Abstract: P1835

Title: CROSS-STUDY COMPARISON OF IBRUTINIB PLUS VENETOCLAX (I+V) VS VENETOCLAX PLUS OBINUTUZUMAB (V+G) IN SUBJECTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITH COMORBIDITIES

Abstract Type: e-Poster Presentation

Topic: Chronic lymphocytic leukemia and related disorders - Clinical

Background:

Ibrutinib in combination with Venetoclax (I+V) and Venetoclax in combination with Obinutuzumab (V+G) are both authorized for use in 1L CLL in the European Union (EU) as a fixed duration treatments for adult patients with previously untreated chronic lymphocytic leukemia (CLL). While the efficacy comparison of these treatments is of interest for clinical practice, there are currently no head-to-head clinical trials investigating it in patients who have comorbidities.

Aims:

To evaluate relative efficacy of the fixed-duration I+V and fixed-duration V+G in previously untreated adult patients with CLL with comorbidities.

Methods:

The efficacy of I+V and V+G were compared to Chlorambucil in combination with Obinutuzumab in patients with comorbidities in GLOW; NCT03462719 and CLL14; NCT02242942 respectively. The inclusion/exclusion criteria of both studies, as well as the patient baseline characteristics were different. Therefore, an anchored matching-adjusted indirect treatment comparison (MAIC) was performed following the guidelines from the National Institute for Health and Care Excellence (Phillipo 2018).

Individual patient-level data (IPD) with median follow-up of 46 months (m) were available for the GLOW study (Niemann 2023). For CLL14, only aggregate level data were available. Several data cuts were published, but none matching that of GLOW. Therefore, data with a median follow-up of both 39.6m (Al-Sawaf 2020) and 52.4m (Al-Sawaf 2021) were used in the MAIC.

The method first excludes patients from the GLOW IPD following the criteria of CLL14, and then reweights the remaining patients so that the average baseline characteristics of the two studies are the same. Characteristics matched are listed under Table 1. The reweighted relative treatment effect from GLOW is then compared to the reported one from CLL14 using a Bayesian indirect treatment comparison. Results are expressed as median hazard ratios (HR) with 95% credible intervals (CrI) and the probability of I+V to be better than V+G are also reported. Endpoints of interest were progression-free survival (PFS) assessed by investigator (INV), time to next treatment or death (TTNT) and overall survival (OS).

Results:

After adjustment, baseline characteristics between both trial populations were balanced, while maintaining a sufficiently large effective sample size (ESS). All relative treatment effects improved within GLOW after matching the population to CLL14. Comparative analysis results between the two trials suggested that I+V improve PFS, TTNT and OS over V+G, with probabilities over 97% (Table 1). Results were consistent across the different datacuts.

There are potential sources of bias that cannot be accounted for in this MAIC. Patients with deletion of 17p were not allowed in GLOW. This difference between populations can therefore not be adjusted for. Treatment with Chlorambucil was longer in CLL14 than in GLOW, which may have impacted relative treatment effect. There may be additional unreported treatment-effect modifying patient baseline characteristics which cannot be accounted for.

Summary/Conclusion: This analysis suggests that I+V outperforms V+G on PFS, TTNT and OS.

Table 1

	I+V vs V+G							
	CLL14 39.6m				CLL14 52.4m			
	Before adjustment (N=211)		After adjustment* (N=158; ESS=89)		Before adjustment (N=211)		After adjustment* (N=158; ESS=89)	
	HR (95% CrI)	**Prob I+V better**	HR (95% CrI)	**Prob I+V better**	HR (95% CrI)	**Prob I+V better**	HR (95% CrI)	**Prob I+V better**
PFS(INV)	0.65 (0.37-1.14)	93.31%	0.49 (0.24-1.03)	97.04%	0.61 (0.36-1.04)	96.53%	0.46 (0.23-0.94)	98.32%
OS	0.47 (0.21-1.08)	96.37%	0.30 (0.11-0.79)	99.24%	0.57 (0.26-1.24)	92.24%	0.36 (0.14-0.92)	98.35%
TTNT	0.50 (0.26-0.96)	98.09%	0.31 (0.13-0.70)	99.75%	0.56 (0.30-1.03)	96.94%	0.34 (0.15-0.76)	99.59%

*After adjustment = cumulative result of applying CLL14 exclusion criteria and matching age, Eastern Cooperative for Oncology Group performance status (ECOG PS), Cumulative Illness Rating Scale (CIRS) score, TP53 mutation status, immunoglobulin heavy-chain variable gene region (IGHV) mutation status, creatinine clearance, gender, β-2 microglobulin level and time from initial diagnosis.
46m GLOW data were used for this MAIC.
CrI=*credible* interval; ESS=effective sample size; HR=hazard ratio; Prob I+V better=probability that I+V is better than V+G

Keywords: Chronic lymphocytic leukemia, ibrutinib, B-CLL