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 achieves 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 resulted 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 were 93%,

87% and 96% [2]. Here, we present the pooled analysis to evaluate the impact of number of prior lines of therapy 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 relapsed/refractory (R/R) groups. Secondly, patients with 1 prior therapy were compared to patients with ≥ 2 prior therapies within the R/R setting.

To control confounding in each analysis, entropy balancing was used to create a weighted sample where the baseline covariates were balanced between groups [3]. In each weighted sample, the efficacy outcomes of zanubrutinib included complete response rate (CRR), ORR (defined as the achievement of complete response [CR], or CRi, partial response [PR], nodular PR, PR with lymphocytosis), PFS and OS. The difference between groups in CRR 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. The extent of exposure and safety profile of each group were summarized.

Results

The analysis data consisted of 19 TN patients, 93 patients with 1 prior therapy, and 99 patients with ≥ 2 prior therapies. Seven patients were excluded due to missing baseline covariates. In the weighted samples, all baseline covariates were balanced between groups.

After weighting, the effective sample sizes were 19 and 31 for the TN and the R/R groups respectively. The median follow-up times were 31.3 and 20.9 months for the TN and R/R group, respectively; 54.4%, 18.8% and 26.8% of the patients in the R/R group had 1, 2 and >2 prior lines of therapy. The ORR and CRR were higher in TN group, compared with R/R groups (100% vs. 92.1% in ORR [$p<0.001$] and 21.05% vs. 6.7% in CRR [$p=0.09$]). PFS of the TN group was superior to the R/R group ($p = 0.13$; HR 0.33 [95% CI: 0.10, 1.09]; Figure 1a). The 24-month

PFS rate was 100% in the TN group and 79.1% in the R/R group. The OS was comparable between two groups. And safety profile was similar for both groups.

After weighting, the effective sample sizes were 77 and 85 for the 1 prior therapy and the ≥ 2 prior therapies groups respectively. The median follow-up times were 17.1 and 15.8 months for the 1 prior therapy and the ≥ 2 prior therapies groups; 56.5%, 20.6% and 22.9% of the patients in the ≥ 2 prior therapies group were treated with 2, 3 and >3 prior lines of therapy. The ORR was numerically higher in the 1 prior therapy group, compared with ≥ 2 prior therapies group (97.0% vs. 88.3%; p=0.05). The CRR was comparable in two groups (9.8% vs. 8.4%; p=0.75). The PFS of 1 prior therapy group was significantly longer than that in ≥ 2 prior therapies group (p<0.001; HR 0.15 [95% CI: 0.05, 0.45]; Figure 1b), and 24-month PFS rates were 94.6% and 75.3%, respectively. The OS was comparable between two groups. And safety profile was similar for both groups.

Conclusion

Zanubrutinib administered in the early lines, including treatment of naïve patients and patients with 1 prior therapy, led to higher overall response rates and greater durability of therapeutic benefit. Safety profile was similar across all lines of therapy.

References

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Figure 1: The PFS curves by groups after weighting.