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

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Krimo Bouabdallah,[1] Shanmei Liao,[2] Richard Delarue,[3] Laura Dima,[4] Dirk Weber,[3] Laurent Dumartin[4]

[1]Hôpital Haut-Lévêque, CHU Bordeaux, Pessac, France; [2]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [3]BeiGene Switzerland, GmbH, Basel, Switzerland; [4]BeiGene, Paris, France

INTRODUCTION

- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma[1]
- The global, randomized, phase 2 ROSEWOOD (NCT03332017) study evaluated zanubrutinib plus obinutuzumab (ZO) vs obinutuzumab monotherapy (O) in patients with relapsed/refractory (R/R) FL who had received ≥2 prior lines of therapy[2]
- Median progression-free survival (PFS) was longer with ZO (28.0 months; 95% CI, 16.1 months-not estimable [NE]) vs O (10.4 months; 95% CI, 6.5-13.8 months) (HR, 0.50; 95% CI, 0.33-0.75; *P*<.001) and compared favorably with PFS with the last prior treatment (12.1 months)[2]
- The absence of clear consensus for standard of care in R/R FL and the heterogeneity of patient populations included in trials limit the ability to make indirect comparisons across different studies
- To overcome this challenge, the Growth Modulation Index (GMI) uses each patient as their own control to evaluate treatment efficacy by comparing PFS durations with successive treatments

METHODS

- This post hoc analysis evaluated the efficacy of ZO in the sequence of treatments received by patients included in the ROSEWOOD study using the GMI clinical endpoint
- PFS was 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, and was assessed by independent central review[2]

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 indicates that the present treatment has extended the duration of PFS compared with the previous treatment
  - A GMI of ≥1.33 is often used as a threshold for significant clinical activity
- The Kaplan-Meier method was used to estimate the GMI distribution, including the median and the proportion of patients in each GMI interval
- The Brookmeyer-Crowley method was used to estimate 95% CIs for median GMI
- The Greenwood formula with logit transformation was used to estimate the 95% CIs for the proportion within each GMI interval

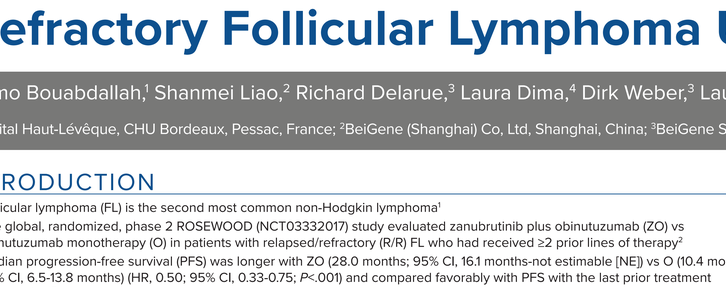
RESULTS

- A total of 217 patients were randomized to the ZO arm (n=145) or the O arm (n=72) in ROSEWOOD
  - Patients with no PFS_{n-1} were excluded from the GMI analysis (ZO, n=5; O, n=3)

PFS Analysis

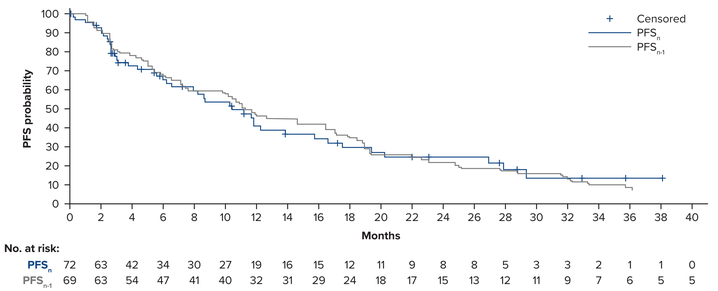
- Median PFS with the current treatment was longer than that with the last prior regimen in the ZO arm (28.0 vs 12.1 months, respectively) but not in the O arm (10.4 vs 11.5 months)
- In the ZO arm, the PFS_n and PFS_{n-1} curves diverged early, and separation was maintained over time (**Figure 1**). In the O arm, there was no separation between PFS_n and PFS_{n-1} curves (**Figure 2**)
- The most frequent last prior treatments 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



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

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

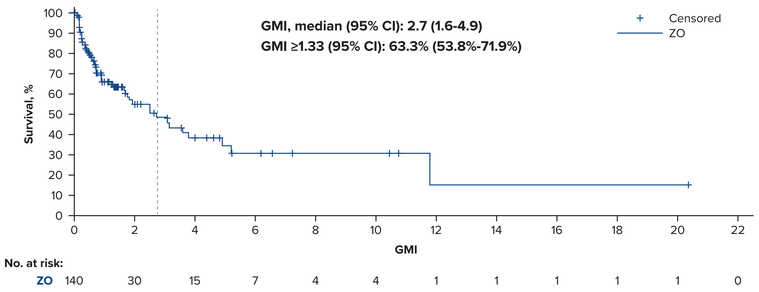


KM, Kaplan-Meier; PFS_n, PFS with the current treatment under evaluation; PFS_{n-1}, PFS with the last prior treatment; O, obinutuzumab.

GMI Analysis

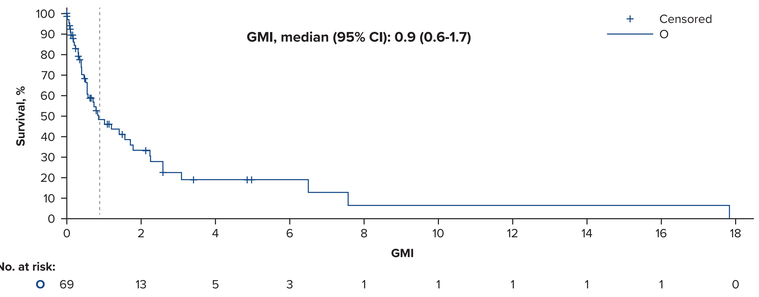
- Median GMI was 2.7 (95% CI, 1.6-4.9) in the ZO arm (**Figure 3**) vs 0.9 (95% CI, 0.5-1.7) in the O arm (**Figure 4**)
- In the ZO arm, 63.3% of patients (95% CI, 53.8%-71.9%) had a GMI of ≥1.33 (**Table 1**)

Figure 3. KM Analysis of GMI in the ZO Arm



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

Figure 4. KM Analysis of GMI in the O Arm



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

Table 1. GMI According to Number of Prior Lines of Therapy in the ZO Arm

	ZO (n=145)
GMI in ITT population, survival (95% CI), %	
<1	34.1 (25.9-43.3)
≥1 and <1.33	2.6 (0-80.2)
≥1.33	63.3 (53.8-71.9)
GMI in patients with 2 prior lines, survival (95% CI), %	
<1	34.4 (22.2-49.2)
≥1 and <1.33	0 (NE-NE)
≥1.33	65.6 (50.8-77.8)
GMI in patients with >2 prior lines, survival (95% CI), %	
<1	34.1 (23.7-46.4)
≥1 and <1.33	4.1 (0.1-75.6)
≥1.33	61.8 (49.2-73.0)

GMI, Growth Modulation Index; ITT, intent to treat; NE, not estimable; ZO, zanubrutinib + obinutuzumab.

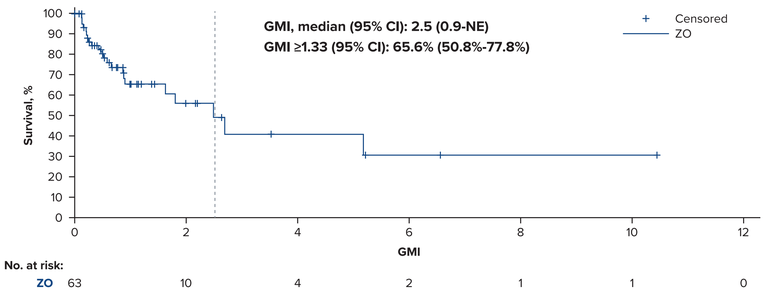
Effect of Prior Lines of Therapy on GMI

- 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 5**)
- 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 6**)

CONCLUSIONS

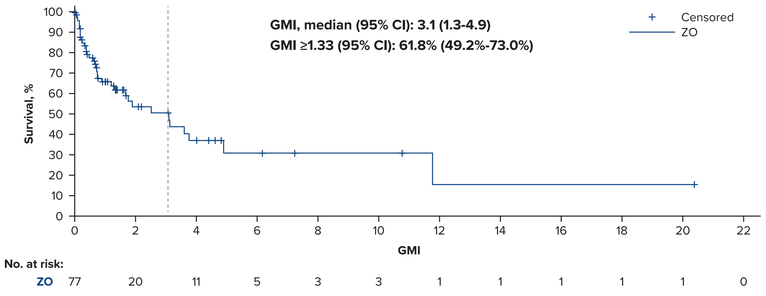
- In this study, a post hoc GMI analysis of data from ROSEWOOD allowed for the generation of comparative efficacy evidence for ZO in R/R FL using each patient as their own control
- The majority of patients with R/R FL receiving ZO had a significant improvement in PFS vs PFS with their last prior treatment, irrespective of the number of prior treatments
  - GMI was ≥1.33 in >60% of patients
  - The median GMI of 2.7 in the overall population 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 5. KM Curves of GMI in Patients With 2 Prior Lines of Therapy in the ZO Arm



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

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



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

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DISCLOSURES

KB: Honoraria: BeiGene, Takeda; Travel, accommodations, expenses: BeiGene, Takeda. **SL:** Employment, stock or other ownership, and travel, accommodations, expenses: BeiGene. **RD:** Past employment: Celgene/Bristol Myers Squibb; Employment: BeiGene; Stock or other ownership: Celgene/Bristol Myers Squibb, BeiGene. **L. Dima, DW:** Employment, may hold stock: BeiGene. **L. Dumartin:** Employment, stock or other ownership: BeiGene, Novartis; Travel and accommodation expenses: BeiGene, Novartis.

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