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

Abstract 7545

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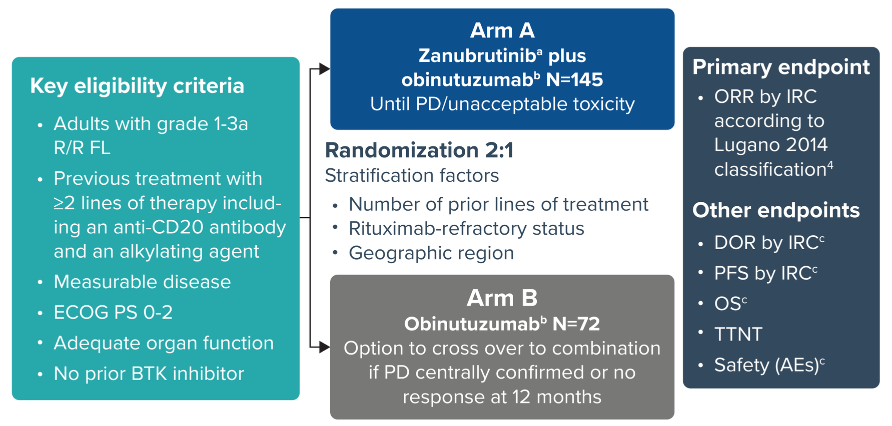
BACKGROUND

- Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma subtype worldwide[1]
- 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]
- 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



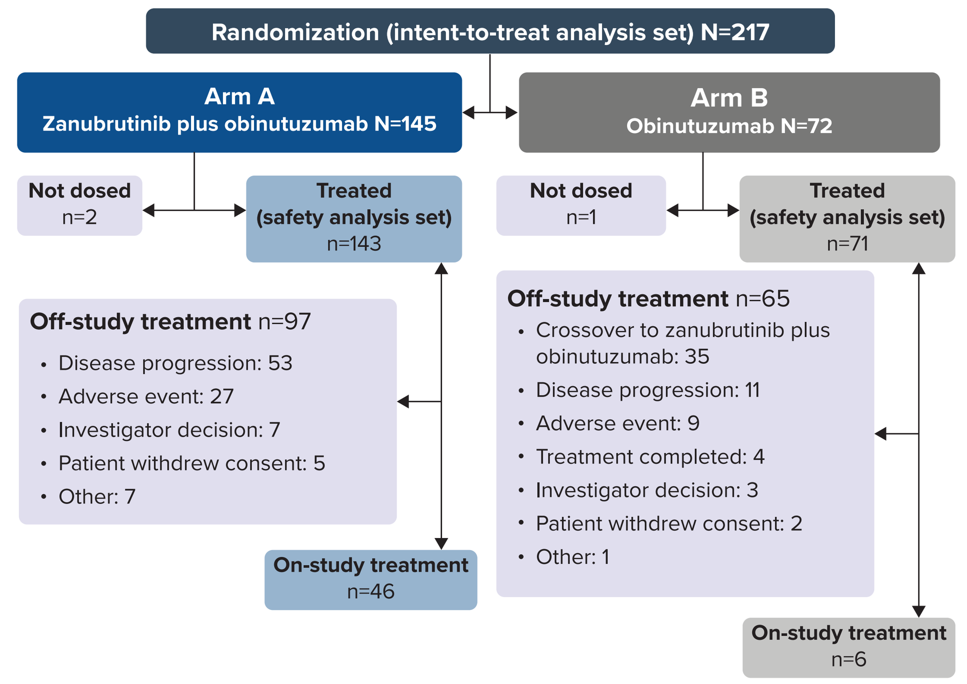
BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Zanubrutinib was given orally at 160 mg twice daily. [b] Obinutuzumab was given intravenously at 1000 mg in both arms on days 1, 8, and 15 of cycle 1 day 1 of cycles 2 to 6 and then every 8 weeks up to 20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

RESULTS

Patients

- A total of 217 patients from 127 sites in 17 countries/regions were randomized between November 2017 and June 2021 (**Figure 2**)
- Median follow-up for this analysis was 20.2 months

Figure 2. Patient Disposition



- 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)
Number 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)
Prior therapy		
Prior 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, median duration of zanubrutinib exposure was 12.2 months (range, 0.5-44.1 months)
  - 56.7% of patients received ≥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)

Efficacy

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

Table 2. Efficacy Outcomes

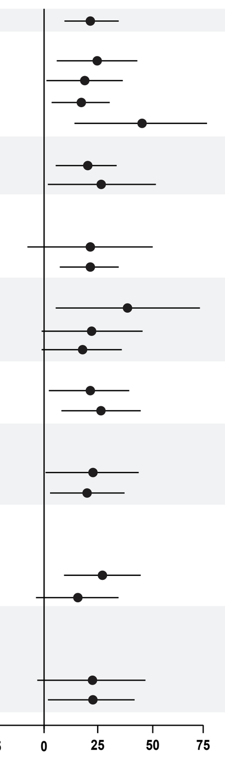
Endpoint	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)	2-sided *P* value
ORR by IRC, (95% CI), %	69.0 (60.8-76.4)	45.8 (34.0-58.0)	.0012
CR	39.3	19.4	.0035
PR	29.7	26.4	–
18-month DOR rate (95% CI), %	69.3 (57.8-78.2)	41.9 (22.6-60.1)	–
DOCR by IRC			
Median (95% CI), mo	NE (26.5-NE)	26.5 (2.7-NE)	–
18-month DOCR rate (95% CI), %	87.4 (73.8-94.2)	51.1 (21.0-74.9)	–
24-month OS rate (95% CI), %	77.3 (68.0-84.2)	71.4 (58.3-81.1)	–

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

- Across prespecified subgroups of patients, zanubrutinib plus obinutuzumab showed consistent benefit over obinutuzumab (**Figure 3**)

Figure 3. ORR by IRC in Predefined Subgroups

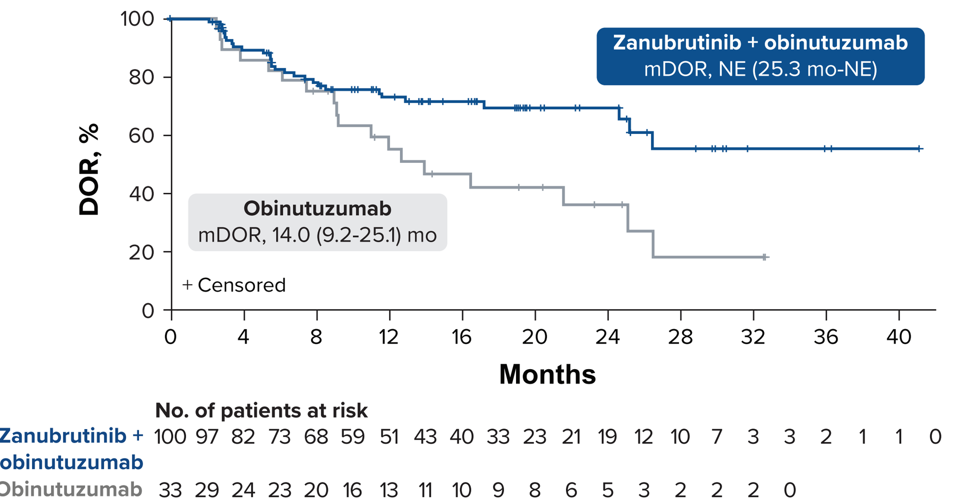
Subgroup	Response/patients: Obinutuzumab	Response/patients: Zanubrutinib + obinutuzumab	Risk difference (95% CI),%
All patients in ITT	33/72	100/145	22.7 (9.0-36.5)
Age, years			
<65	14/32	58/83	26.1 (6.3-45.9)
≥65	19/40	42/62	20.2 (0.9-39.6)
<75	30/60	89/130	18.5 (3.5-33.4)
≥75	3/12	11/15	48.3 (15.2-81.5)
Prior lines of therapy			
2-3	27/54	77/108	21.3 (5.5-37.1)
>3	6/18	23/37	28.8 (2.0-55.6)
Bulky disease: any target lesion longest diameter ≥7 cm			
Yes	3/12	11/23	22.8 (-9.1 to 54.7)
No	30/60	89/122	23.0 (8.0-37.9)
FLIPI risk category			
Low (0-1)	3/9	21/29	39.1 (4.3-73.9)
Intermediate (2)	13/24	26/34	22.3 (-2.2 to 46.8)
High (≥3)	17/37	49/77	17.7 (-1.6 to 37.0)
Rituximab-refractory status			
Refractory	14/36	47/78	21.4 (2.1-40.6)
Not refractory	19/36	53/67	26.3 (7.3-45.3)
Refractory status to the most recent line of therapy			
Refractory	11/29	29/47	23.8 (1.3-46.2)
Not refractory	21/42	66/93	21.0 (3.3-38.7)
Progression of disease within 6 months of completion of the most recent line of therapy			
Yes	12/39	42/71	28.4 (9.9-46.8)
No	19/30	53/67	15.8 (-4.0 to 35.6)
Progression of disease within 24 months of starting the first line of chemoimmunotherapy			
Yes	9/22	25/39	23.2 (-2.3 to 48.7)
No	14/31	40/59	22.6 (1.4-43.8)



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 (**Figure 4**)

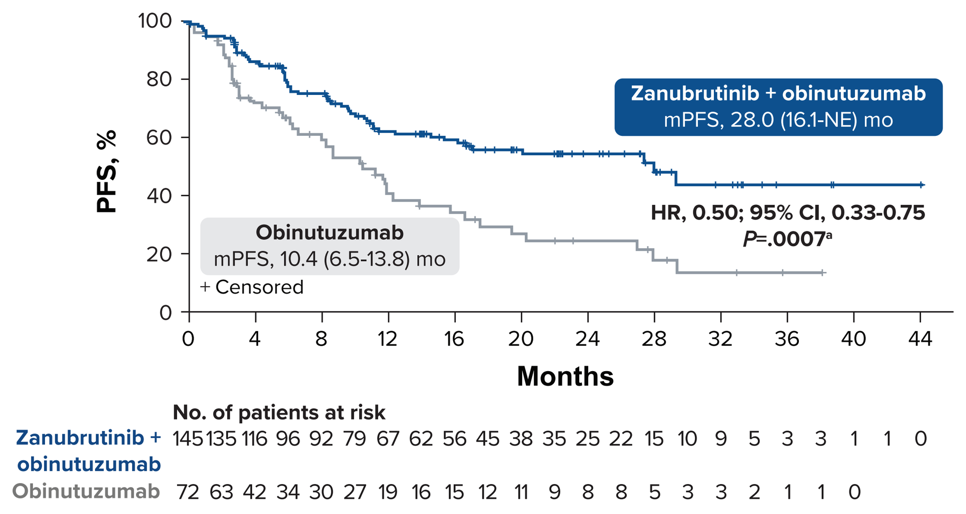
Figure 4. Duration of Response by IRC



mDOR, median duration of response; NE, not estimable.

- Median progression-free survival (PFS) was longer with zanubrutinib plus obinutuzumab vs obinutuzumab (**Figure 5**)

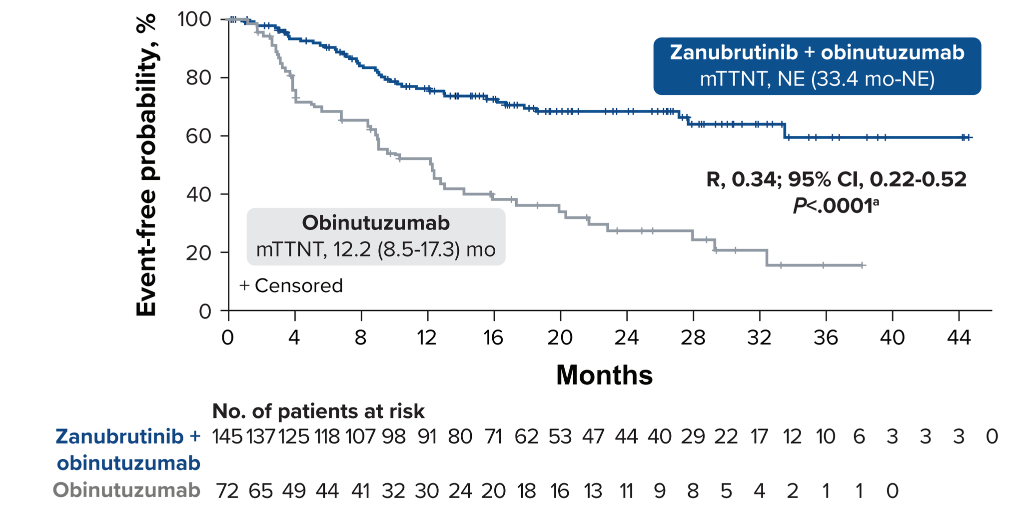
Figure 5. Progression-Free Survival by IRC



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

- Time to next antilymphoma treatment (TTNT) was prolonged with zanubrutinib plus obinutuzumab (**Figure 6**)

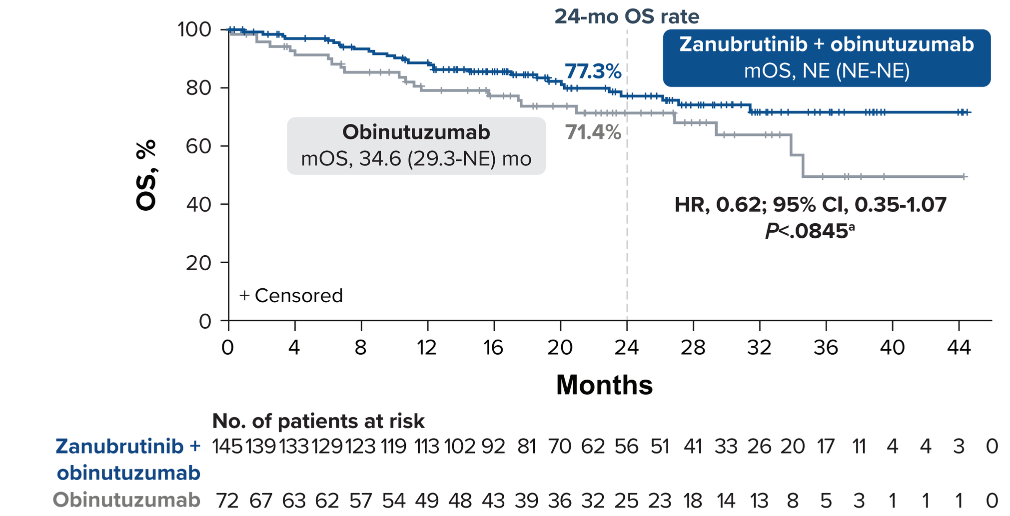
Figure 6. Time to Next Antilymphoma Treatment



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

- The estimated overall survival rate at 24 months was numerically higher with zanubrutinib plus obinutuzumab vs obinutuzumab (**Figure 7**)

Figure 7. Overall Survival

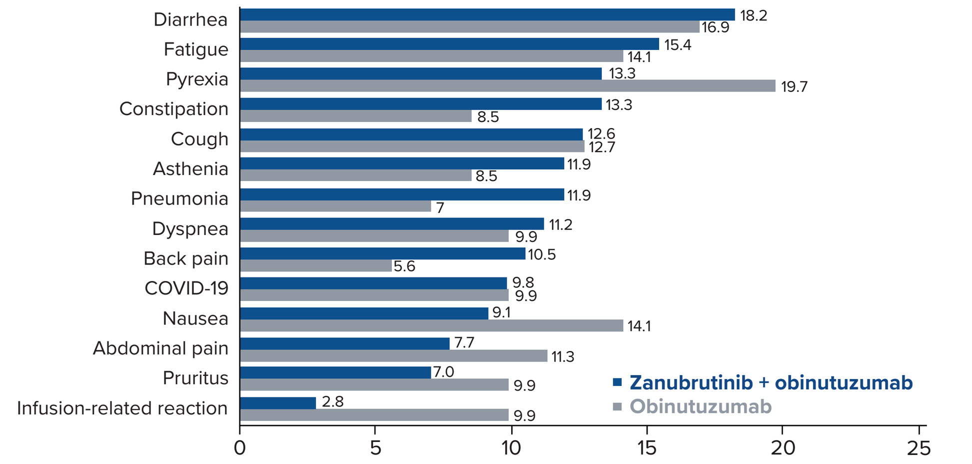


mOS, median overall survival; NE, not estimable.
[a] Descriptive 2-sided *P* value.

Safety

- There were no unexpected safety findings with zanubrutinib plus obinutuzumab (**Figure 8**; **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 9**
  - Incidences of atrial fibrillation and hypertension were low and similar in both treatment arms
  - Two patients in each arm reported major hemorrhage

Figure 8. Common Nonhematologic TEAEs (Any Grade)



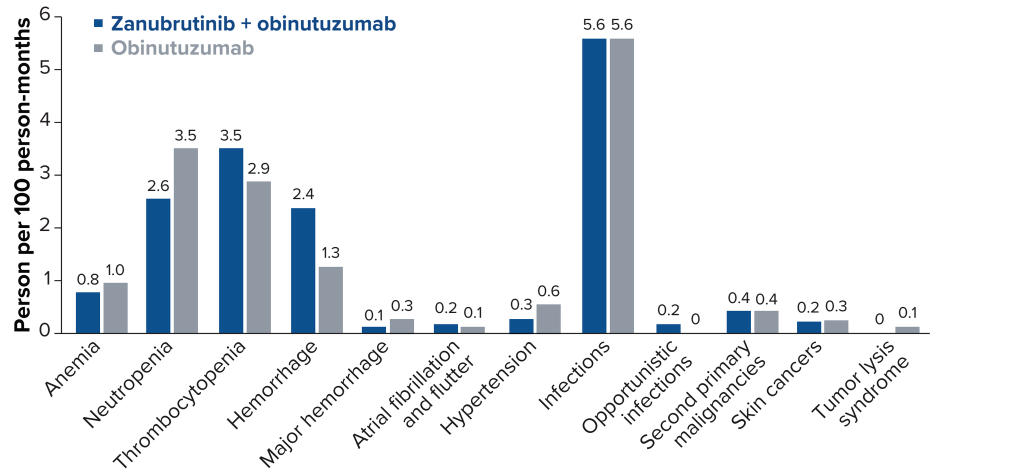
CONCLUSIONS

- **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**
  - **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)**

Table 3. Selected Grade ≥3 Nonhematologic TEAEs

	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 9. EAIRs for TEAEs of Special Interest



EAIR, exposure-adjusted incidence rate.

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