Intrapatient Comparative Analysis of Zanubrutinib Plus Obinutuzumab Efficacy in Relapsed/Refractory Follicular Lymphoma Using the Growth Modulation Index

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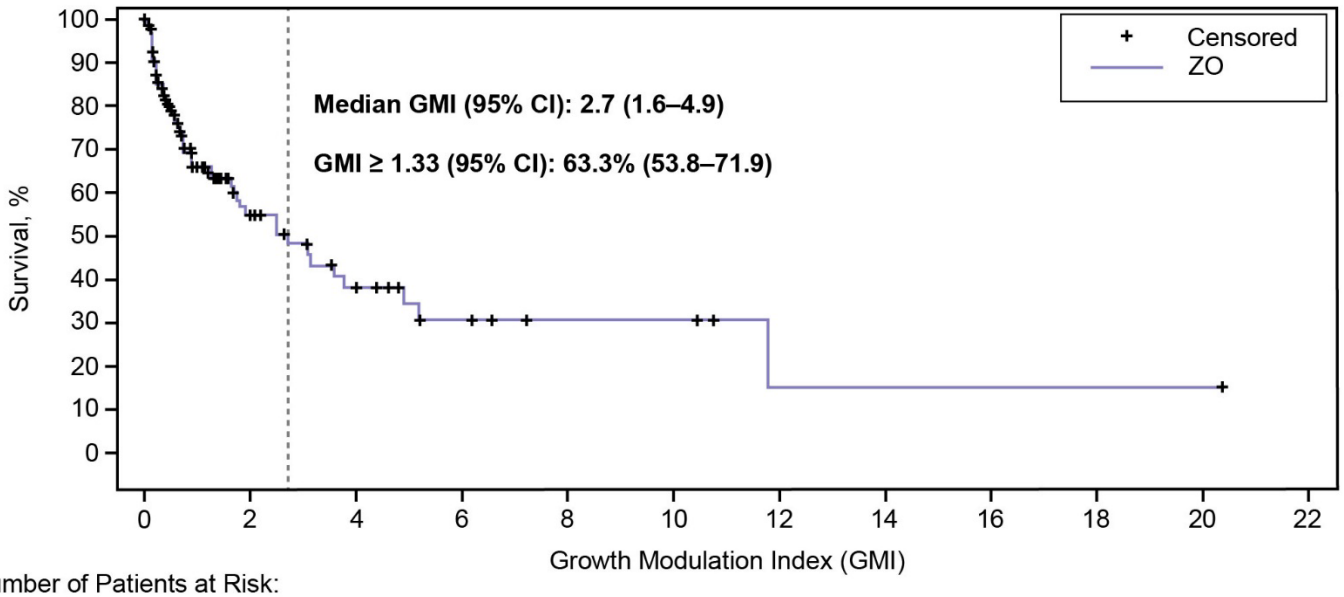
Background: Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma. ROSEWOOD (NCT03332017), a global, randomized, open-label phase 2 study, compared the efficacy and safety of zanubrutinib plus obinutuzumab (ZO) with obinutuzumab (O) alone in patients with relapsed/refractory (R/R) FL 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]; HR, 0.50 [95% CI, 0.33-0.75]; *P*<.001) and compared favorably with PFS with the last prior treatment (12.1 months) (Zinzani et al. *JCO*; 2023). The absence of clear consensus for standard of care 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 treatments by comparing PFS durations with successive treatments. A GMI >1 indicates that the present treatment extends the PFS duration vs the previous treatment, and a GMI ≥1.33 is often used as a threshold for significant clinical activity.

Aims: To analyze the efficacy of ZO in the sequence of treatment 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 (ICR) 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 Greenwood's formula with logit transformation.

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. PFS analysis of the KM curves confirmed previous observations that median PFS with ZO, but not with O, was longer compared with the last prior treatment (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 (**Figure**) 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 analysis showed that patients in the ZO arm with 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 in the ZO arm 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.

Summary/Conclusion: In this study, GMI allowed the generation of comparative efficacy evidence for ZO in R/R FL. 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 treatment, irrespective of the number of prior treatments. 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 treatment. These data further support the benefit of ZO as a novel treatment option for patients with R/R FL.



Number of Patients at Risk:

Zanubrutinib	140	30	15	7	4	4	1	1	1	1	0