PF587

Cross-Study Comparison of Ibrutinib in Combination with Venetoclax (I+V) vs Acalabrutinib in Combination with Venetoclax (A+V) in Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)

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Key takeaway

The I+V regimen yields statistically significantly better efficacy compared to the A+V regimen. Patients treated with I+V are more likely to achieve disease clearance from peripheral blood and bone marrow and experience prolonged progression-free survival (PFS).

Conclusions

Based on MAIC comparison patients treated with I+V were statistically significantly more likely to achieve uMRD at EOT+3 than patients treated with A+V, regardless of site of measurement.

The findings also indicate that patients receiving I+V had a longer PFS compared to patients treated with A+V and the difference was statistically significant.

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Poster

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Introduction

Ibrutinib has a unique target profile which clinical trials have shown to be effective when used in combination with B-cell Lymphoma 2 (BCL2) agent Venetoclax as a fixed duration (FD) treatment for adult patients with previously untreated CLL.[1,2] This combination therapy is widely reimbursed across the European Union. Recently Acalabrutinib, another Bruton's Tyrosine Kinase inhibitor (BTKi) has also been investigated in combination with Venetoclax.

In the absence of prospective head-to-head trials investigating different BTKi+BCL2 FD strategies, this study aimed to indirectly compare I+V regimen with A+V regimen. The objectives were to assess achievement of undetectable minimal residual disease (uMRD) at 3 months after end of treatment (EOT+3) and to evaluate progression-free survival (PFS).

Methods

- Due to the lack of a common comparator arm, an unanchored MAIC was performed to compare I+V with A+V.
- The efficacy of 15 cycle FD I+V regimen authorised in the EU was studied in the GLOW study and in the FD cohort of the CAPTIVATE study.
  - Individual patient-level data (IPD) with a median follow-up (mFUP) of approximately 4.6 years were used from the GLOW[3] and CAPTIVATE FD cohort [4]. Data from both studies were pooled (mFUP 55.7m) for the purpose of this analysis. This allowed to address the important differences between patients in each I+V study and AMPLIFY and have a broader population to better match with the AMPLIFY study population.
- For the A+V 14 cycle FD regimen only aggregate level data were available from AMPLIFY study with a mFUP of 41 months.[5]

Matching

- In the first step, patients who did not meet inclusion/exclusion criteria of AMPLIFY (presence or unknown status of deletion of 17p and/or TP53 mutation, Cumulative Illness Rating Scale score (CIRS)>6, creatinine clearance<50ml/min) were excluded from the pooled I+V data.
- The remaining patients, were reweighted to align the potentially prognostic baseline characteristics with those reported by the comparator, using a method of inverse probability weighting as described by Signorovitch et al.[6]
- Patients in I+V IPD who had missing information for any of the characteristics used in matching process were excluded from the analysis (N=10).
- The following 8 characteristics were included in the matching process (Main Analysis): age, immunoglobulin heavy-chain variable gene region (IGHV) status, creatinine clearance level, deletion l11q, gender, Rai stage, bulky disease status and median time from initial diagnosis.
  - Sensitivity analyses (SA) were performed, either excluding patients with small lymphocytic lymphoma (SLL) or additionally matching on Eastern Cooperative for Oncology Group performance status (ECOG PS), which led to a small effective sample size (ESS) due to poor overlap.
  - Imputation was explored in separate analysis for variables with missing values as a separate analysis to assess their impact on th results.

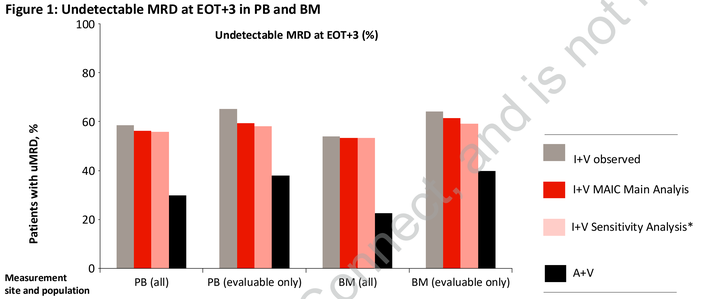
Indirect Treatment Comparison

- In the next step, the relative treatment effect between I+V and A+V is estimated by using the outcomes from the reweighted I+V population compared to the reported A+V outcomes from AMPLIFY.[6]
- uMRD was defined as $1/10^{-4}$ cells as measured in peripheral blood or bone marrow using multicolor flow cytometry.

Results

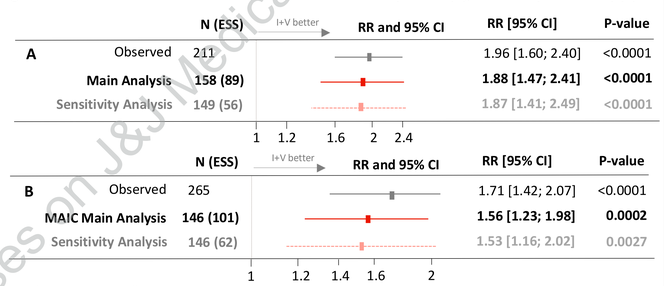
- Matching the 8 characteristics for Main Analysis resulted in a cohort with the same characteristics as A+V arm in AMPLIFY and an effective sample size (ESS) of 101 patients (Table 1).
- Comparative analyses between the two trials suggested that I+V leads to statistically significantly higher probability of patients reaching uMRD at EOT+3 over A+V, regardless of measurement site or whether only evaluable or all patients were considered.
  - Analysis of all patients showed patients receiving I+V were 1.9 times and 2.4 times more likely to achieve uMRD at EOT+3 in PB and BM respectively (Figure 2).
  - Analysis of only those patients with a sample available showed the patients receiving I+V were 1.6 times and 1.5 times more likely to achieve uMRD at EOT+3 in PB and BM respectively (Figure 3).
- Comparative analyses between the two trials suggested that I+V reduces the risk of progression or death by 47% (HR 0.53; 95% CI: 0.33-0.85) which shows a statistically significant advantage over A+V (Figure 4, Figure 5).
- Sensitivity analysis that included ECOG PS in matching process reduced ESS to 62 (Table 1), without leading to substantially different outcomes for uMRD at EOT+3 (Figures 1 and 2) but slightly improved outcomes for PFS (Figure 5).

Figure 1: Undetectable MRD at EOT+3 in PB and BM



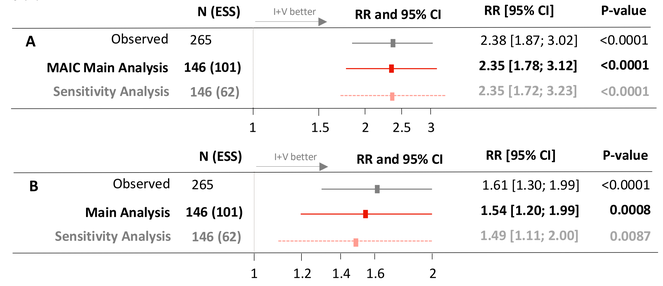
A+V=acalabrutinib+venetoclax; BM=bone marrow; EOT+3=end of trial + 3 months; I+V=ibrutinib+venetoclax; PB=peripheral blood.
*sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching

Figure 2: Relative Risk of uMRD at EOT+3 I+V vs A+V in PB for all patients (A), evaluable patients only (B)



CI: confidence interval; ESS: effective sample size; MA: main analysis; MAIC: matching adjusted indirect comparison; N: sample size; PB: peripheral blood; RR: relative risk; SA: sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching; uMRD at EOT+3: undetectable minimal residual disease at end of treatment +3 months

Figure 3: Relative Risk of uMRD at EOT+3 I+V vs A+V in BM at EOT+3 for all patients (A), evaluable patients only (B)



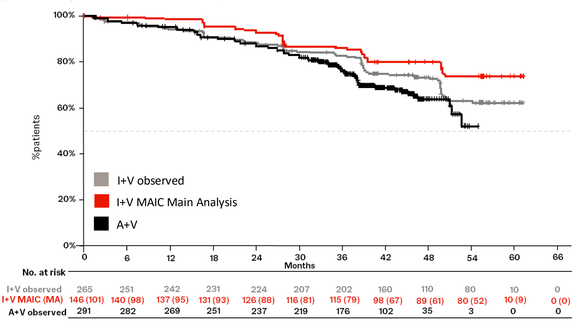
BM: bone marrow; CI: confidence interval; ESS: effective sample size; MA: main analysis; MAIC: matching adjusted indirect comparison; N: sample size; RR: relative risk; SA: sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching; uMRD at EOT+3: undetectable minimal residual disease at end of treatment +3 months

Table 1: Patient Baseline Characteristics Before and After Matching

Characteristic	A+V (N=291)	Pooled I+V			
		Observed N=265	After exclusion* N=156	MA N=146 ESS=101	SA N=146 ESS=62
Age					
Median	61	65	61	61	61
≤65 years	73%	55%	65%	73%	73%
Unmutated IGHV	57%	61%	56%	57%	57%
CrCl <60ml/min	58%	17%	7%	13%	13%
del11q	18%	19%	22%	18%	18%
Male	61%	62%	60%	61%	61%
Rai stage					
0-I	17%	28%	36%	17%	17%
II	36%	33%	32%	36%	36%
III	24%	21%	17%	24%	24%
IV	23%	19%	15%	23%	23%
Buky disease (≥5cm)	39%	34%	35%	39%	39%
Median time from diagnosis	28.5m	35.5m	37.8m	26.8m	26.8m
ECOG PS					
0-1	90%	95%	99%	99%	90%
2	10%	5%	1%	1%	10%

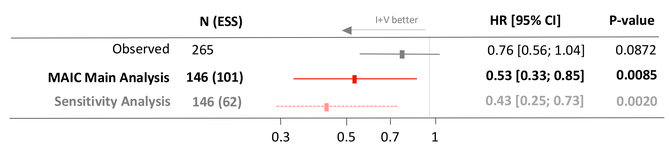
ESS=effective sample size; MA: main analysis; N=sample size; SA: sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching. % is based on number of patients with reported characteristic information
*after exclusion of patients who did not meet AMPLIFY inclusion criteria

Figure 4: Progression-Free Survival Kaplan-Meier Curve of I+V vs A+V



A+V=acalabrutinib+venetoclax; MA: main analysis; MAIC: matching adjusted indirect comparison; I+V=ibrutinib+venetoclax.

Figure 5: Hazard Ratios for Progression-Free Survival of I+V vs A+V



CI: confidence interval; ESS: effective sample size; HR: hazard ratio; MA: main analysis; MAIC: matching adjusted indirect comparison; N: sample size; SA: sensitivity analysis including Eastern Cooperative for Oncology Group performance status in matching.

Limitations

- There are some limitations - potential sources of bias - that cannot be accounted for in this MAIC. They need to be considered for the interpretation of the results:
  - Measurement of progression was stricter in GLOW and CAPTIVATE, requiring computer or magnetic imaging at specific timepoints regardless of suspected progression. Data follow-up is also longer for I+V. Both may have biased PFS results in favour of A+V.
  - AMPLIFY reported multicolor flow cytometry use but with no details on the number of colors and comparability is assumed with the 8-color assay used in I+V studies
  - As in any non-randomized comparison there may be additional unreported clinically important prognostic patient baseline characteristics which cannot be accounted for. For example, CIRS data was not collected in CAPTIVATE and therefor could not be used in matching.

References
1. Kater et al. NEJM Evidence 2022; doi: 10.1056/EVIDoa2200006; 2.Tam et al., Blood 2022 Jun 2;139(22):3278-3289. doi: 10.1182/blood.2021014488. 3. Moreno et al. ASH 2023; 4. Ghia et al. ASH 2023; 5. Brown JR, et al. New England Journal of Medicine 2025. DOI: 10.1056/NEJMoa2409804; 6. Signorovitch JE, et al. Value Health. 2012;15(6):940-7.

B-cell Malignancies

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