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

Abstract P1080

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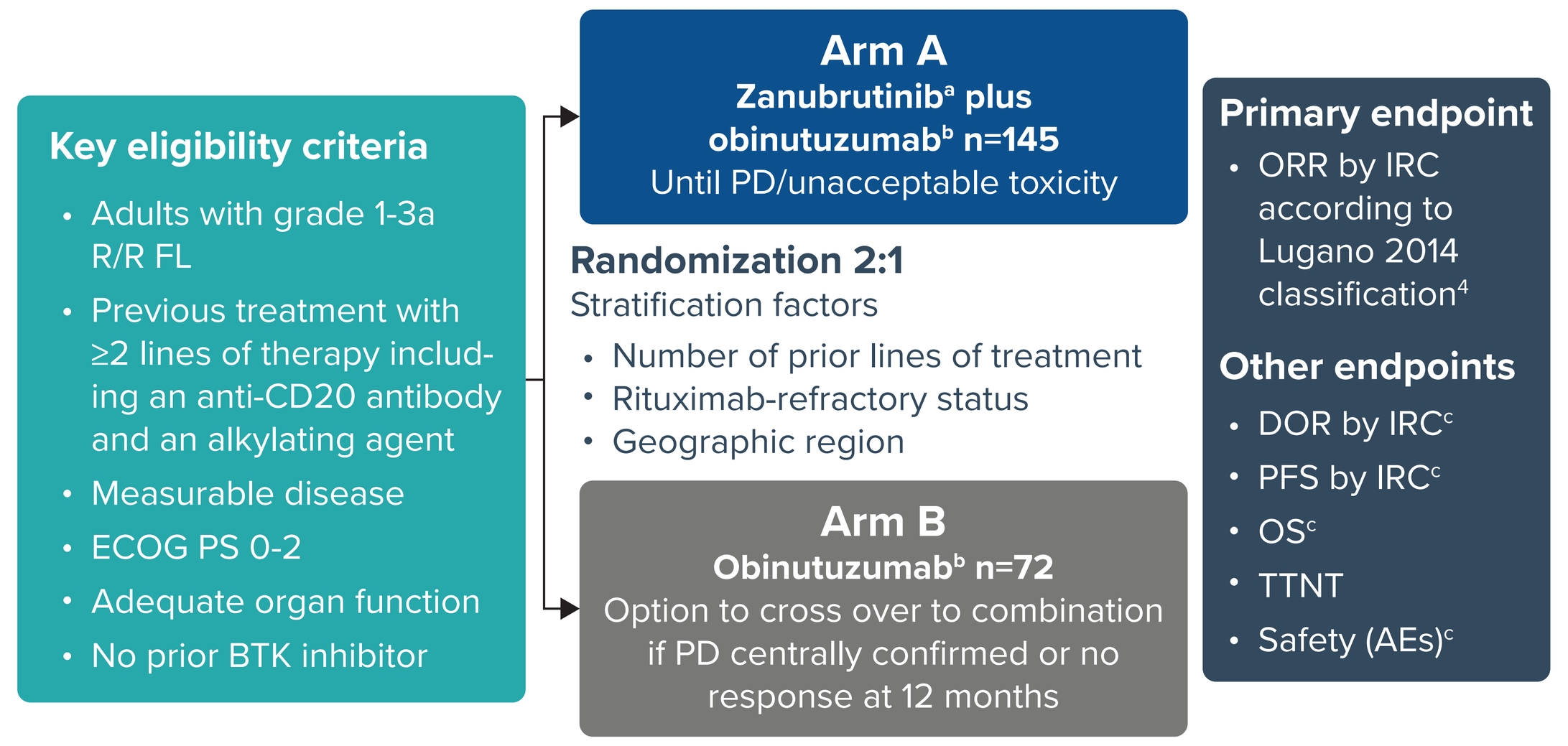
BACKGROUND

- 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


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

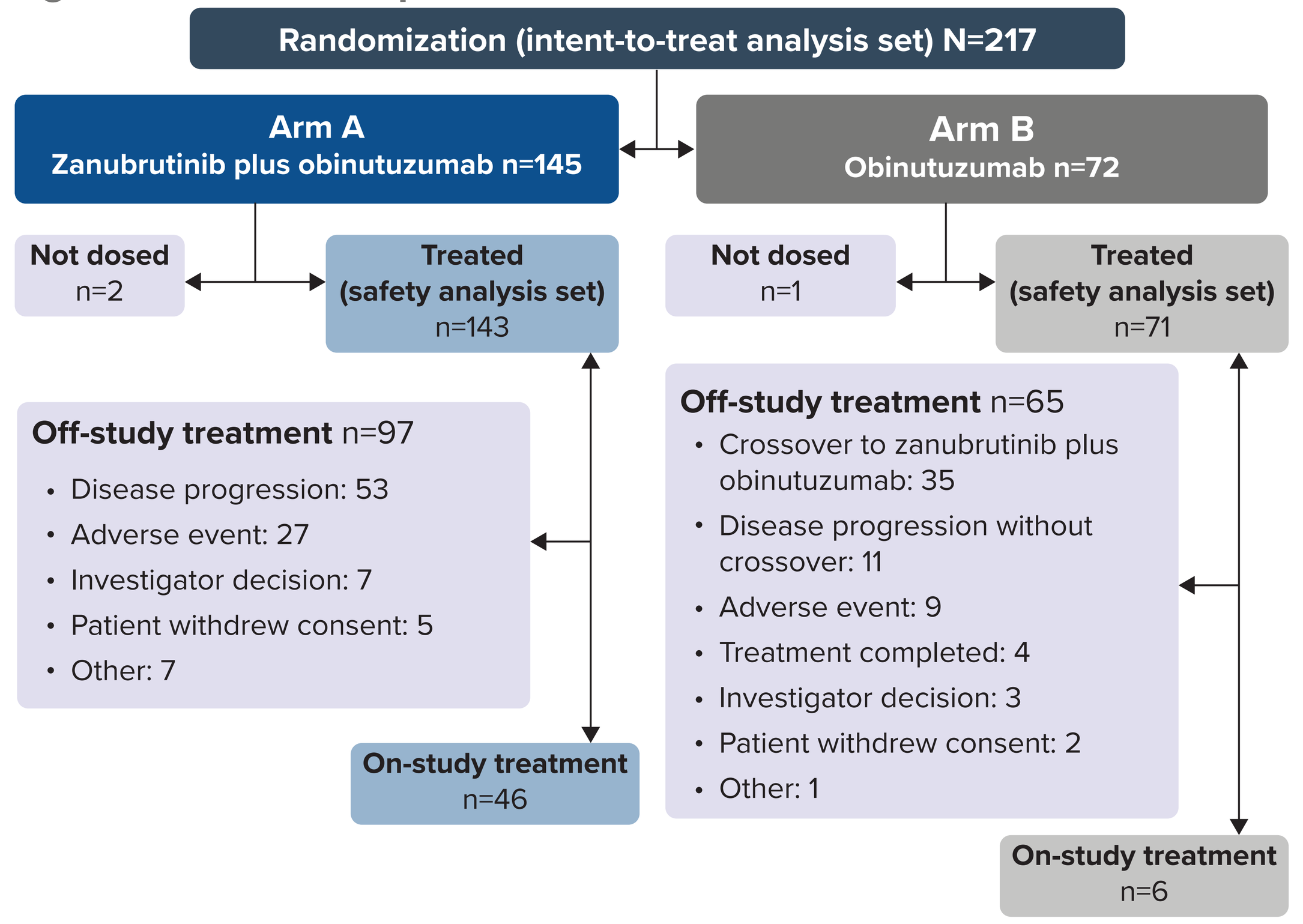
BTK, Bruton tyrosine kinase; ECOG PS, Eastern Cooperative Oncology Group performance status.
[a] Zanubrutinib was given orally at 160 mg twice daily. [b] Obinutuzumab was given intravenously at 1000 mg in both arms on days 1, 8, and 15 of cycle 1, day 1 of cycles 2 to 6, and then every 8 weeks up to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

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


Randomization (intent-to-treat analysis set) N=217
Arm A
Zanubrutinib plus obinutuzumab n=145
Arm B
Obinutuzumab n=72
Not dosed n=2
Treated (safety analysis set) n=143
Not dosed n=1
Treated (safety analysis set) n=71
Off-study treatment n=97
Disease progression: 53
Adverse event: 27
Investigator decision: 7
Patient withdrew consent: 5
Other: 7
On-study treatment n=46
Off-study treatment n=65
Crossover to zanubrutinib plus obinutuzumab: 35
Disease progression without crossover: 11
Adverse event: 9
Treatment completed: 4
Investigator decision: 3
Patient withdrew consent: 2
Other: 1
On-study treatment n=6

- 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)
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, 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

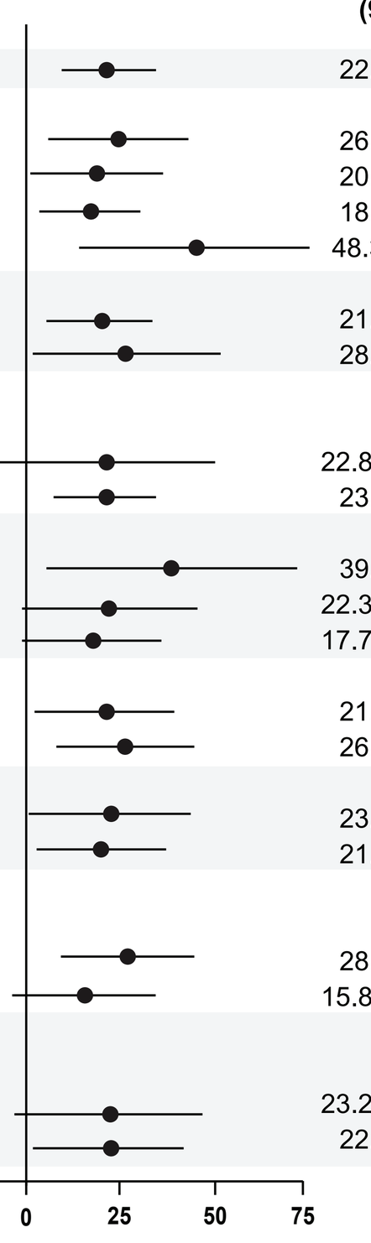
Endpoint	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)	2-sided *P* value
ORR by IRC (95% CI), %	69.0 (60.8-76.4)	45.8 (34.0-58.0)	.0012
CR	39.3	19.4	.0035
PR	29.7	26.4	–
DOR by IRC			
Median (95% CI), mo	NE (25.3-NE)	14.0 (9.2-25.1)	–
18-month DOR rate (95% CI), %	69.3 (57.8-78.2)	41.9 (22.6-60.1)	–
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 3**)

Figure 3. ORR by IRC in Predefined Subgroups

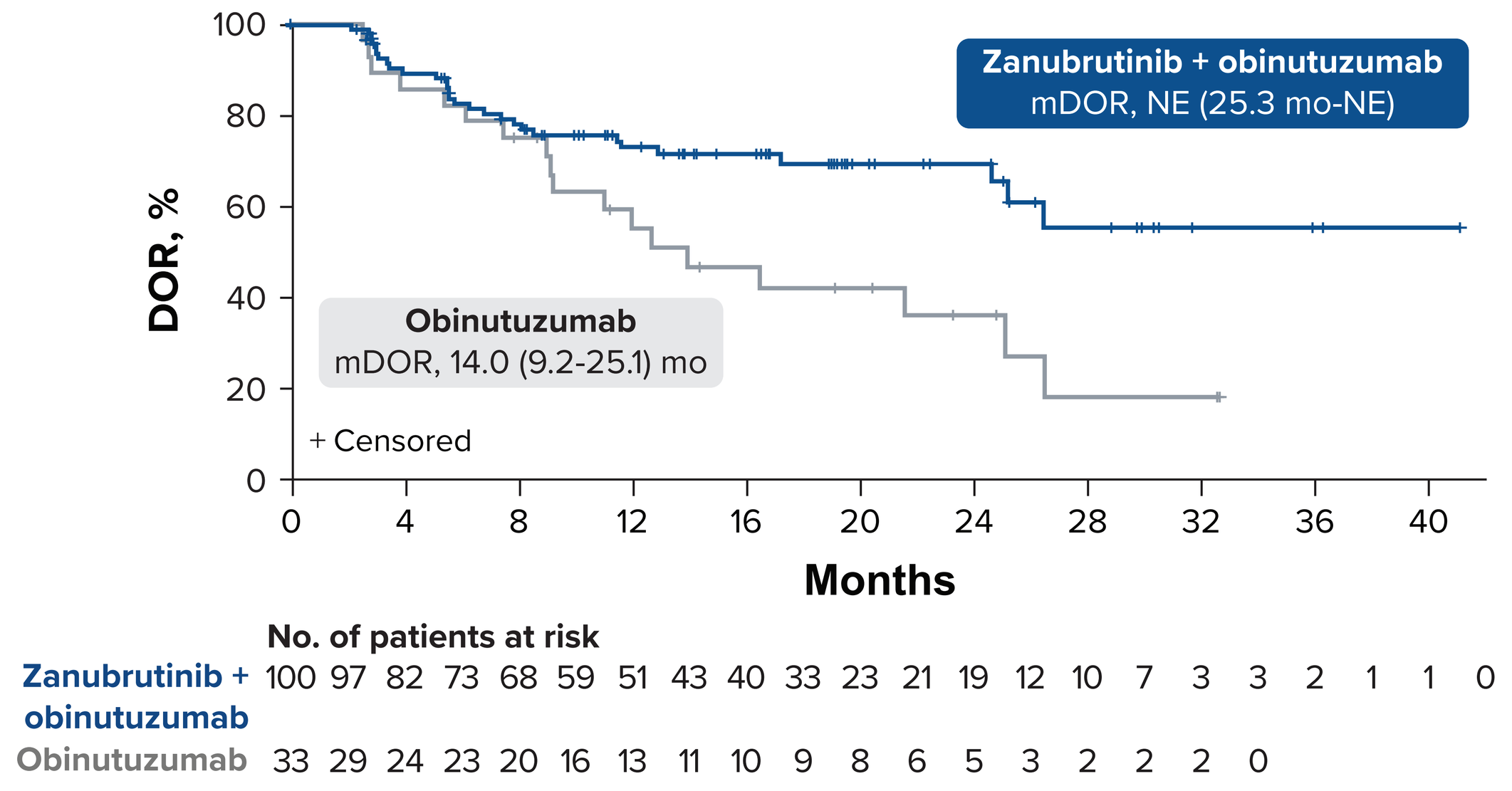
Subgroup	Response/patients: Obinutuzumab	Response/patients: Zanubrutinib + obinutuzumab	Risk difference (95% CI),%
All patients in ITT	33/72	100/145	22.7 (9.0-36.5)
Age, years			
<65	14/32	58/83	26.1 (6.3-45.9)
≥65	19/40	42/62	20.2 (0.9-39.6)
<75	30/60	89/130	18.5 (3.5-33.4)
≥75	3/12	11/15	48.3 (15.2-81.5)
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**)

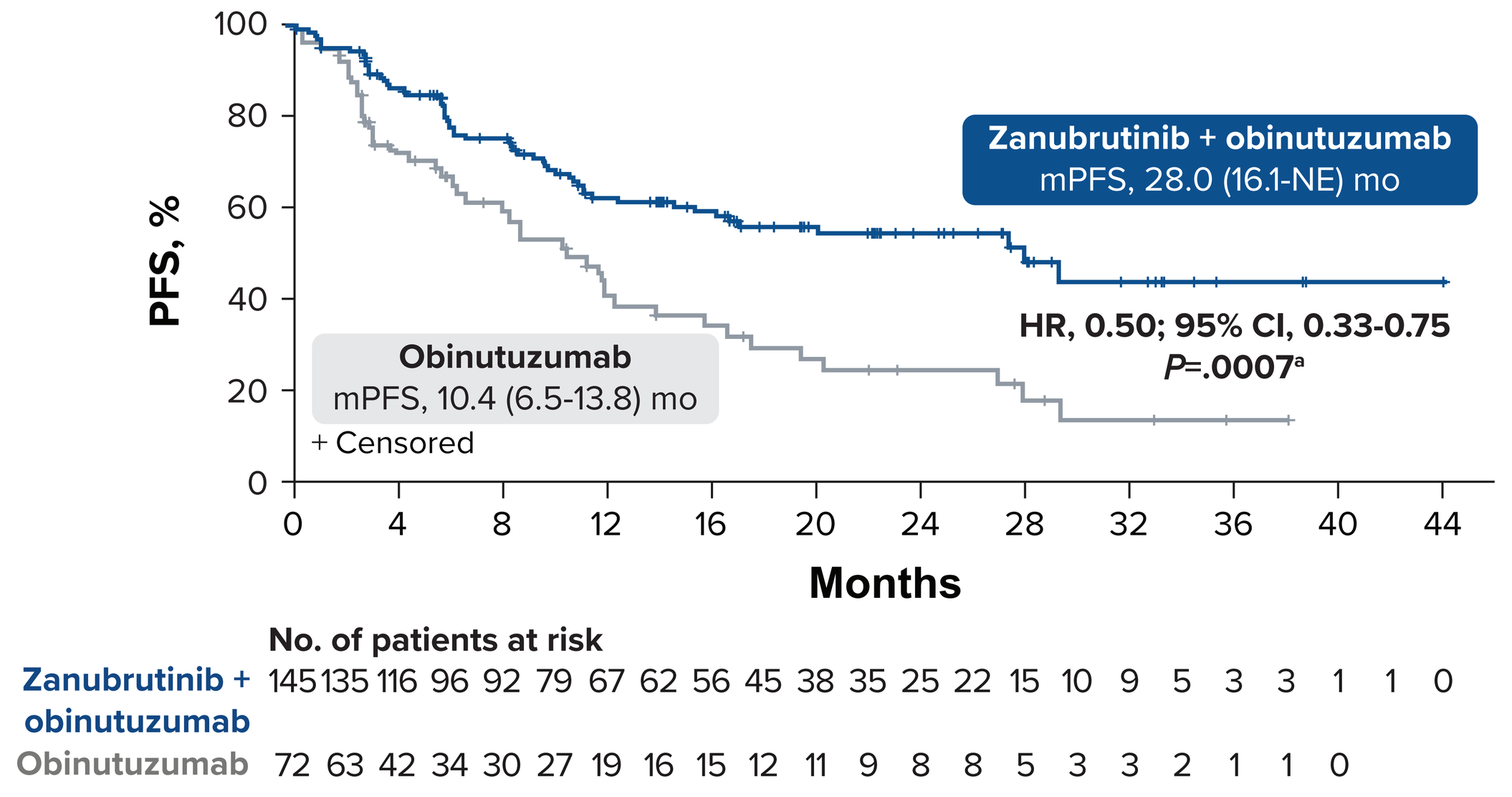
Figure 4. Duration of Response by IRC



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

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

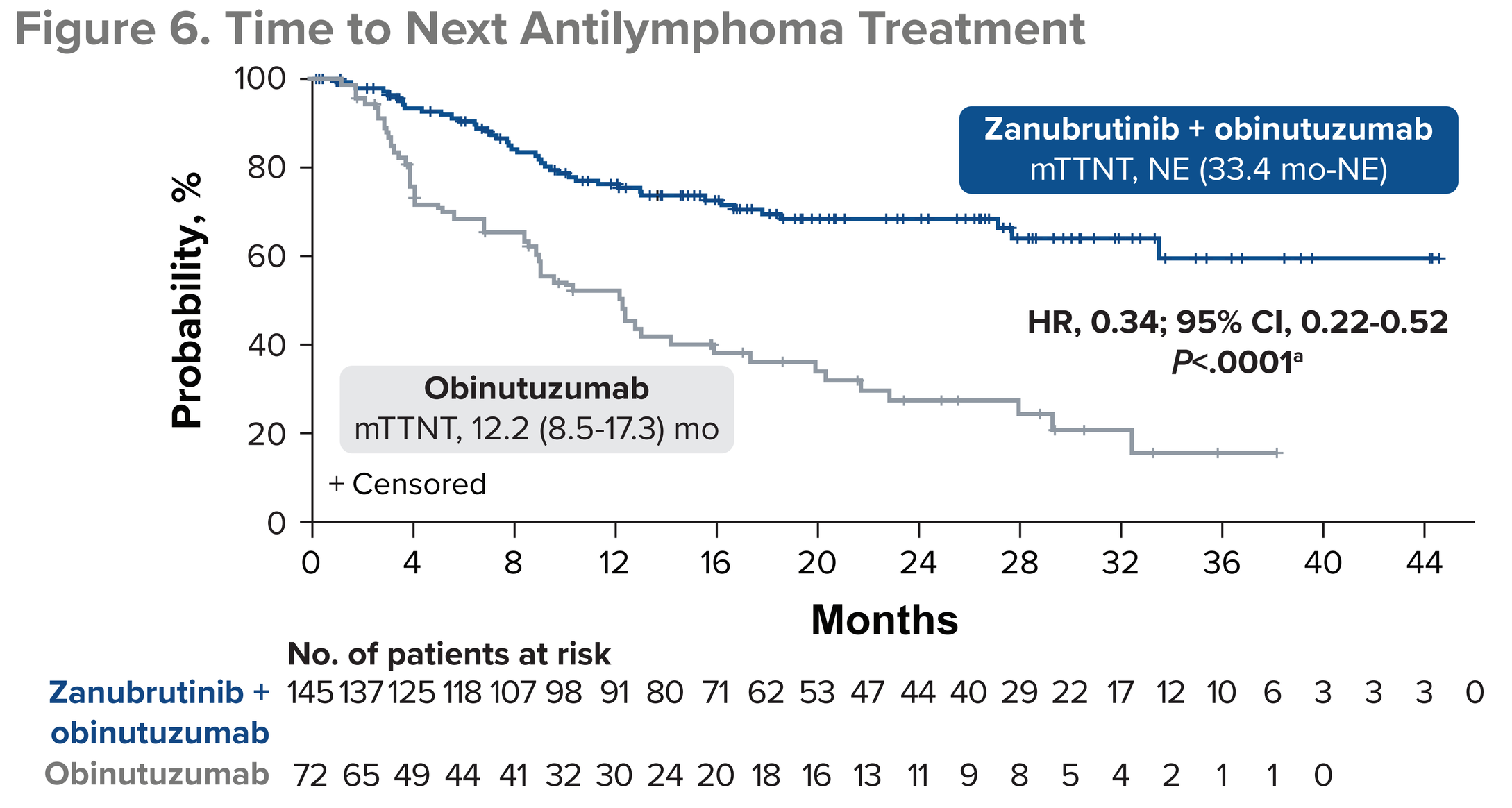
Figure 5. Progression-Free Survival by IRC


PFS, %
Zanubrutinib + obinutuzumab
mPFS, 28.0 (16.1-NE) mo
HR, 0.50; 95% CI, 0.33-0.75
P=.0007[a]
Obinutuzumab
mPFS, 10.4 (6.5-13.8) mo
+ Censored
Months
No. of patients at risk
Zanubrutinib + obinutuzumab 145 135 116 96 92 79 67 62 56 45 38 35 25 22 15 10 9 5 3 3 1 1 0
Obinutuzumab 72 63 42 34 30 27 19 16 15 12 11 9 8 8 5 3 3 2 1 1 0

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

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

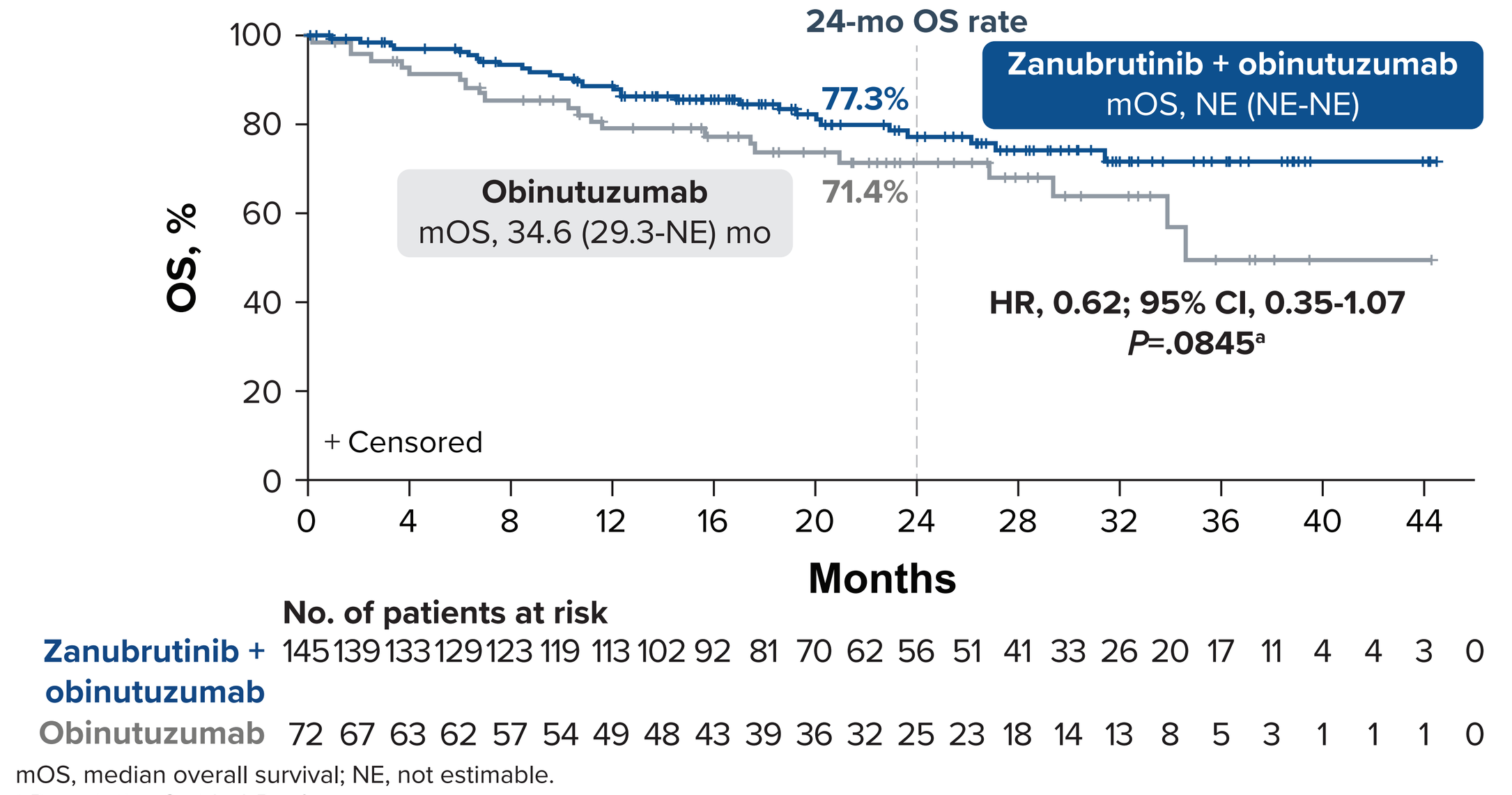
Figure 6. Time to Next Antilymphoma Treatment


Probability, %
Zanubrutinib + obinutuzumab
mTTNT, NE (33.4 mo-NE)
HR, 0.34; 95% CI, 0.22-0.52
P<.0001[a]
Obinutuzumab
mTTNT, 12.2 (8.5-17.3) mo
+ Censored
Months
No. of patients at risk
Zanubrutinib + obinutuzumab 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 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.

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

Figure 7. Overall Survival

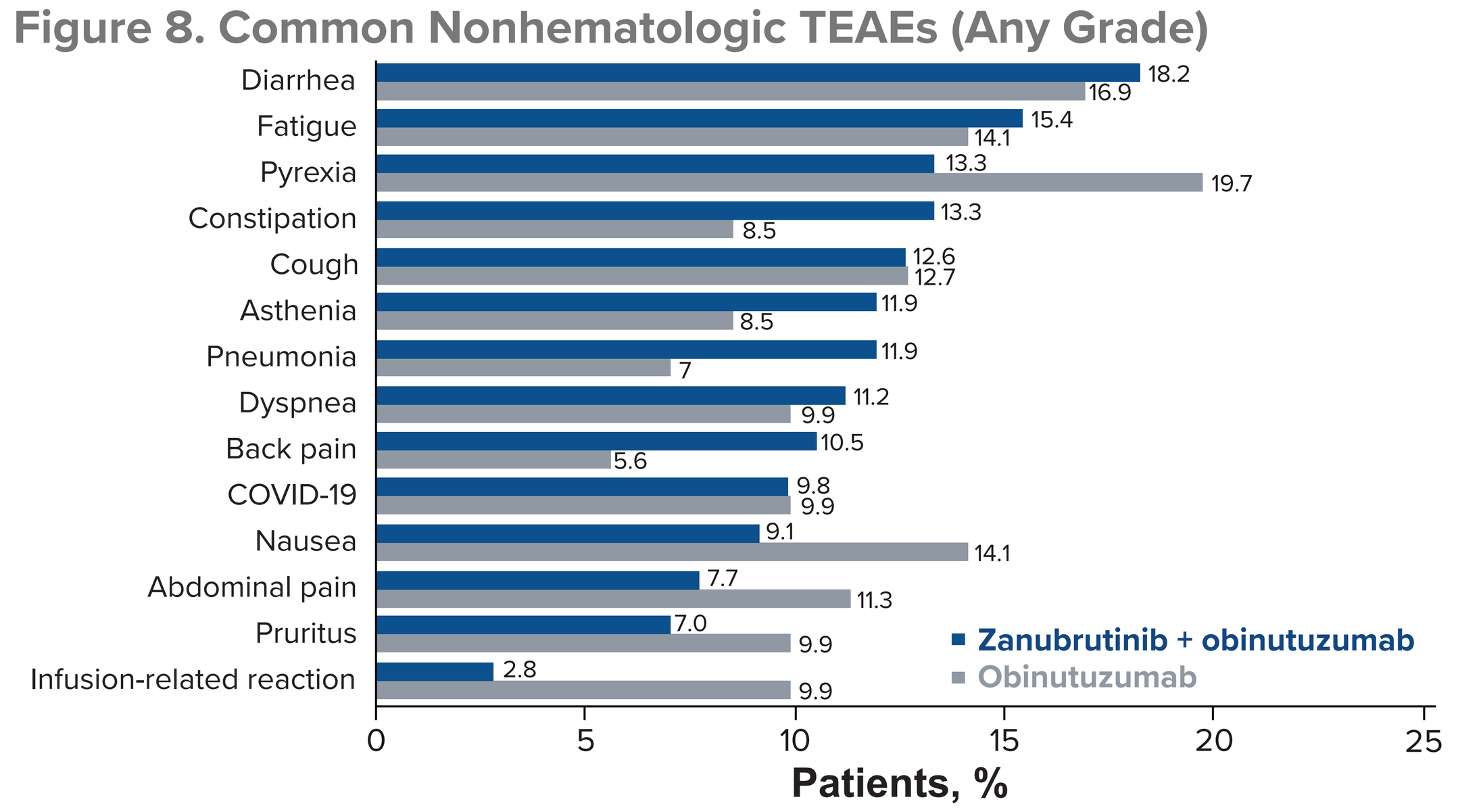

24-mo OS rate
77.3%
71.4%
OS, %
Zanubrutinib + obinutuzumab
mOS, NE (NE-NE)
Obinutuzumab
mOS, 34.6 (29.3-NE) mo
HR, 0.62; 95% CI, 0.35-1.07
P=.0845[a]
+ Censored
Months
No. of patients at risk
Zanubrutinib + obinutuzumab 145 139 133 129 123 119 113 102 92 81 70 62 56 51 41 33 26 20 17 11 4 4 3 0
Obinutuzumab 72 67 63 62 57 54 49 48 43 39 36 32 25 23 18 14 13 8 5 3 1 1 1 0

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)


Diarrhea 18.2 16.9
Fatigue 15.4 14.1
Pyrexia 13.3 19.7
Constipation 13.3 8.5
Cough 12.6 12.7
Asthenia 11.9 8.5
Pneumonia 11.9 7
Dyspnea 11.2 9.9
Back pain 10.5 5.6
COVID-19 9.8 9.9
Nausea 9.1 14.1
Abdominal pain 7.7 11.3
Pruritus 7.0 9.9
Infusion-related reaction 2.8 9.9
Zanubrutinib + obinutuzumab
Obinutuzumab
Patients, %

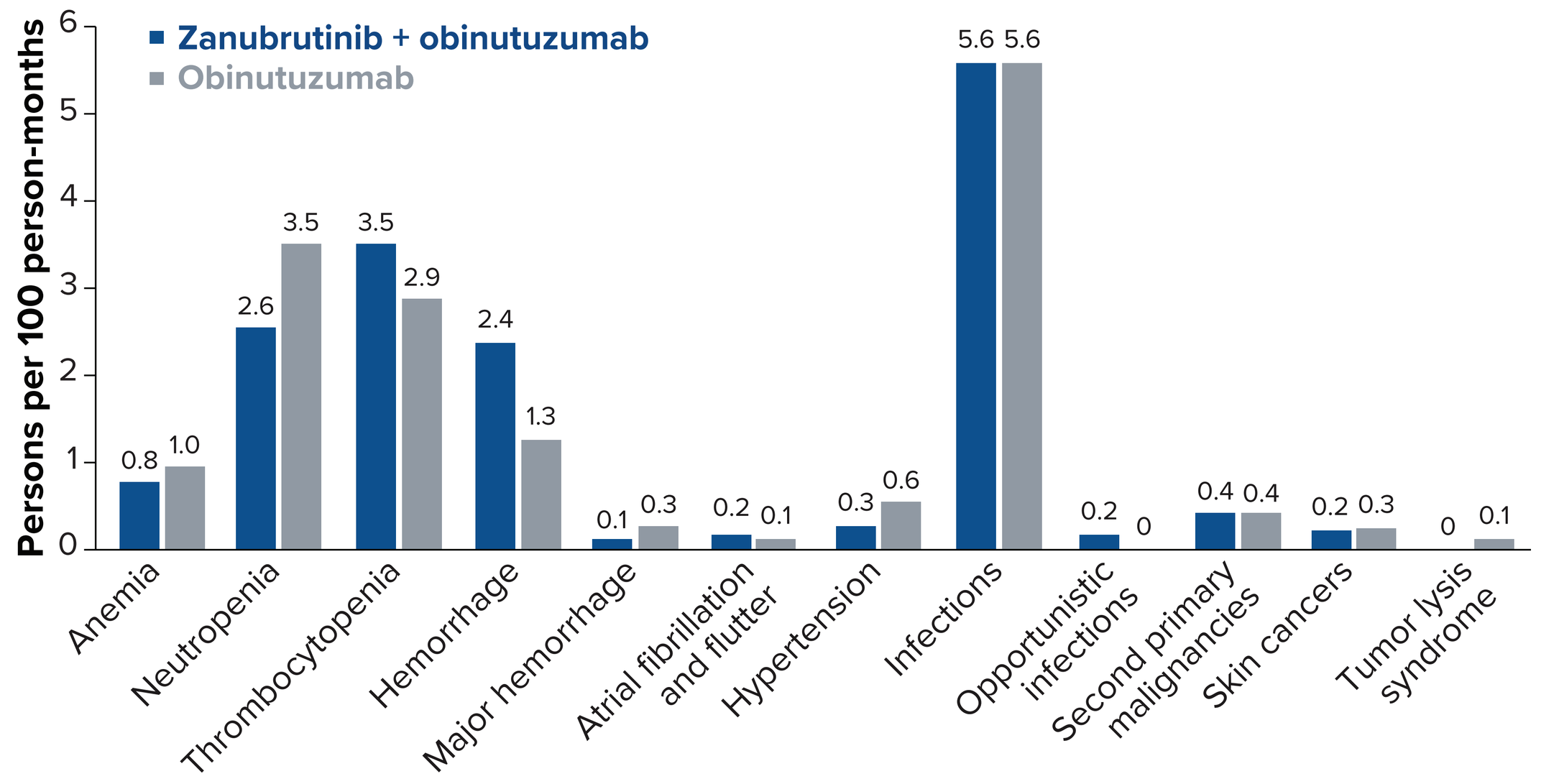
CONCLUSIONS

- 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

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 9. EAIRs for TEAEs of Special Interest


Persons per 100 person-months
Zanubrutinib + obinutuzumab
Obinutuzumab
Anemia 0.8 1.0
Neutropenia 2.6 3.5
Thrombocytopenia 3.5 2.9
Hemorrhage 2.4 1.3
Major hemorrhage 0.1 0.3
Atrial fibrillation and flutter 0.2 0.1
Hypertension 0.3 0.6
Infections 5.6 5.6
Opportunistic infections 0.2 0
Second primary malignancies 0.4 0.4
Skin cancers 0.2 0.3
Tumor lysis syndrome 0 0.1

EAIR, exposure-adjusted incidence rate.

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DISCLOSURES

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