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Cross-Study Comparison of Ibrutinib in Combination with Venetoclax (I+V) versus Venetoclax in Combination with Obinutuzumab (V+G) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL) and Comorbidities

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Conclusion

The results of this MAIC suggest that I+V could have a PFS, TTNT and OS advantage over V+G in the previously untreated CLL patients with comorbidities. However, limitations apply.

Discussion

After matching, probabilities of I+V being better than V+G exceeded 97% and 98% for all endpoints. when compared to 39.6m and 52.4m follow-up data from CLL14 respectively.

While there are several limitations to this MAIC, it uses all the available evidence to compare I+V and V+G in absence of a head-to-head study.

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Poster

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Disclosures

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Introduction

- I+V and V+G are both authorized for use in frontline (1L) CLL in the European Union as fixed duration treatments for adult patients with 1L CLL.[1]
- There are currently no head-to-head clinical trials investigating efficacy of I+V and V+G in 1L CLL patients with comorbidities.
- The objective of this study was to evaluate relative efficacy of I+V and V+G for Progression-Free Survival (PFS), Time-to-Next treatment or Death (TTNT) and Overall survival (OS) of 1L CLL patients with comorbidities.

Methods

Data and Method Selection

- The efficacy of I+V and V+G were compared to Chlorambucil in combination with Obinutuzumab (C+O) in patients with comorbidities in GLOW (NCT03462719) and CLL14 (NCT02242942) respectively.
- As both studies had different incl/excl criteria and the populations from both trials differ on baseline characteristics which may impact the relative treatment effect, an anchored MAIC was performed.
- Individual patient-level data (IPD) with a median follow-up of 46 months (m)[2] are used from the GLOW study.
- For CLL14, only aggregate level data were available. Data with a median follow-up of 39.6m[3] and 52.4m[4] were the closest to 46m. Hazard ratios (HRs) for PFS, OS and TTNT did not remain consistent between these datacuts in CLL14. OS and TTNT improved substantiallly while PFS HR slightly worsened in 52.4m datacut. Therefore, both were used in the MAIC.

Matching

- First, patients who would did not meet inclusion/exclusion criteria of CLL14 (concurrent CIRS ≤ 6 and CrCl≥70 mL/min) were excluded from GLOW.
- For the remaining patients, all baseline characteristics which could potentially affect relative treatment effect and that were reported in CLL14, were matched using a form of inverse probability weighting as described by Signorovitch et al.[5]
- Patients in GLOW IPD who had missing information about any of the characteristics used in matching process were excluded from analysis (53 from main and 62 from sensitivity analysis).
  - The following 9 characteristics were used in the matching process (Main Analysis): age, Eastern Cooperative for Oncology Group performance status (ECOG PS), Cumulative Illness Rating Scale score (CIRS), tumor protein 53 mutation (TP53mut) status, immunoglobulin heavy-chain variable gene region (IGHV) status, creatinine clearance (CrCl) level, gender, β2 microglobulin (β2-M) level and median time from initial diagnosis.
  - Binet stage was used in a sensitivity analysis because of the very poor overlap between the distribution of Binet stages of CLL14 and GLOW severely reduced the effective sample size (ESS).

Bayesian Indirect Treatment Comparison

- The adjusted HRs calculated based on the reweighted GLOW data were compared to the reported HRs from CLL14 to estimate the indirect treatment effect of I+V versus V+O using a Bayesian framework[5,6] with C+O as the common comparator across both studies.
- For all endpoints, HR with 95% Credible intervals (CrI) and the probability for I+V to be more effective than V+O are reported.

Results

- Matching the 9 characteristics for main analysis resulted in an effective sample size (ESS) of 89 (**Table1**). Sensitivity analysis population that included Binet stage in matching process reduced ESS to 56.
- Comparative analyses between the two trials suggested that I+V improves PFS, TTNT and OS over V+G, with probabilities over 97% (**Figure 1**), 99% (**Figure 2**) and 98% (**Figure 3**) respectively.
  - Results were consistent across the different datacuts of CLL14.
  - Inclusion of binet stage in matching process further improved the HRs and probabilities in favour of I+V, however due to the reduction in ESS these results must be interpeted with caution.

Table 1: Patient Baseline Characteristics Before and After matching

Characteristic	CLL14 (N=423)	GLOW N=211	GLOW MA N=158 ESS=89	GLOW SA N=149 ESS=56
Age				
Median	71.5	71	71	71
>75 years	35%	34%	35%	35%
ECOG PS				
0	45%	35%	45%	45%
1	43%	53%	43%	43%
2 or 3	12%	12%	12%	12%
CIRS				
Median	8	8	8	8
>6	84%	64%	84%	84%
TP53mut	10%	4%	10%	10%
Unmutated IGHV	61%	65%	61%	61%
CrCl				
Median (ml/min)	66.4	64.8	66.1	66.1
<70ml/min	58%	60%	58%	58%
Male	67%	58%	67%	67%
β2-M >3.5 mg/L	61%	72%	61%	61%
Median time from diagnosis	30.2m	35.5m	28.3m	28.3m
Binet stage				
A	21%	8%	6%	21%
B	36%	50%	48%	36%
C	43%	42%	46%	43%

ESS=effective sample size; MA: main analysis; N=sample size;
SA: sensitivity analysis.
% is based on number of patients with reported characteristic information

Figure 1: PFS (INV) of I+V (46m) vs V+G 39.6m (A) and 52.4m (B)

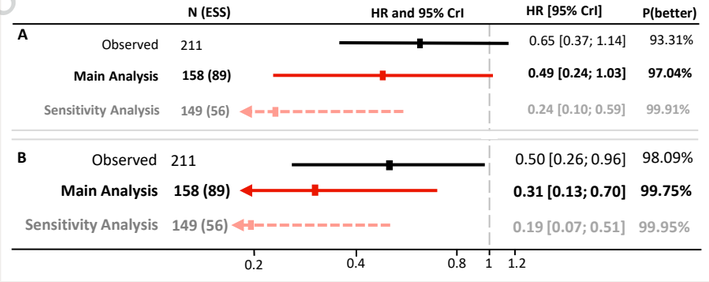


Figure 2: TTNT of I+V (46m) vs V+G 39.6m (A) and 52.4m (B)

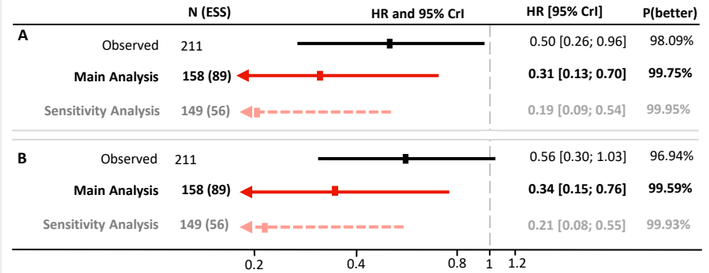
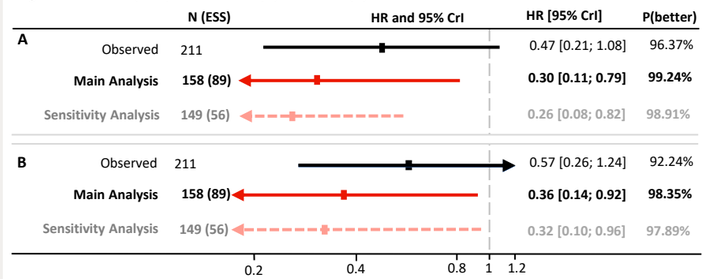


Figure 3: OS of I+V (46m) vs V+G 39.6m (A) and 52.4m (B)



CrI=Credible interval; ESS=effective sample size; HR=hazard ratio; INV: investigator-assessed
N=sample size; P(better)=probability that I+V is better than V+G

Limitations

- There are several limitations - potential sources of bias - that cannot be accounted for in this MAIC. They need to be considered for the interpretation of the results:
  - Patients with deletion of 17p were not allowed in GLOW. This difference between populations can not be adjusted for.
  - Treatment with Chlorambucil was longer in CLL14 than in GLOW, which may have impacted relative treatment effect. The same limitation also applies in several published indirect comparisons.[8-10]
  - Measurement of progression was more strict in GLOW, requiring computer or magnetic imaging regardless of suspected progression. However, the impact on the anchored MAIC is expected to be minimal as it affects both active and comparator arm.
  - There may be additional unreported treatment-effect modifying patient baseline characteristics which cannot be accounted for.

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B-cell Malignancies