Comparative efficacy of zanubrutinib plus obinutuzumab versus last prior treatment in relapsed/refractory follicular lymphoma: Growth modulation index analysis from ROSEWOOD study

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Introduction: Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma. ROSEWOOD (NCT03332017), a global, randomized, open-label, phase 2 study, compared the efficacy and safety of zanubrutinib plus obinutuzumab (ZO) with obinutuzumab (O) alone in patients with relapsed/refractory (R/R) FL who had received ≥2 prior lines of systemic therapy. Median progression-free survival (PFS) was longer with ZO vs O (28.0 months [95% CI, 16.1-not evaluable {NE}] vs 10.4 months [95% CI, 6.5-13.8]; hazard ratio [HR], 0.50 [95% CI, 0.33-0.75]) and compared favorably with PFS with the last prior treatment (tx; 12.1 months) (Zinzani et al. JCO; 2023). The absence of clear consensus on standard of care and sequencing in R/R FL and the heterogeneity of patient populations included in trials limit the possibility of indirect comparisons across different studies. To overcome this challenge, the Growth Modulation Index (GMI) uses each patient as their own control to evaluate the efficacy of txs by comparing PFS durations with successive txs. A GMI >1 indicates that the present tx extends the PFS duration vs the previous tx, and a GMI ≥1.33 is often used as a threshold for significant clinical activity. To analyze the efficacy of ZO in the sequence of tx received by patients included in the ROSEWOOD study, we performed an intrapatient comparison analysis using the GMI clinical endpoint.

Methods: PFS was assessed by independent central review, and censoring rules were defined in the ROSEWOOD study. GMI was defined as (PFS_n from ZO or O)/(PFS_{n-1}

from last prior line). The distribution, including the median and the proportion within each interval, of GMI was estimated using the Kaplan-Meier (KM) method. The 95% CIs for median GMI were estimated using the Brookmeyer and Crowley method, and the 95% CIs for the proportion within each interval were estimated using the Greenwood formula with logit transformation. Analyses in subgroups of high clinical interest in the ZO arm were conducted.

Results: In ROSEWOOD, 145 patients were randomized to the ZO arm and 72 to the O arm. Five patients were excluded from the GMI analysis in the ZO arm and 3 in the O arm, as no PFS_{n-1} data were available. Analysis confirmed previous observations that median PFS with ZO, but not with O, was longer compared with the last prior tx (ZO, 28.0 vs 12.1; O, 10.4 vs 11.5 months), the most frequent of which were rituximab-containing regimens (ZO, 69%; O, 60%) and immunochemotherapy (ZO, 54%; O, 51%). In the overall population, median GMI was 2.7 (95% CI, 1.6-4.9) in the ZO arm and 0.9 (95% CI, 0.5-1.7) in the O arm. In the ZO arm, 63.3% (95% CI, 53.8-71.9) of patients had a GMI ≥1.33, and 34.1% (95% CI, 25.9-43.3) had a GMI <1. Subgroup analyses showed that patients in the ZO arm with only 2 prior lines (n=63) had a median GMI of 2.5 (95% CI, 0.9-NE), with 65.6% (95% CI, 50.8-77.8) of patients having a GMI ≥1.33. Patients with >2 prior lines (n=77) had a median GMI of 3.1 (95% CI, 1.3-4.9), with 61.8% (95% CI, 49.2-73.0) of patients having a GMI ≥1.33. Patients who had received immunochemotherapy as their last tx had a median GMI of 2.5 (95% CI, 0.9-3.8), with 62.9% (95% CI, 49.9-74.3) having a GMI ≥1.33. Those who received rituximab-containing regimens as their last tx had a median GMI of 2.5 (95% CI, 1.6-3.8), with 65.2% (95% CI, 53.5-75.2) having a GMI ≥1.33. The median GMIs in patients who were refractory to their most recent line of therapy and who were refractory to rituximab were 3.1 (95% CI, 1.8-NE) and 2.5 (95% CI, 1.6-3.6), with GMIs ≥1.33 in 77.4% (95% CI, 61.8-87.8) and 64.6% (95% CI, 52.1-75.4) of patients, respectively. In patients with progressive disease ≤24 months after starting first line of therapy (POD24), the median GMI was 2.7 (95% CI, 0.9-NE) and 66.8% (95% CI, 50.5-79.8) had a GMI ≥1.33.

Conclusions: Post hoc GMI analysis of data from ROSEWOOD showed that the majority (>60%) of patients with R/R FL receiving ZO had a significant (GMI ≥1.33)

improvement in PFS vs their last prior tx, irrespective of the number of prior lines (only 2 or >2) and in all tested subgroups of high clinical interest. The median GMI of 2.7 in the overall population was more than double the 1.33 threshold for meaningful clinical activity compared with the last prior tx. These data further support the benefit of ZO as a novel therapeutic option for patients with R/R FL.