Abstract #2229

Earlier Use of Zanubrutinib Monotherapy in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma is Associated with Greater Efficacy: A Pooled Analysis from 3 Studies

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INTRODUCTION

- Zanubrutinib is a highly specific, potent BTK inhibitor with minimal off-target inhibition of other kinases such as EGFR, JAK3, TEC and ITK. Zanubrutinib has shown 100% BTK occupancy, sustained over 24-hours, in both the peripheral blood and lymph node biopsies from patients treated at 160 mg twice daily and has achieved durable responses in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). [1]
- In a phase 2 study conducted in patients with relapsed/refractory (R/R) CLL/SLL, treatment with zanubrutinib results in an overall response rate (ORR) of 85%. In addition, duration of response (DOR), progression free survival (PFS) and overall survival (OS) of zanubrutinib monotherapy at 12 months are 93%, 87% and 96%. [2]
- We present the pooled analysis to evaluate the impact of number of prior lines of treatment on outcomes of zanubrutinib treatment for CLL/SLL patients.

METHODS

- Our analysis was based on a pooled data including CLL/SLL patients treated with zanubrutinib monotherapy in two phase 1 studies (ClinicalTrials.gov NCT02343120, and ClinicalTrials.gov NCT03189524) and one phase 2 study (ClinicalTrials.gov NCT03206918), with median study follow-up time of 29.2, 21.1 and 15.1 months, respectively.
- Firstly, efficacy and safety outcomes were compared between the treatment naïve (TN) and the relapsed/refractory (R/R) groups. Secondly, patients with 1 prior line of treatment (LOT=1) were compared to patients with ≥ 2 prior lines of treatment (LOT ≥ 2).
- To control confounding in each analysis, entropy balancing was used to create a weighted sample where the baseline covariates were balanced between groups. [3]
- Baseline covariates used for balancing included age, sex, ECOG, cancer type, BMI, disease stage, bulky disease, lactic acid dehydrogenase, cytogenetic abnormalities, IGHV and TP53 mutation, hemoglobin, platelet count, white blood cell count, neutrophil count and lymphocyte count.
- In each weighted sample, the efficacy outcomes of zanubrutinib included complete response (CR) rate, ORR (defined as the achievement of CR, or CR with incomplete marrow recovery [CRi], partial response [PR], nodular PR, PR with lymphocytosis), PFS and OS. The difference between groups in CR rate and ORR was investigated by logistic regression, and those in PFS and OS by Cox proportional hazards models and log-rank test. The 24-month PFS and OS rates were calculated by the Kaplan-Meier method. Exposure-adjusted safety profiles were summarized.
- P values less than 0.05 were considered as statistically significant.

RESULTS

- The analysis data consisted of 19 TN patients, 93 patients in LOT=1, and 99 patients in LOT ≥ 2 (**Table 1** and **Table 2**). Seven patients were excluded due to missing baseline covariates.

Table 1. Sample Sizes in the Pooled Analysis by TN vs. R/R

	Original Sample			Weighted Sample		
	TN	R/R	Total	TN	R/R	Total
Sample size	19	192	211	19	25	43
Median follow-up	31.5	17.1	17.9	31.3	21.0	29.5

Abbreviations: R/R, relapsed/refractory; TN, treatment-naïve.
Note: Effective sample sizes were calculated by Kish's formula in the weighted sample. With Kish's formula, the total was not necessarily equal to the sum of subgroup sizes.

Table 2. Sample Sizes in the Pooled Analysis by LOT=1 vs. LOT ≥ 2

	Original Sample			Weighted Sample		
	LOT=1	LOT ≥ 2	Total	LOT=1	LOT ≥ 2	Total
Sample size	93	99	192	78	84	162
Median follow-up	17.1	16.8	17.1	17.3	15.8	16.9

Abbreviations: LOT=1, 1 prior line of treatment; LOT≥2, ≥2 prior lines of treatment.
Note: Effective sample sizes were calculated by Kish's formula in the weighted sample. With Kish's formula, the total was not necessarily equal to the sum of subgroup sizes.

- In the weighted sample for TN vs. R/R analysis, the effective sample sizes were 19 and 25 in the TN and the R/R group, respectively.
- The median follow-up time was 31.3 vs. 21.0 months in the TN and the R/R group, respectively.
- All baseline covariates were balanced between groups (**Table 3**).
- The prevalence of prior medication use in the R/R group was kept from the one pre weighting (94% prior use of alkylator, 67% prior use of nucleoside analog, 77% prior use of anti-CD20 containing therapy and 5% prior use of target drugs).
- 55.5%, 17.5% and 27.0% of the patients in the R/R group had 1, 2 and >2 prior lines of treatment.

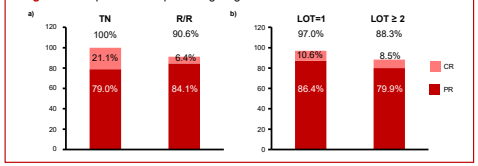
Table 3. Summary of Baseline Covariates by TN and R/R pre and post Weighting

Baseline Covariates	Original Sample			Weighted Sample		
	TN	R/R	Mean Diff., (Var. Ratio)	TN	R/R	Mean Diff., (Var. Ratio)
Age, mean (SD)	68.4 (8.2)	62.5 (10.7)	0.553 (0.60)	68.4 (8.5)	68.2 (8.5)	0.017 (0.998)
Sex, female	16%	33%	-0.175	16%	16%	-0.004
ECOG, ≥ 1	53%	54%	-0.015	53%	53%	0.000
Stage, III, IV or V	37%	56%	-0.189	37%	37%	-0.002
Del (17p), yes	11%	15%	-0.041	11%	11%	-0.004
TP53 mutation, positive	26%	50%	-0.232	26%	27%	-0.003
IGHV, unmutated	11%	41%	-0.301	11%	12%	-0.011

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IGHV, Immunoglobulin Heavy-chain Variable; R/R, relapsed/refractory; SD, standard deviation; TN, treatment-naïve.
Note: Balance criteria was defined as the absolute value of the standardized mean difference was no more than 0.1 for a continuous covariate and the absolute value of the percentage difference was no more than 0.1 for a categorical or binary covariate.

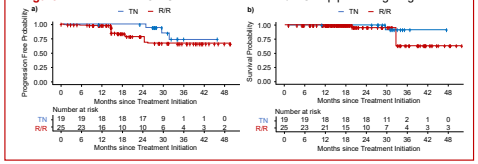
- Compared with the R/R group, the ORR was significantly higher in the TN group (100% vs. 90.6%, p<0.001, **Figure 1a**). The CR rate was numerically higher in the TN group (21.1% vs. 6.4%, p=0.09, **Figure 1a**).

Figure 1: Response Rates post Weighting



- PFS of the TN group was numerically superior to the R/R group (HR 0.32 [95% CI: 0.09, 1.11]; log-rank p = 0.14; **Figure 2a**). The 24-month PFS rate was 100% in the TN group and 78.1% in the R/R group.
- The OS was comparable between two groups (**Figure 2b**).
- In general, the exposure-adjusted safety profile was better in the TN group, especially in adverse events of special interest, such as diarrhea, hypertension and atrial fibrillation/flutter (**Table 6**).

Figure 2: The PFS and OS Curves in the TN and R/R Group post Weighting



- In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 78 and 84 in the LOT=1 and the LOT ≥ 2 group, respectively.
- The median follow-up times were 17.3 and 15.8 months in the LOT=1 and the LOT ≥ 2 group.
- All baseline covariates were balanced between groups and the prevalence of prior medication use in each group was preserved (**Table 4 and Table 5**).
- 56.5%, 20.6% and 22.9% of the patients in the LOT ≥ 2 group were treated with 2, 3 and >3 prior lines of treatment.

Table 4. Summary of Baseline Covariates by LOT=1 and LOT ≥ 2 pre and post Weighting

Baseline Covariates	Original Sample			Weighted Sample		
	LOT=1	LOT ≥ 2	Mean Diff., (Var. Ratio)	LOT=1	LOT ≥ 2	Mean Diff., (Var. Ratio)
Age, mean (SD)	62.8 (11.1)	62.1 (10.3)	0.068 (1.14)	62.5 (11.6)	62.5 (10.2)	0.000 (1.31)
Sex, female	31%	35%	-0.042	33%	33%	-0.001
ECOG, ≥ 1	55%	54%	0.013	54%	54%	0.000
Stage, III, IV or V	58%	54%	0.045	56%	56%	0.001
Del (17p), yes	16%	13%	0.030	15%	15%	0.000
TP53 mutation, positive	16%	14%	0.020	15%	15%	0.000
IGHV, unmutated	18%	14%	0.041	16%	16%	0.001

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IGHV, Immunoglobulin Heavy-chain Variable; LOT=1, 1 prior line of treatment; LOT≥2, ≥2 prior lines of treatment; SD, standard deviation
Note: Balance criteria was defined as the absolute value of the standardized mean difference was no more than 0.1 for a continuous covariate and the absolute value of the percentage difference was no more than 0.1 for a categorical or binary covariate.

Table 5. Summary of Prior Anti-cancer Therapy by LOT=1 and LOT ≥ 2 pre and post Weighting

Prior Medication Use	Original Sample		Weighted Sample	
	LOT=1	LOT ≥ 2	LOT=1	LOT ≥ 2
Prior Alkylator Use	90%	98%	88%	98%
Prior Nucleoside Analog Use	48%	85%	51%	83%
Prior Anti-CD20 Containing Therapy Use	69%	85%	74%	79%
Prior Target Drug Use	1%	9%	1%	7%
Prior Lenalidomide/ Thalidomide Use	2%	14%	2%	14%

Abbreviations: LOT=1, 1 prior line of treatment; LOT≥2, ≥2 prior lines of treatment.

- The ORR was numerically higher in the LOT=1 group, compared with the LOT ≥ 2 group (97.0% vs. 88.3%; p=0.05, **Figure 1b**). The CR rate was comparable in two groups (10.6% vs. 8.5%; p=0.63, **Figure 1b**).
- The PFS of the LOT=1 group was significantly longer than that in the LOT ≥ 2 group (HR 0.13 [95% CI: 0.04, 0.4]; log-rank p<0.001; **Figure 3a**), and 24-month PFS rates were 95% and 75.3%, respectively.
- The OS was comparable between two groups (**Figure 3b**).
- In general, exposure-adjusted safety profiles were similar for both groups. However, lower rates of adverse events of special interest were found in the LOT=1 group (**Table 6**).

Figure 3: The PFS and OS Curves in the LOT=1 and the LOT ≥ 2 Group post Weighting

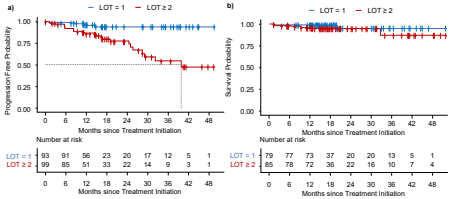


Table 6. Summary of Exposure-adjusted Adverse Events post Weighting

AE Rates Per Patient-years of Exposure	TN vs R/R		LOT=1 vs LOT ≥ 2	
	TN	R/R	LOT=1	LOT ≥ 2
At Least One AE	16.0	24.2	19.4	18.6
At Least One ≥ Grade 3 AE	0.3	0.4	0.9	0.8
At Least One AE leading to Death	0.0	0.0	0.0	0.0
At Least One SAE	0.2	0.3	0.3	0.4
AE of Special Interest				
Diarrhea	0.1	0.5	0.2	0.2
Hypertension	0.0	0.1	0.1	0.1
Major Hemorrhage	0.0	0.0	0.0	0.0
Atrial Fibrillation/Flutter	0.0	0.0	0.0	0.0

Abbreviations: AE, adverse events; LOT=1, 1 prior line of treatment; LOT≥2, ≥2 prior lines of treatment; R/R, relapsed/refractory; TN, treatment-naïve.
Note: Exposure-adjusted adverse events was defined as the number of patients with a specific adverse event divided by the total duration of exposure. [4]

CONCLUSIONS

- Zanubrutinib administered in the early lines, including treatment of naïve patients and patients with 1 prior line of treatment, led to higher overall response rates and greater durability of therapeutic benefit.
- Exposure-adjusted safety profiles in early lines were better, especially for adverse events of special interest.

REFERENCES

1. Tam CS, et al. Blood. 2019; 134 (11): 851-859.
2. Xu W, et al. J Hematol Oncol. 2020; 13 (1): 48.
3. Hainmueller, J. Political Analysis. 2012; 20 (1): 25-46.
4. Liu FG, et al. Statist Med. 2006; 25: 1275-1286.

DISCLOSURES

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