Poster #:1417

XXI iwCLL International Workshop on CLL

Acalabrutinib Monotherapy versus Acalabrutinib plus Obinutuzumab Combination Therapy in Treatment-Naïve and Relapsed/Refractory Chronic Lymphocytic Leukemia: A 'Real-World' Study of Efficacy and Safety

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OBJECTIVES

- Compare the efficacy and safety of acalabruntinb monotherapy (AM) versus acalabruntinb + obinutuzumab combination therapy (AO) in treatment-naïve (TN) and relapsed/refractory (RR) CLL/SLL patients in real-world settings.
  - Assess differences in overall survival (OS), progression-free survival (PFS), best overall response at any time, and negative minimal residual disease (MRD(-))
  - Evaluate frequency of adverse events (AE)

CONCLUSIONS

- In comparison to AM, AO was associated with greater rates of AE across both TN and R/R cohorts.
- Despite increased toxicity, AO demonstrated improved efficacy with respect to OS, PFS, and rates of complete response and MRD(-) in both TN and R/R settings.
- The benefits of AO may outweigh risks in select patients, although larger sample sizes are needed to better understand the optimal patient selection in which combination therapy would be preferred.

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INTRODUCTION

- At present, there is no single consensus treatment regimen for CLL in either the treatment-naïve (TN) or relapsed/refractory (R/R) settings.
- For TN patients, common options currently include:
  - Bruton tyrosine kinase inhibitors (BTKi) (i.e., acalabrutinib, ibrutinib, zanubrutinib), used as monotherapy or in combination with anti-CD20 monoclonal antibodies (rituximab, obinutuzumab)
  - BCL-2 inhibitors (venetoclax) in combination with anti-CD20 antibody
- The phase III ELEVATE-TN study demonstrated significant improvement in progression-free survival (PFS) for TN CLL/SLL patients who received acalabrutinib +/- obinutuzumab versus chemoimmunotherapy (obinutuzumab-chlorambucil).[1]
- However, the study was not powered to assess the differences between acalabrutinib monotherapy and acalabrutinib-obinutuzumab combination therapy.
- Combination therapy is anecdotally thought to provide deeper responses at the expense of increased toxicity, though both randomized trial and retrospective "real-life" data remain limited.

METHODS

- This is a retrospective study using real-world data to evaluate the differences in efficacy and safety between BTKi monotherapy (acalabrutinib (AM)) and BTKi and anti-CD20 antibody combination therapy (acalabrutinib + obinutuzumab (AO)) in both TN and R/R settings.
- We conducted an IRB-approved, retrospective review of adult CLL/SLL patients managed at our tertiary academic medical center between 2018 and 2024, and who received treatment with acalabrutinib +/- obinutuzumab.
- 114 patients were assessed in four groups: AM-TN, AO-TN, AM-RR, and AO-RR.
- Statistical analysis was limited due to small sample sizes.

Table 1. Baseline Demographics and Disease Characteristics

	AM TN (n=15)	AO TN (n=47)	AM R/R (n=30)	AO R/R (n=22)
Age (years)				
Median (IQR)	60 (56 - 73)	65 (55 - 73)	64 (55 - 71)	57 (52 - 66)
Sex				
Female	4 (26.7%)	22 (46.8%)	9 (30.0%)	7 (31.8%)
Male	11 (73.3%)	25 (53.2%)	21 (70.0%)	15 (68.2%)
ECOG Performance Status (PS)				
≤1	15 (100%)	46 (97.9%)	23 (76.7%)	19 (86.4%)
≥2	0 (0.0%)	1 (2.1%)	7 (23.3%)	3 (13.6%)
High-Risk Genetic Features				
Chromosome 17p13.1 deletion	4 (26.7%)	13 (27.7%)	6 (20.0%)	7 (31.8%)
Chromosome 11q22.3 deletion	0 (0.0%)	13 (27.7%)	11 (36.7%)	6 (27.3%)
Unmutated IGHV	9 (60.0%)	30 (63.8%)	19 (63.3%)	12 (54.5%)
Mutated TP53	5 (33.3%)	11 (23.4%)	6 (20.0%)	7 (31.8%)
Complex/abnormal karyotype	8 (53.3%)	40 (85.1%)	19 (63.3%)	18 (81.8%)
Including chr. 17p13.1 deletion	2 (13.3%)	11 (23.4%)	6 (20.0%)	6 (27.3%)
Without chr. 17p13.1 deletion	6 (40.0%)	29 (61.7%)	13 (43.3%)	12 (54.5%)
Indication for Treatment[2]				
Progressive marrow failure	9 (60.0%)	27 (57.4%)	15 (50.0%)	8 (36.4%)
Massive, progressive, or symptomatic splenomegaly	6 (40.0%)	4 (8.5%)	3 (10.0%)	2 (9.1%)
Massive, progressive, or symptomatic lymphadenopathy	7 (46.7%)	23 (48.9%)	11 (36.7%)	6 (27.3%)
Progressive lymphocytosis	1 (6.7%)	3 (6.4%)	6 (20.0%)	2 (9.1%)
Autoimmune complications	0 (0.0%)	1 (2.1%)	2 (6.7%)	2 (9.1%)
Symptomatic or functional extranodal involvement	5 (33.3%)	3 (6.4%)	5 (16.7%)	2 (9.1%)
Disease-related symptoms	1 (6.7%)	10 (21.3%)	3 (10.0%)	8 (36.4%)
Other (not previously specified)	2 (13.3%)	2 (4.3%)	6 (20.0%)	4 (18.2%)

[2] Patients may meet multiple indications for treatment. Progressive marrow failure defined as development/worsening of anemia and/or thrombocytopenia; massive splenomegaly defined as ≥6 cm below left costal margin; massive lymphadenopathy defined as ≥10 cm in longest diameter; autoimmune complications defined as anemia or thrombocytopenia poorly responsive to corticosteroids; disease-related symptoms defined as new onset unintentional weight loss ≥10% within the last 6 months, ECOG ≥2, fevers, ≥100.5 for >2 weeks without evidence of infection, and/or night sweats for ≥1 month without evidence of infection

RESULTS

Figure 1. Best Overall Response

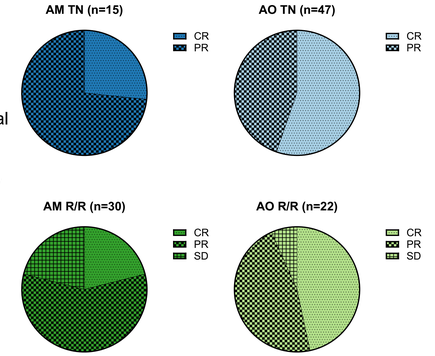


Figure 2. Rates of Minimal Residual Disease Among Assessed

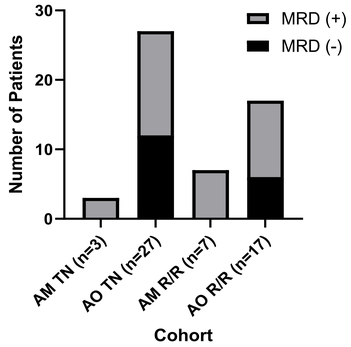
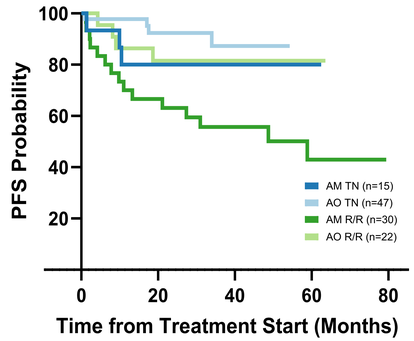
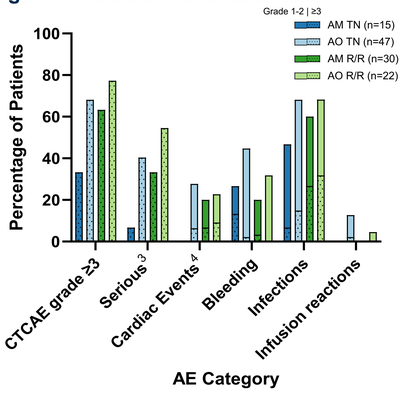


Figure 3. Progression-Free Survival



- At median follow-up of 28.5 months, patients who received combination AO in the front-line setting had improved outcomes, including:
  - OS (97.9% vs 73.3%)
  - PFS (89.4% vs 72.7%)
  - Clinical complete response +/- complete marrow recovery (CR/CRi) (73.9% vs 13.3%)
  - MRD(-) (26.0% vs 0%)
- At median follow-up of 38.4 months, patients who received combination AO in the relapsed setting also had improved outcomes, including:
  - OS (81.8% vs 60.0%)
  - PFS (80.0% vs 46.7%)
  - CR/CRi (59.0% vs 30.0%)
  - MRD(-) (27.0% vs 0%)

Figure 4. Rates of Adverse Events



- AE were greater for AO-TN vs AM-TN, including the proportion of patients experiencing:
  - CTCAE grade ≥3 events (68.1% vs. 33.3%)
  - Cardiac events (27.7% vs 0%)
  - Bleeding (44.7% vs 26.7%)
  - Infections (68.1% vs 46.7%)
- Rates of AE were comparable, albeit slightly greater, for AO-RR vs AM-RR, including the proportion of patients experiencing:
  - CTCAE grade ≥3 events (77.3% vs. 63.3%)
  - Cardiac events (22.7% vs 20.0%)
  - Bleeding (31.8% vs 20.0%)
  - Infections (68.2% vs 60.0%)

[3] An adverse event is classified as "serious" if it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity

[4] Cardiac events observed in >1 patient included (in decreasing frequency): palpitations, atrial fibrillation, sinus bradycardia, sinus tachycardia, chest pain – cardiac, and myocardial infarction

REFERENCES

[1] Sharma Blood 2020.

DISCLOSURES

None.