak[9], Martin Simkovic[10], Don Stevens[11], Sergey Voloshin[12], Vladimir Vorobyev[13], Munci Yagci[14], Loic Ysebaert[15], Qianya Qi[16], Andrew J. Steele[17], Natasha Schuier[18], Kurt Baeten[19], Donne Bennett Caces[16], Carsten U. Niemann[20], Arnon P. Kater[21]

[1]St James's Hospital, Leeds, UK; [2]Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Spain; [3]Tom Baker Cancer Centre, Calgary, Canada; [4]Addenbrookes Hospital, Cambridge, UK; [5]Sheba Medical Center, Ramat Gan, Israel; [6]UZ Leuven Gasthuisberg, Leuven, Belgium; [7]Albert Schweitzer Hospital, Dordrecht, Netherlands; [8]Karolinska University Hospital, Stockholm, Sweden; [9]Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland; [10]University Hospital Hradec Kralove, Hradec Kralove, Czech Republic; [11]Norton Cancer Institute, Louisville, KY, USA; [12]Russian Scientific and Research Institute of Hematology and Transfusiology, St. Petersburg, Russia; [13]S.P. Botkin Moscow City Clinical Hospital, Moscow, Russia; [14]Gazi Universitesi Tip Fakultesi, Ankara, Turkey; [15]Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France; [16]Janssen Research & Development, Raritan, NJ, USA; [17]Janssen Research & Development, Spring House, PA, USA; [18]Janssen Research & Development, Düsseldorf, Germany; [19]Janssen Research & Development, Beerse, Belgium; [20]Rigshospitalet Copenhagen University Hospital, Copenhagen, Denmark; [21]Amsterdam University Medical Centers, Cancer Center Amsterdam, University of Amsterdam, Netherlands

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

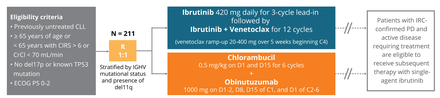


OBJECTIVES

- 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

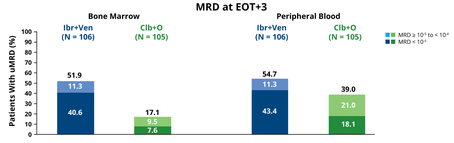
B-CELL MALIGNANCIES

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

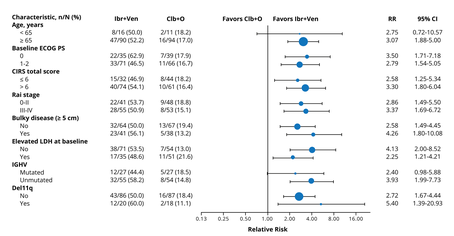
Figure 3 MRD results by next-generation sequencing at EOT+3



BM, bone marrow; 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**)

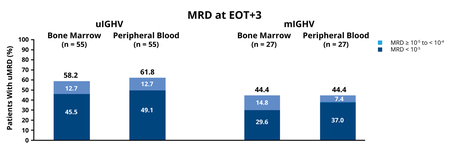
Figure 4 MRD results by next-generation sequencing at EOT+3 in pre-specified subgroups



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

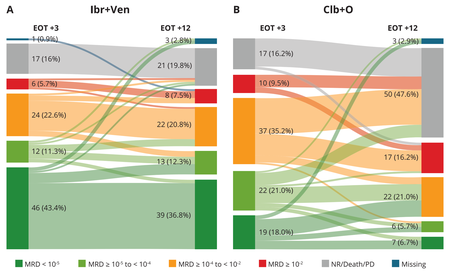


Patients with IGHV status not available (n = 24): 45.8% (BM) and 50.0% (PB) had uMRD $< 10^{-4}$. BM, bone marrow; EOT, end of treatment; mIGHV, mutated IGHV; PB, peripheral blood; uIGHV, unmutated IGHV.

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

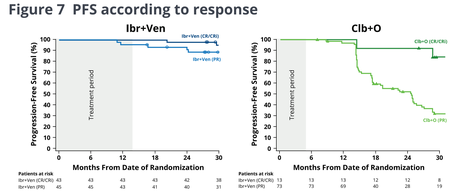


EOT, end of treatment; NR, nonresponder; PB, peripheral blood; PD, progressive disease.

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)

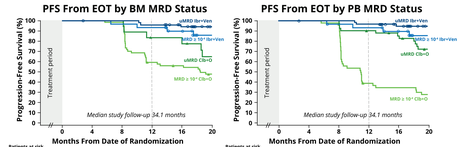
Figure 7 PFS according to response



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

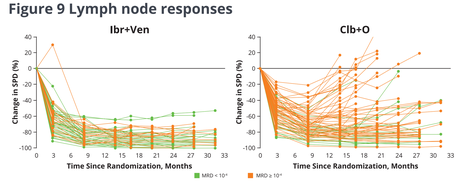


MRD assessed by next-generation sequencing. BM, bone marrow; EOT, end of treatment; PB, peripheral blood.

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



BM, bone marrow; 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

ACKNOWLEDGEMENTS

We thank the patients who participated in the study, their families, and the investigators and clinical research staff from the study centers. This study was sponsored by Janssen Research & Development, LLC. Editorial support was provided by Min Yu of Parexel and Agnieszka Looney of ApotheCom, and funded by Janssen Global Services, LLC, and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC..

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.

Originally presented at ASH 2021; Dec 11-14, 2021; Atlanta, GA, USA