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[1]
- The global, randomized, open-label, phase 2 ROSEWOOD study (NCT03332017) compared the efficacy and safety of zanubrutinib + obinutuzumab (ZO) with obinutuzumab (O) alone in patients with relapsed/refractory (R/R) FL who had received ≥2 prior lines of systemic therapy[2]
- Median progression-free survival (PFS) was longer with ZO (28.0 months; 95% CI, 16.1 months-not evaluable [NE]) vs O (10.4 months; 95% CI, 6.5-13.8 months) (hazard ratio, 0.50; 95% CI, 0.33-0.75; *P*<.001) and compared favorably to the PFS of the last prior treatment (12.1 months)[2]
- 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) considers each patient as their own control and evaluates treatment efficacy by comparing PFS durations with successive treatments

METHODS

- In this post hoc analysis, the efficacy of ZO in the sequence of treatments received by patients in the ROSEWOOD study was evaluated using the GMI clinical endpoint
- PFS was assessed by independent central review and defined in the ROSEWOOD study as the time from random assignment to the first documentation of progressive disease or death due to any cause, whichever occurred first[2]
- This post-hoc analysis of results from the ROSEWOOD study was not pre-specified in the protocol; therefore, the results are descriptive in nature
- Methodological limitations include that the results of primary (overall response rate) and PFS endpoints from ROSEWOOD were already known before implementation of this analysis

GMI Model

- GMI was defined for each patient as the ratio of the PFS with the current treatment under evaluation to the PFS with the last prior treatment (PFS_n/PFS_{n-1})[3-5]
  - A GMI of >1 indicated that the present treatment had extended the duration of PFS compared with the previous treatment[3-5]
  - A GMI of ≥1.33 is often used as a threshold for significant clinical activity[3-5]
- Analyses in subgroups of clinical interest were conducted in the ZO arm
  - The subgroups analyzed include patients with 2 prior lines of therapy, >2 prior lines of therapy, immunochemotherapy in the last prior regimen, rituximab in the last prior regimen, disease refractory to the last prior therapy, disease refractory to rituximab, and progression of disease within 24 months of initiating the first line of therapy (POD24)
- The GMI distribution, including the median and proportion in each GMI interval, was estimated using the Kaplan-Meier method
- The 95% CIs for median GMI were estimated using the Brookmeyer-Crowley method
- The 95% CIs for the proportion in each GMI interval were estimated using the Greenwood formula

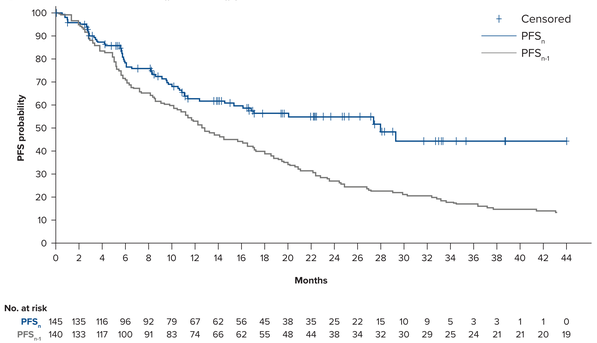
RESULTS

- In ROSEWOOD, 145 patients were randomized to the ZO arm and 72 to the O arm
  - Patients with no PFS_{n-1} data available were excluded from the GMI analysis (ZO, n=5; O, n=3)

PFS Analysis

- Analysis confirmed previous observations: median PFS with ZO, but not with O, was longer compared with the last prior treatment (ZO, 28.0 vs 12.1 months; O, 10.4 vs 11.5 months)
  - In the ZO arm, the PFS_n and PFS_{n-1} curves diverged early, and separation was maintained over time (**Figure 1**)
  - In the O arm, no separation between the PFS_n and PFS_{n-1} was observed (**Figure 2**)
- The most frequent last prior treaments were rituximab-containing regimens (ZO, 69%; O, 60%) and immunochemotherapy (ZO, 54%; O, 51%)

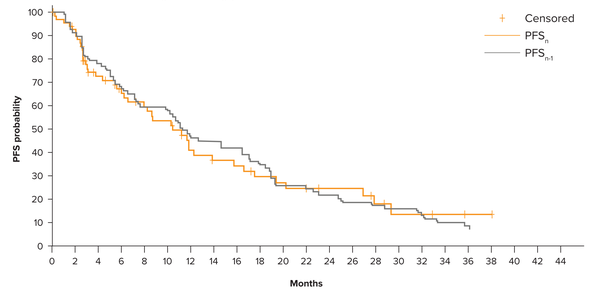
Figure 1. KM Curves of PFS_n and PFS_{n-1} in the ZO Arm



No. at risk																						
PFS_n	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
PFS_{n-1}	140	133	117	100	91	83	74	66	62	55	48	44	38	34	32	30	29	25	24	21	21	20	19

KM, Kaplan-Meier; PFS_n, progression-free survival with the current treatment under evaluation; PFS_{n-1}, progression-free survival with the last prior treatment; ZO, zanubrutinib + obinutuzumab.

Figure 2. KM Curves of PFS_n and PFS_{n-1} in the O Arm



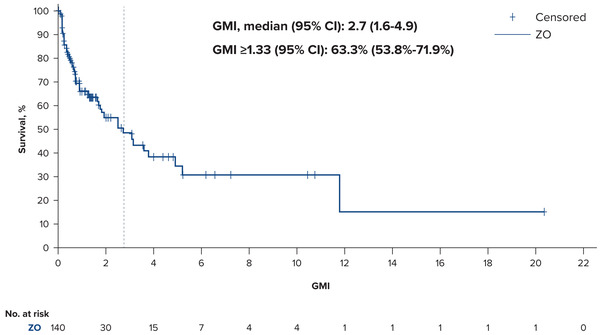
No. at risk																						
PFS_n	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0	
PFS_{n-1}	69	63	54	47	41	40	32	31	29	24	18	17	15	13	12	11	9	7	6	5	5	

KM, Kaplan-Meier; O, obinutuzumab; PFS_n, progression-free survival with the current treatment under evaluation; PFS_{n-1}, progression-free survival with the last prior treatment.

GMI Analysis in the Overall Population

- Median GMI was 2.7 (95% CI, 1.6-4.9) in the ZO arm (**Figure 3**)
- In the ZO arm, 63.3% of patients (95% CI, 53.8%-71.9%) had a GMI of ≥1.33

Figure 3. KM Analysis of GMI in the ZO Arm

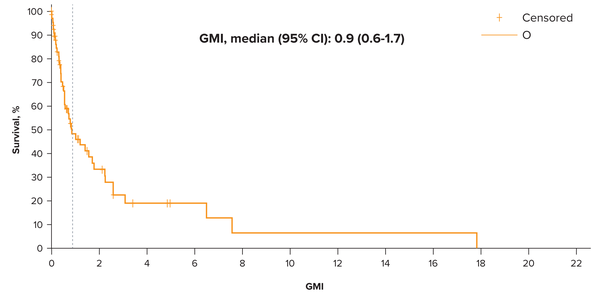


No. at risk												
ZO	140	30	15	7	4	4	1	1	1	1	1	0

GMI, Growth Modulation Index; KM, Kaplan-Meier; ZO, zanubrutinib + obinutuzumab.

- Median GMI was 0.9 (95% CI, 0.5-1.7) in the O arm (**Figure 4**)

Figure 4. KM Analysis of GMI in the O Arm



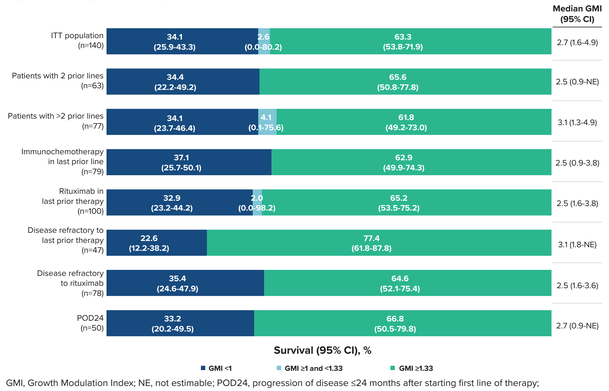
No. at risk												
O	69	13	5	3	1	1	1	1	1	0		

GMI, Growth Modulation Index; KM, Kaplan-Meier; O, obinutuzumab.

GMI Analysis in Subgroups of Clinical Interest in the ZO Arm

- In the ZO arm, the median GMI and distribution of GMI in subgroups of interest are shown in **Figure 5**
- Across all subgroups analyzed, >60% of patients treated with ZO had a GMI of ≥1.33
  - 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% of patients (95% CI, 50.8%-77.8%) having a GMI of ≥1.33 (**Figure 6**)
  - 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% of patients (95% CI, 49.2%-73.0%) having a GMI of ≥1.33 (**Figure 7**)
  - Patients who had received immunochemotherapy as their last treatment (n=79) 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 of ≥1.33
  - Those who received rituximab-containing regimens as their last treatment (n=100) 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 of ≥1.33
  - Median GMIs in patients with disease refractory to their most recent line of therapy (n=47) and disease refractory to rituximab (n=78) were 3.1 (95% CI, 1.8-NE) and 2.5 (95% CI, 1.6-3.6), respectively, with GMIs of ≥1.33 in 77.4% (95% CI, 61.8%-87.8%) and 64.6% (95% CI, 52.1%-75.4%) of patients
  - In patients with POD24 (n=50), the median GMI was 2.7 (95% CI, 0.9-NE), and 66.8% (95% CI, 50.5%-79.8%) had a GMI of ≥1.33

Figure 5. Subgroup Analysis of GMI in the ZO Arm

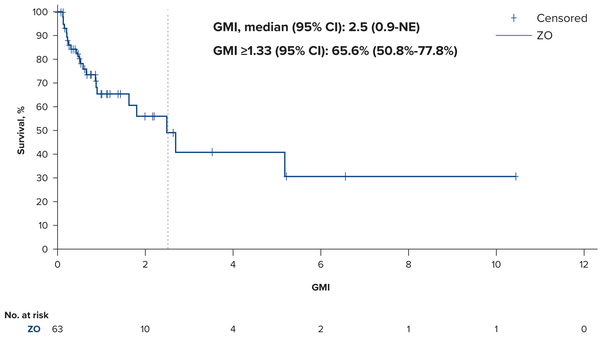


GMI, Growth Modulation Index; NE, not estimable; POD24, progression of disease ≤24 months after starting first line of therapy; ZO, zanubrutinib + obinutuzumab.

CONCLUSIONS

- This post hoc GMI analysis of data from ROSEWOOD allowed for the generation of comparative efficacy evidence for ZO in R/R FL using each patient as their own control
- The majority of patients with R/R FL receiving ZO had a significant improvement in PFS compared with the PFS with their last prior treatment, irrespective of the number of prior treatments
  - GMI was ≥1.33 in >60% of patients in the overall group and across multiple subgroups of clinical interest in the ZO arm
  - The median GMI of 2.7 in the ZO arm was more than double the 1.33 threshold for meaningful clinical activity compared with the last prior treatment
- These data further confirm the benefit of ZO as a novel treatment option for R/R FL

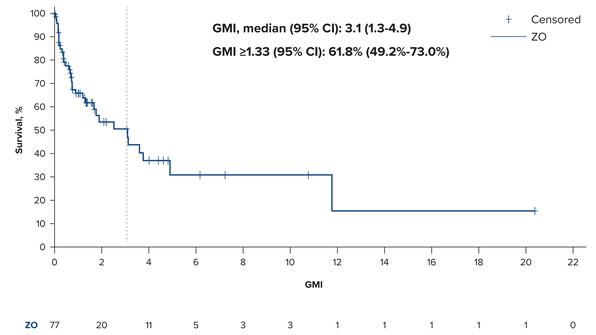
Figure 6. KM Curve of GMI in Patients With 2 Prior Lines of Therapy in the ZO Arm



No. at risk												
ZO	63	10	4	2	1	1	0					

GMI, Growth Modulation Index; KM, Kaplan-Meier; NE, not estimable; ZO, zanubrutinib + obinutuzumab.

Figure 7. KM Curve of GMI in Patients With >2 Prior Lines of Therapy in the ZO Arm



No. at risk												
ZO	77	20	11	5	3	3	1	1	1	1	1	0

GMI, Growth Modulation Index; KM, Kaplan-Meier; ZO, zanubrutinib + obinutuzumab.

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