Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab in Patients With Relapsed/Refractory Follicular Lymphoma: Updated Analysis of the ROSEWOOD Study

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BACKGROUND

- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma subtype worldwide¹
- In a phase 1b/2 study that included patients with relapsed/refractory (R/R) FL, the combination of zanubrutinib plus obinutuzumab was generally well tolerated, with an objective response rate (ORR) of 72% and a complete response rate of 39%²

Efficacy

• With a median study follow-up of 20.2 months, the difference in the ORR by IRC was 22.7% (95% CI, 9.0%-36.5%) in favor of zanubrutinib plus obinutuzumab (**Table 2**)

 Table 2. Efficacy Outcomes

	Zanubrutinib + obinutuzumab	Obinutuzumab	2-sided
dpoint	(n=145)	(n=72)	<i>P</i> value

CONCLUSIONS

- In the ROSEWOOD study, zanubrutinib plus obinutuzumab demonstrated meaningful efficacy and a manageable safety profile in heavily pretreated patients with R/R FL
- This longer follow-up analysis provides evidence of the significant complete response rate, with longer PFS and TTNT, with zanubrutinib plus obinutuzumab vs obinutuzumab

- The phase 2 ROSEWOOD trial (BGB-3111-212; NCT03332017) examined zanubrutinib plus obinutuzumab vs obinutuzumab monotherapy in patients with R/R FL who have received ≥2 prior lines of therapy
- In the previously reported primary analysis, the trial met its primary endpoint, with significant improvement in the ORR with zanubrutinib plus obinutuzumab vs obinutuzumab (68.3% vs 45.8%, respectively; P=.0017)³
- Here, we report an updated analysis of the ROSEWOOD trial with a median follow-up of 20.2 months

METHODS

 ROSEWOOD was a global study that assessed the efficacy and safety of zanubrutinib plus obinutuzumab vs obinutuzumab (Figure 1)

Figure 1. Study Design

 Key eligibility criteria Adults with grade 1-3a 	Arm A Zanubrutinibª plus obinutuzumab ^b n=145 Until PD/unacceptable toxicity	 Primary endpoint ORR by IRC according to
R/R FL • Previous treatment with	Randomization 2:1 Stratification factors	Lugano 2014 classification ⁴
≥2 lines of therapy includ- ing an anti-CD20 antibody and an alkylating agent	 Number of prior lines of treatment Rituximab-refractory status Geographic region 	• DOR by IRC ^c
 Measurable disease ECOG PS 0-2 Adequate organ function No prior BTK inhibitor 	Arm B Obinutuzumab ^b n=72 → Option to cross over to combination if PD centrally confirmed or no response at 12 months	 PFS by IRC^c OS^c TTNT Safety (AEs)^c

BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status. ^a Zanubrutinib was given orally at 160 mg twice daily. ^b Obinutuzumab was given intravenously at 1000 mg in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2 to 6, and then every 8 weeks up to 20 doses maximum. ^c Secondary endpoint.

ORR by IRC (95% CI), %	69.0 (60.8-76.4)	45.8 (34.0-58.0)	.0012
CR	39.3	19.4	.0035
PR	29.7	26.4	_
DOR by IRC			
Median (95% CI), mo	NE (25.3-NE)	14.0 (9.2-25.1)	_
18-month DOR rate (95% CI), %	69.3 (57.8-78.2)	41.9 (22.6-60.1)	_
DOCR by IRC			
Median (95% CI), mo	NE (26.5-NE)	26.5 (2.7-NE)	_
18-month DOCR rate (95% CI), %	87.4 (73.8-94.2)	51.1 (21.0-74.9)	_

DOCR, duration of complete response; NE, not estimable.

 Across prespecified subgroups of patients, zanubrutinib plus obinutuzumab showed consistent benefit over obinutuzumab (Figure 2)

Figure 2. ORR by IRC in Predefined Subgroups

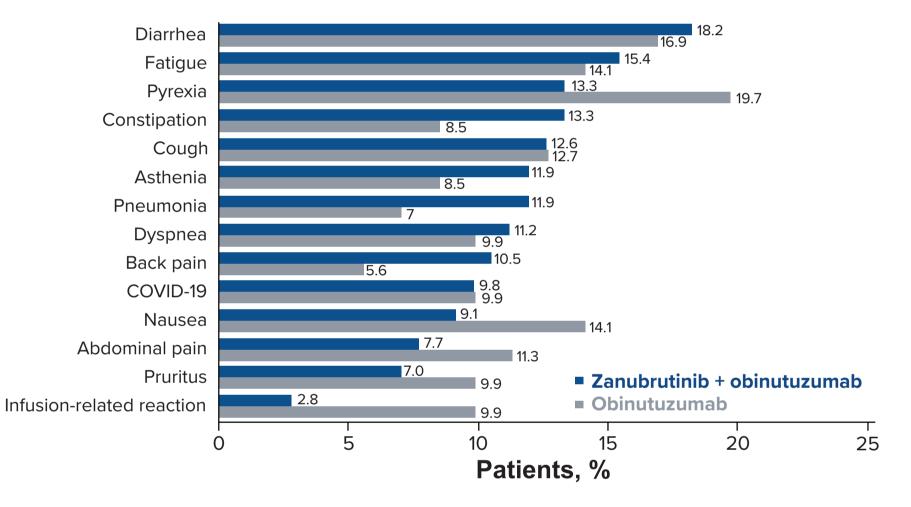
Subgroup	Response Obinutuzumab	/patients Zanubrutinib + obinutuzumab		Risk difference (95% Cl),%
All patients in ITT	33/72	100/145		22.7 (9.0-36.5)
Age, years <65 ≥65 <75 ≥75	14/32 19/40 30/60 3/12	58/83 42/62 89/130 11/15		26.1 (6.3-45.9) 20.2 (0.9-39.6) 18.5 (3.5-33.4) 48.3 (15.2-81.5)
Prior lines of therapy 2-3 >3	27/54 6/18	77/108 23/37	_	21.3 (5.5-37.1)
Bulky disease: any target lesion longest diameter ≥7 cm Yes No	3/12 30/60	11/23 89/122		- 22.8 (-9.1 to 54.7 23.0 (8.0-37.9)
FLIPI risk category Low (0-1) Intermediate (2) High (≥3)	3/9 13/24 17/37	21/29 26/34 49/77		39.1 (4.3-73.9) 22.3 (-2.2 to 46.8 17.7 (-1.6 to 37.0)
Rituximab-refractory status Refractory Not refractory	14/36 19/36	47/78 53/67		21.4 (2.1-40.6) 26.3 (7.3-45.3)
Refractory status to the most receiptine of therapy Refractory Not refractory	nt 11/29 21/42	29/47 66/93		23.8 (1.3-46.2) 21.0 (3.3-38.7)
Progression of disease within 6 months of completion of the most recent line of therapy Yes No	12/39 19/30	42/71 53/67		28.4 (9.9-46.8) 15.8 (-4.0 to 35.6
Progression of disease within 24 months of starting the first line of chemoimmunotherapy Yes No	9/22 14/31	25/39 40/59		23.2 (-2.3 to 48.7 22.6 (1.4-43.8)
		-75 -50 -2	25 0 25 5	50 75

- A consistent benefit was observed across key prespecified subgroups
- The combination of zanubrutinib and obinutuzumab demonstrates a favorable risk-benefit profile and may represent a potential novel combination therapy for patients with R/R FL
- A phase 3 study of zanubrutinib plus obinutuzumab in patients who previously received ≥1 line of systemic therapy is now underway (MAHOGANY; NCT05100862)

Safety

- There were no unexpected safety findings with zanubrutinib plus obinutuzumab (Figure 5; Table 3)
- Among common nonhematologic treatment-emergent adverse events (TEAEs) of any grade, pyrexia and infusion-related reactions occurred more frequently with obinutuzumab (>5% difference vs zanubrutinib plus obinutuzumab)
- Exposure-adjusted incidence rates for TEAEs of special interest are given in Figure 6
- Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms
- Two patients in each arm reported major hemorrhage

Figure 5. Common Nonhematologic TEAEs (Any Grade)



Patients

- Between November 2017 and June 2021, 217 patients from 127 sites in 17 countries/regions were randomized to the zanubrutinib plus obinutuzumab arm (n=145; 2 were not treated) or obinutuzumab monotherapy arm (n=72; 1 was not treated)
- As of June 25, 2022, 46 patients in the zanubrutinib plus obinutuzumab arm and 6 in the obinutuzumab arm remained on treatment
- Zanubrutinib plus obinutuzumab arm: 97 discontinuations (53 disease progression, 27 AE, 7 investigator decision, 5 patient withdrawal, 7 other)
- Obinutuzumab arm: 65 discontinuations (35 crossover to zanubrutinib plus obinutuzumab, 11 disease progression without crossover, 9 AE, 4 treatment completed, 3 investigator decision, 2 patient withdrawal, 1 other)
- Baseline characteristics are shown in **Table 1**

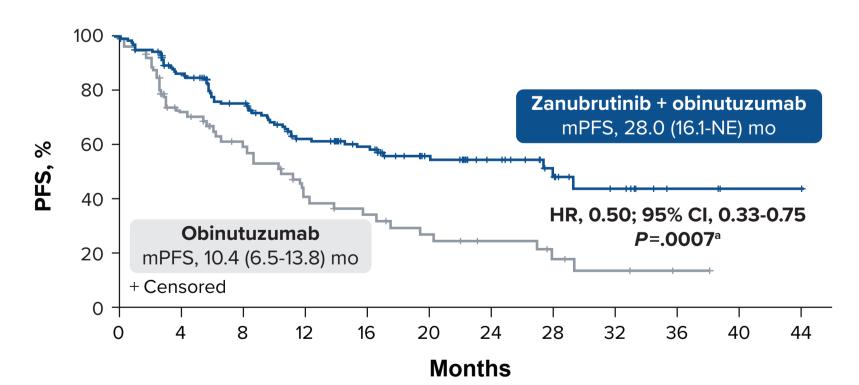
Table 1. Patient Characteristics

Characteristic	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)
Age, median (range), years	63.0 (31-84)	65.5 (32-88)
ECOG PS ≥1, n (%)	59 (40.6)	41 (57.0)
FLIPI score ≥3, n (%)	77 (53.1)	37 (51.4)
Ann Arbor stage III-IV, n (%)	119 (82.1)	60 (83.3)
Bulky disease (≥7 cm), n (%)	23 (15.9)	12 (16.7)
High LDH level (>ULN), n (%)	49 (33.8)	29 (40.3)
High tumor burden per GELF criteria, n (%)	83 (57.2)	40 (55.6)
No. of prior lines of therapy, median (range)	3 (2-11)	3 (2-9)
Refractory to rituximab, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent line of therapy, n (%)	47 (32.4)	29 (40.3)
PD ≤24 months after starting first line of therapy, n (%)	50 (34.5)	30 (41.7)

FLIPI, Follicular Lymphoma International Prognostic Index; ITT, intent to treat.

- Median duration of response by IRC was 14.0 months with obinutuzumab and was not reached in the zanubrutinib plus obinutuzumab arm
- Median progression-free survival (PFS) was longer with zanubrutinib plus obinutuzumab vs obinutuzumab (Figure 3)
- Time to next antilymphoma treatment (TTNT) was prolonged with zanubrutinib plus obinutuzumab (**Figure 4**)
- The estimated overall survival rate at 24 months was numerically higher with zanubrutinib plus obinutuzumab (77.3%) vs obinutuzumab (71.4%; HR, 0.62; 95% CI, 0.35-1.07; P=.0845)

Figure 3. Progression-Free Survival by IRC



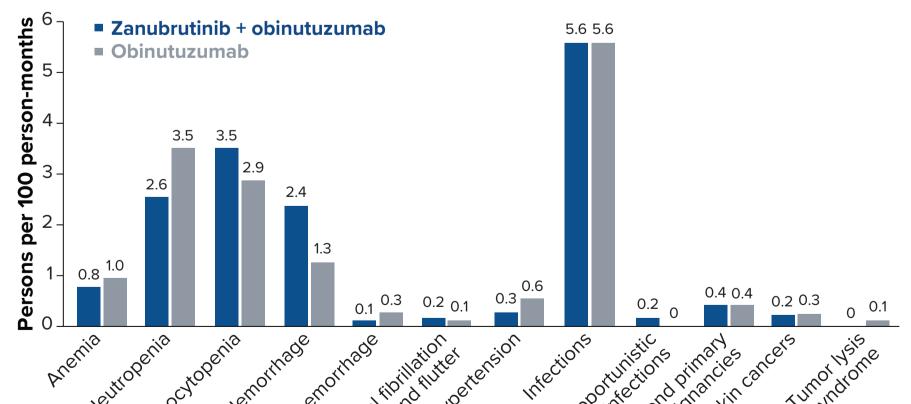
No. of patients at risk Zanubrutinib + 145 135 116 96 92 79 67 62 56 45 38 35 25 22 15 obinutuzumab

Obinutuzumab 72 63 42 34 30 27 19 16 15 12 11 9 8 8 5 3 3 2 1 1 0

Table 3. Selected Grade ≥3 Nonhematologic TEAEs

n (%)	Zanubrutinib + obinutuzumab (n=143)	Obinutuzumab (n=71)
Pneumonia	14 (9.8)	3 (4.2)
COVID-19	8 (5.6)	2 (2.8)
COVID-19 pneumonia	5 (3.5)	2 (2.8)
Diarrhea	4 (2.8)	1 (1.4)
Febrile neutropenia	3 (2.1)	1 (1.4)
Atrial fibrillation	2 (1.4)	0 (0)
Infusion-related reaction	1 (0.7)	3 (4.2)
Hypertension	1 (0.7)	1 (1.4)

Figure 6. EAIRs for TEAEs of Special Interest



Prior therapy, n (%)

Immunochemotherapy	143 (98.6)	71 (98.6)
Anthracyclines	118 (81.4)	57 (79.2)
Cyclophosphamide	136 (93.8)	68 (94.4)
Bendamustine	79 (54.5)	40 (55.6)

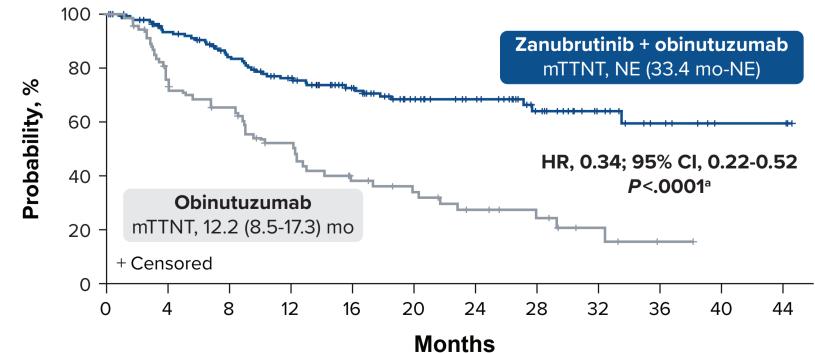
ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Treatment Exposure

- In the zanubrutinib plus obinutuzumab arm, the median duration of zanubrutinib exposure was 12.2 months (range, 0.5-44.1 months)
- 56.7% of patients received \geq 12 cycles
- Median relative dose intensity was 98.9% (range, 30.7%-100%)
- Median number of obinutuzumab infusions was 11 (range, 3-20)
- In the obinutuzumab arm, median exposure was 6.5 months (range, 0.1-28.7 months)
- Median number of infusions was 9 (range, 3-20)

NE, not estimable. ^a Descriptive 2-sided *P* value.

Figure 4. Time to Next Antilymphoma Treatment



No. of patients at risk

Zanubrutinib + 145 137 125 118 107 98 91 80 71 62 53 47 44 40 29 22 17 12 10 6 3 3 3 0

obinutuzumab

Obinutuzumab 72 65 49 44 41 32 30 24 20 18 16 13 11 9 8 5 4 2 1 1 0

mTTNT, median time to next antilymphoma treatment; NE, not estimable ^a Descriptive 2-sided *P* value.



EAIR, exposure-adjusted incidence rate.

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