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FIXED-DURATION IBRUTINIB AND VENETOCLAX (I+V) VERSUS CHLORAMBUCIL PLUS OBINUTUZUMAB (CLB+O) FOR FIRST-LINE (1L) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): PRIMARY ANALYSIS OF THE PHASE 3 GLOW STUDY

Topic: 06. Chronic lymphocytic leukemia and related disorders - Clinical

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Arnon Kater¹, Carolyn Owen², Carol Moreno³, George Follows⁴, Talha Munir⁵, Mark-David Levin⁶, Ohad Benjamini⁷, Ann Janssens⁸, Anders Osterborg⁹, Tadeusz Robak¹⁰, Martin Simkovic¹¹, Don Stevens¹², Sergey Voloshin¹³, Vladimir Vorobyev¹⁴, Munci Yagci¹⁵, Loic Ysebaert¹⁶, Rui Qin¹⁷, Sriram Balasubramanian¹⁸, Natasha Schuier¹⁹, Kurt Baeten²⁰, Donne Bennett Caces¹⁷, Carsten Niemann²¹

¹ Amsterdam Medical Centers, University of Amsterdam, Amsterdam, Netherlands

² Tom Baker Cancer Centre, Calgary, Canada

³ Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

⁴ Addenbrooke's Hospital, Cambridge, United Kingdom

⁵ St. James's Hospital, Leeds, United Kingdom

⁶ Albert Schweitzer Hospital, Dordrecht, Netherlands

⁷ Sheba Medical Center, Ramat Gan, Israel

⁸ UZ Leuven Gasthuisberg, Leuven, Belgium

⁹ Karolinska University Hospital, Stockholm, Sweden

¹⁰ Medical University of Lodz, Copernicus Memorial Hospital, Lodz, Poland

¹¹ University Hospital Hradec Kralove, Hradec Kralove, Czech Republic

¹² Norton Cancer Institute, Louisville, United States

¹³ Russian Scientific and Research Institute of Hematology and Transfusiology, Saint-Petersburg, Russian Federation

¹⁴ S.P. Botkin Moscow City Clinical Hospital, Moscow, Russian Federation

¹⁵ Gazi Universitesi Tip Fakultesi, Ankara, Turkey

¹⁶ Institut Universitaire du Cancer Toulouse Oncopole, Toulouse, France

¹⁷ Janssen Research & Development, Raritan, United States

¹⁸ Janssen Research & Development, San Diego, United States

¹⁹ Janssen Research & Development, Düsseldorf, Germany

²⁰ Janssen Research & Development, Beerse, Belgium

²¹ Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

Background: Ibrutinib and venetoclax have complementary mechanisms of action. With ibrutinib inhibiting CLL proliferation and mobilizing cells from protective lymphoid niches and venetoclax efficiently killing circulating CLL cells, I+V may allow for an all-oral, fixed-duration (FD) treatment. GLOW is the first randomized study of first-line FD I+V in CLL/small lymphocytic lymphoma (SLL).

Aims: To evaluate efficacy and safety of FD I+V vs Clb+O in previously untreated CLL/SLL.

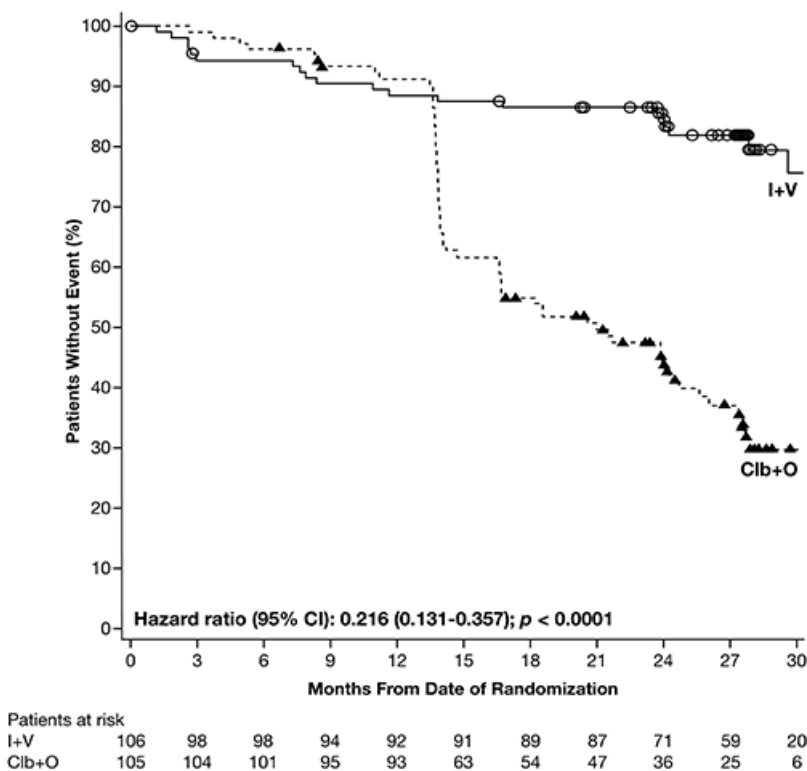
Methods: GLOW (NCT03462719) enrolled patients (pts) aged ≥65 years or 18-64 years with cumulative illness rating scale (CIRS) score >6 or creatinine clearance <70 mL/min. Pts with del(17p) or known *TP53* mutations were excluded. Pts were randomized 1:1, stratified by IGHV mutation and del(11q) status, to I+V (3 cycles ibrutinib 420 mg/d, followed by 12 cycles I+V with venetoclax ramp-up to 400 mg/d) or 6 cycles of standard dose Clb+O (1 cycle is 28 d). Primary endpoint was progression-free survival (PFS) assessed by independent review committee (IRC). Secondary endpoints included undetectable minimal residual disease (uMRD) in bone marrow (BM) via next-generation sequencing (cut-off 10⁻⁴) and complete response (CR) rate.

Results: 106 pts were randomized to I+V and 105 to Clb+O. Median age was 71.0 years (34.1% ≥75 years); 57.8% were male. More I+V pts had CIRS >6 vs Clb+O (69.8% vs 58.1%; median score, 9 vs 8) and more Clb+O pts had

elevated lactate dehydrogenase (48.6% vs 33.0%). Treatment arms were otherwise balanced. With median follow-up of 27.7 months (mo), IRC-assessed PFS for I+V was superior to Clb+O (hazard ratio [HR] 0.216 [95% confidence interval (CI), 0.131-0.357]; $p < 0.0001$) (Figure 1). Median PFS was not reached for I+V and 21.0 (95% CI, 16.6-24.7) mo for Clb+O. PFS improvement with I+V vs Clb+O was consistent across predefined subgroups, including CIRS >6 (HR 0.248) and age ≥ 65 (HR 0.234). PFS by investigator (INV) was similar to IRC. At 3 mo after end of treatment (EOT+3), rate of uMRD was significantly higher for I+V vs Clb+O in BM (51.9% vs 17.1%; $p < 0.0001$) and peripheral blood (PB; 54.7% vs 39.0%; $p = 0.0259$). With I+V, 84.5% (49/58) of pts maintained PB uMRD from EOT+3 to the assessment 12 mo post-EOT. CR rate (including CRi) was significantly higher for I+V vs Clb+O by IRC (38.7% vs 11.4%; $p < 0.0001$) and INV (45.3% vs 13.3%; $p < 0.0001$). Time to subsequent therapy was longer for I+V (HR 0.143, 95% CI 0.05-0.41). Median treatment duration (range) was 13.8 (0.7-19.5) mo for I+V and 5.1 (1.8-7.9) mo for Clb+O. After ibrutinib lead-in, 84.6% of pts with high tumor lysis syndrome (TLS) risk by tumor burden shifted to medium/low risk. Most common grade ≥ 3 treatment-emergent adverse events (AE) were neutropenia/neutrophil count decreased (34.9%), diarrhea (10.4%), and hypertension (7.5%) for I+V, and neutropenia/neutrophil count decreased (49.5%), thrombocytopenia (20.0%), and pneumonia and TLS (5.7% each) for Clb+O. Grade 5 AEs occurred in 7 pts on I+V and 2 pts on Clb+O. At time of analysis, overall survival was immature, with 11 deaths in the I+V arm and 12 in the Clb+O arm (HR 1.048).

Image:

Figure 1. Progression-free survival assessed by independent review committee



Summary/Conclusion: All-oral, once-daily, FD I+V demonstrated superior PFS vs Clb+O as first-line treatment for CLL, independent of CIRS score and other covariates. I+V significantly improved depth and duration of remission, and thus extended time to next treatment. uMRD with I+V was largely maintained 1 year after EOT. The safety profile for I+V was consistent with treatment in an elderly comorbid population. These first randomized data demonstrate the positive clinical profile of FD I+V in older pts.

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