Zanubrutinib is a highly specific, potent BTK inhibitor with minimal off-target inhibition.

In the weighted sample for TN vs. R/R analysis, the effective sample sizes were 19 and 56.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 73 and 20.

In the weighted sample for all TN vs. R/R analysis, the effective sample sizes were 99 and 33.

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), PR with (PRw), partial response with (PRw), and the difference between groups in CR rate and ORR was investigated by logistic regression, and those in PFS and OS were calculated by the Kaplan-Meier method. Exposure-adjusted safety profiles were summarized. If P values less than 0.05 were considered as statistically significant.

The analysis data consists of 19 TN patients, 93 patients in LOT=1, and 97 patients in LOT ≥ 2 (Table 1 and Table 2); Seven patients were excluded due to missing baseline covariates.

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).

PFS of the TN group was numerically superior to the R/R group (HR 0.32 [95% CI 0.09, 1.11], logrank p = 0.14, Figure 2a). The 24-month PFS rate was 100% in the TN group and 76.1% in the R/R group.

The ORR was numerically higher in the TN group, compared with the LOT ≥ 2 group (97.0% vs. 88.3%, p=0.03, Figure 1b). The CR rate was comparable in two groups (10.6% vs. 8.5%, p=0.3, Figure 1b). The OS of the TN and R/R group were 95% and 75.3%, respectively.

The CR was numerically higher in the TN group, compared with the LOT ≥ 2 group (97.0% vs. 86.8%, logrank p=0.01, Figure 1b)

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 TN group (Table 4).

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 76 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). The 24-month PFS rates were 97.0% and 88.3%, respectively.

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 ± 21.0 months in the TN and the R/R group, respectively.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 73 and 20 in the TN and the R/R group, respectively.

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).

55.6%, 17.5% and 27.0% of the patients in the R/R group had 1, 2 and >2 prior lines of treatment.

Information on adverse events of special interest, such as diarrhea, hypertension and atrial fibrillation/flutter (Table 6).

Abbreviations: AE, adverse events; LOT=1, 1 prior line of treatment; LOT ≥ 2, ≥ 2 prior lines of treatment; SD, standard deviation

REFERENCES


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.

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

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

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

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

Table 5. Summary of Prior Anti-cancer Therapy post Weighting and

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

DISCLOSURES

WX, YS, KS, LZ, WS, LP, SJ, ZS, YF, AH, IH, and JL did not receive financial consideration to disclose OPI firms from Janseen, AbbVie and BeiGene, research funding from Janssen and AbbVie, consulting honoraria from Roche, AbbVie, Janssen, Merck, Genentech and Mirari, membership on an entity’s board of directors or advisory committees and research funding from Roche, AbbVie, Janssen, Merck, Astroteca, BeiGene, Genentech and CSL; research funding from Elyma-JE; research funding from Roche, Merck, Janssen, and BeiGene, and consultant operation general hospital SJU, 2W, and NL; employment and equity holder in public-listed company from CSL

ACKNOWLEDGMENT

We thank the investigators, site support staff, and especially the patients participating in the study. This study was sponsored by BeiGene.

METHODS

Our analysis was based on a pooled data including CLL/PLL patients treated with zanubrutinib monotherapy in two phase 1 trials (ClinicalTrials.gov: NCT02392730, and ClinicalTrials.gov NCT01135934) and one phase 2 study (ClinicalTrials.gov: NCT00938016), with median study follow-up time of 32.7, 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 factors, each analysis was used to create a weighted sample where the baseline covariates were balanced between groups.

Baseline covariates used in balancing included age, sex, ECOG, cancer type, BMI, disease stage, bulky disease, lactate acid dehydrogenase, cytopenia abnormalities, GHR and TPSS 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), partial response with (PRw), and the difference between groups in CR rate and ORR was investigated by logistic regression, and those in PFS and OS were calculated by the Kaplan-Meier method. Exposure-adjusted safety profiles were summarized. If P values less than 0.05 were considered as statistically significant.

The analysis data consisted of 19 TN patients, 93 patients in LOT=1, and 97 patients in LOT ≥ 2 (Table 1 and Table 2); Seven patients were excluded due to missing baseline covariates.

RESULTS

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.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 73 and 20 in the TN and the R/R group, respectively.

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.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 73 and 20 in the TN and the R/R group, respectively.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 76 and 84 in the LOT=1 and the LOT ≥ 2 group, respectively.

In the weighted sample for LOT=1 vs. LOT ≥ 2 analysis, the effective sample sizes were 76 and 84 in the LOT=1 and the LOT ≥ 2 group, respectively.

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.

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.

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.

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.