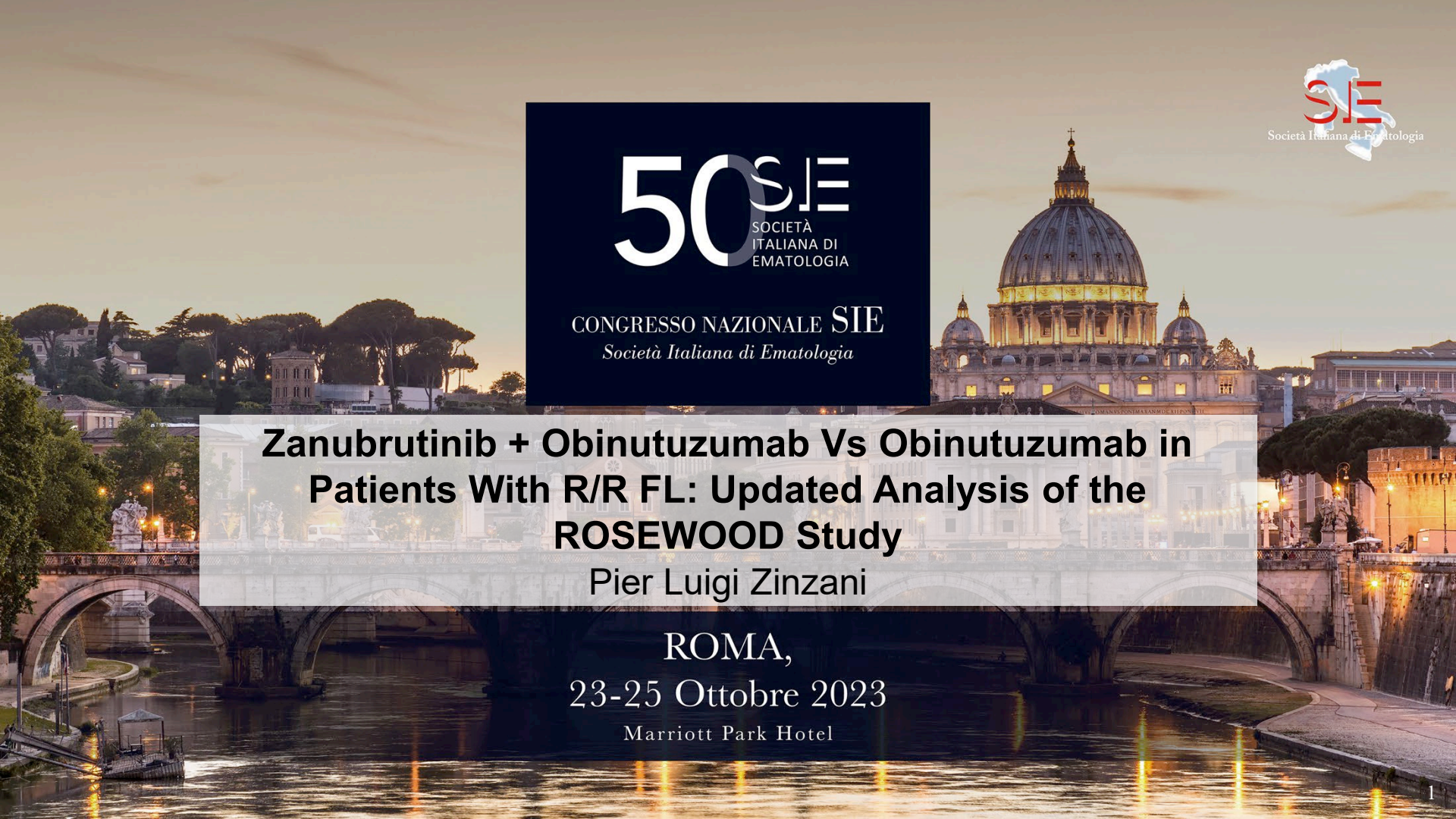

Zanubrutinib + Obinutuzumab Vs Obinutuzumab in Patients With R/R FL: Updated Analysis of the ROSEWOOD Study

Pier Luigi Zinzani

Speaker Disclosures

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Background

- In a phase 1b/2 study that included patients with R/R FL, the combination of zanubrutinib[a] + obinutuzumab was generally well tolerated, with an ORR of 72% and a complete response rate of 39%[1]
- The ROSEWOOD trial (BGB-3111-212; NCT03332017) examined zanubrutinib + obinutuzumab vs obinutuzumab in patients with R/R FL who received ≥2 prior lines of therapy
- At the primary analysis, the trial met its primary endpoint of ORR[2]
  - Zanubrutinib + obinutuzumab, 68.3%
  - Obinutuzumab, 45.8%

} *P*=.0017

Here we report an updated analysis of the ROSEWOOD trial with a median follow-up of 20.2 months

FL, follicular lymphoma; ORR, objective response rate; R/R, relapsed or refractory.

[a] Zanubrutinib monotherapy is approved in the US and EU for the treatment of adult patients with chronic lymphocytic leukemia; marginal zone lymphoma after ≥1 prior anti-CD20–based therapy; Waldenström macroglobulinemia (in EU: after ≥1 prior therapy, or as first-line treatment if unsuitable for chemoimmunotherapy); and mantle cell lymphoma after ≥1 prior therapy (US only).

1. Tam CS, et al. *Blood Adv*. 2020;4(19):4802-4811; 2. Zinzani PL, et al. ASCO 2022. Abstract 7510.

ROSEWOOD study design

Key eligibility criteria
- Age ≥18 years
- 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 of 0-2
- Adequate organ function
- No prior BTK inhibitor

127 sites; 17 countries/regions
Randomized November 2017 to June 2021

Arm A
Zanubrutinib[a] + obinutuzumab[b] (n=145)
Until PD or unacceptable toxicity

Randomization 2:1
Stratification factors
- Number of prior lines of treatment
- Rituximab-refractory status
- Geographic region

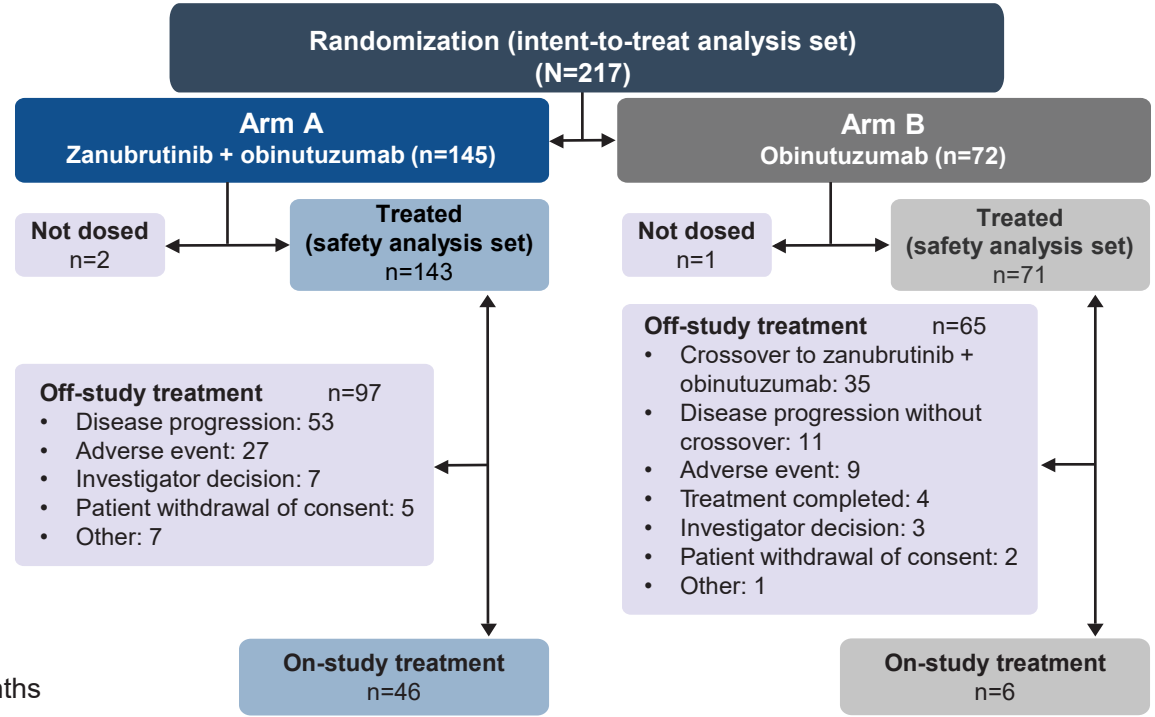
Arm B
Obinutuzumab[b] (n=72)
Option to cross over to combination if PD is centrally confirmed or if there is no response at 12 months

Primary endpoint
- ORR by IRC according to Lugano 2014 classification[1]

Other endpoints
- DOR by IRC[c]
- PFS by IRC[c]
- OS[c]
- TTNT
- Safety (AEs)[c]

AE, adverse event; BTK, Bruton tyrosine kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; IRC, independent review committee; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; R/R, relapsed or refractory; TTNT, time to next treatment.
[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 2-6, and then every 8 weeks up to a maximum of 20 doses. [c] Secondary endpoint.
1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3068.

One-third of patients were still receiving zanubrutinib + obinutuzumab at the time of this updated analysis



Median follow-up, 20.2 months

The study population was heavily pretreated and had refractory disease

Characteristics	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)
Age, median (range), years	63.0 (31-84)	65.5 (32-88)
ECOG PS of ≥1, n (%)	59 (40.6)	41 (57.0)
FLIPI score of ≥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 (%)		
Chemoimmunotherapy	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; PD, progressive disease; ULN, upper limit of normal.

Median treatment exposure for zanubrutinib + obinutuzumab was twice that for obinutuzumab alone

Zanubrutinib + obinutuzumab

- Median 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)

Obinutuzumab

- Median exposure was 6.5 months (range, 0.1-28.7 months)
  - Median number of infusions was 9 (range, 3-20)

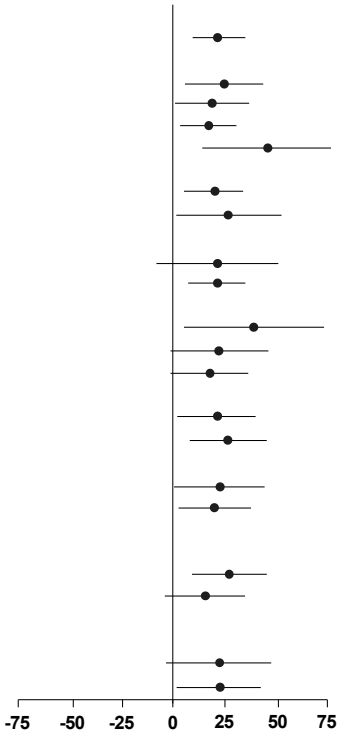
ORR difference by IRC was 22.7% in favor of zanubrutinib + obinutuzumab at the median study follow-up of 20.2 months

Endpoint	Zanubrutinib + obinutuzumab (n=145)	Obinutuzumab (n=72)	2-sided *P* value
ORR by IRC[a] (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), months	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), months	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)	–

CR, complete response; DOCR, duration of CR; DOR, duration of response; IRC, independent review committee; NE, not estimable; ORR, objective response rate; PR, partial response.
[a] ORR difference by IRC was 22.7%; 95% CI, 9.0%-36.5%.

Zanubrutinib + obinutuzumab showed consistent benefit over obinutuzumab across prespecified subgroups

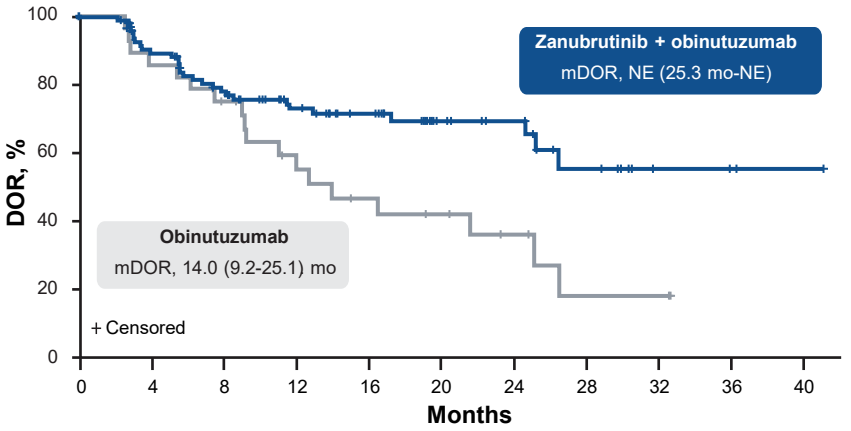
Subgroups	Response/patients		Risk difference (95% CI), %
	Obinutuzumab	Zanubrutinib + obinutuzumab	
All patients in ITT	33/72	100/145	22.7 (9.0-36.5)
Age, years			
<65	14/32	58/83	26.1 (6.3-45.9)
≥65	19/40	42/62	20.2 (0.9-39.6)
<75	30/60	89/130	18.5 (3.5-33.4)
≥75	3/12	11/15	48.3 (15.2-81.5)
No. of prior 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 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 ≥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 ≥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.

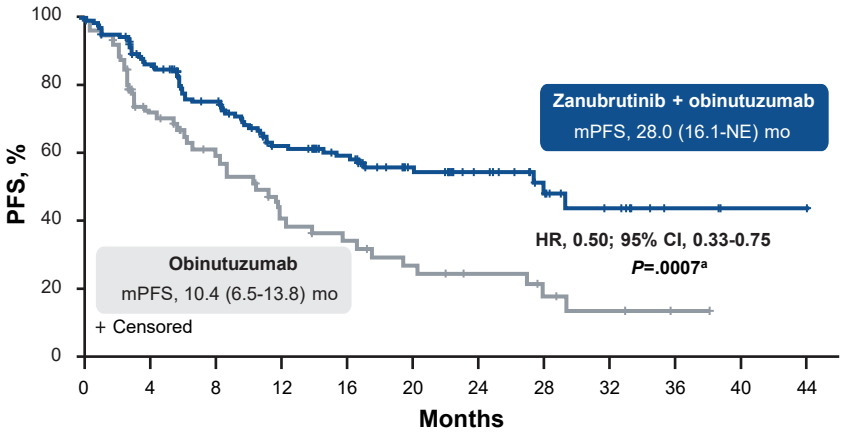
DOR and PFS were longer with zanubrutinib + obinutuzumab

DOR by IRC



No. at risk																					
Zanubrutinib + obinutuzumab	100	97	82	73	68	59	51	43	40	33	23	21	19	12	10	7	3	3	2	1	1	0
Obinutuzumab	33	29	24	23	20	16	13	11	10	9	8	6	5	3	2	2	2	0				

PFS by IRC

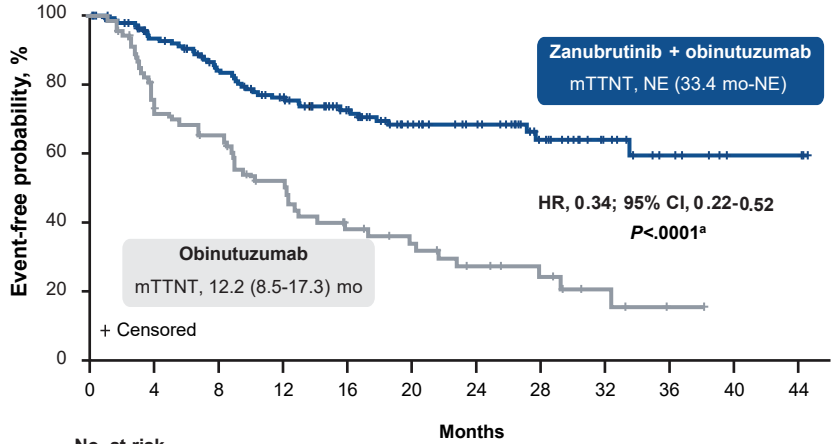


No. at risk																					
Zanubrutinib + obinutuzumab	145	135	116	96	92	79	67	62	56	45	38	35	25	22	15	10	9	5	3	3	1	1	0
Obinutuzumab	72	63	42	34	30	27	19	16	15	12	11	9	8	8	5	3	3	2	1	1	0		

HR, hazard ratio; IRC, independent review committee; mDOR, median duration of response; mPFS, median progression-free survival; NE, not estimable.
[a] Descriptive 2-sided *P* value.

TTNT and OS were prolonged with zanubrutinib + obinutuzumab

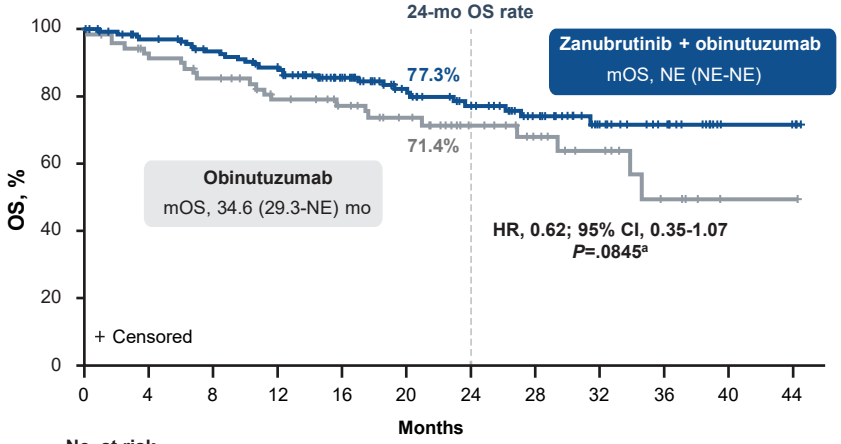
TTNT



No. 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			

OS



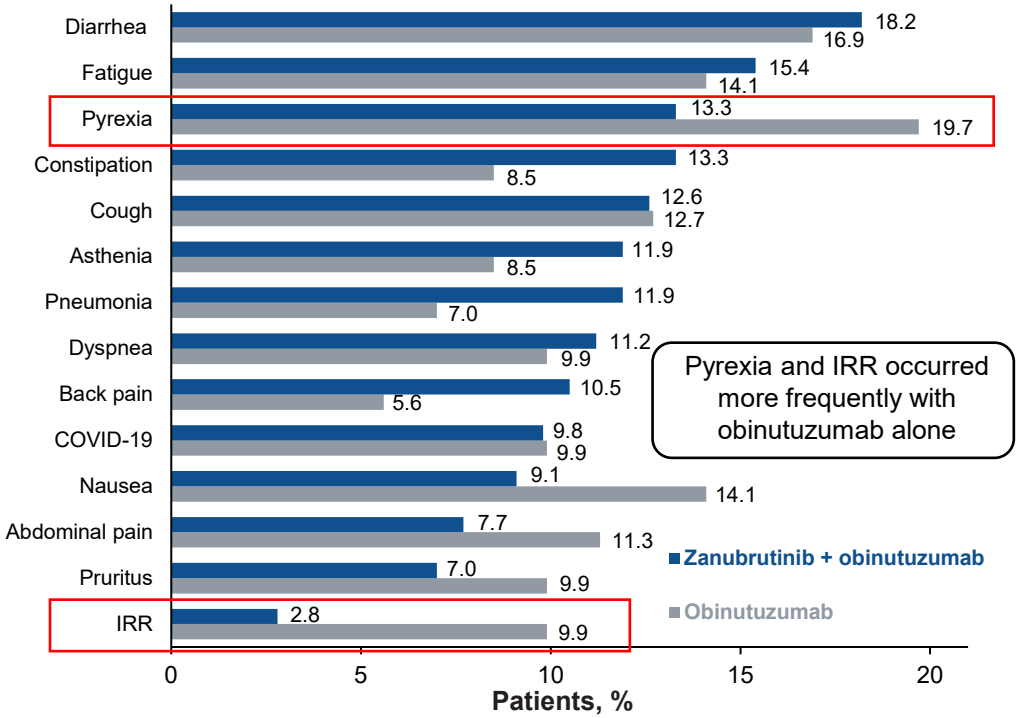
No. at risk

	145	139	133	129	123	119	113	102	92	81	70	62	56	51	41	33	26	20	17	11	4	4	3	0
	72	67	63	62	57	54	49	48	43	39	36	32	25	23	18	14	13	8	5	3	1	1	1	0

HR, hazard ratio; mOS, median overall survival; mTTNT, median time to next treatment; NE, not estimable.
[a] Descriptive 2-sided *P* value.

There were no unexpected safety findings with zanubrutinib + obinutuzumab

Common nonhematologic TEAEs (any grade)



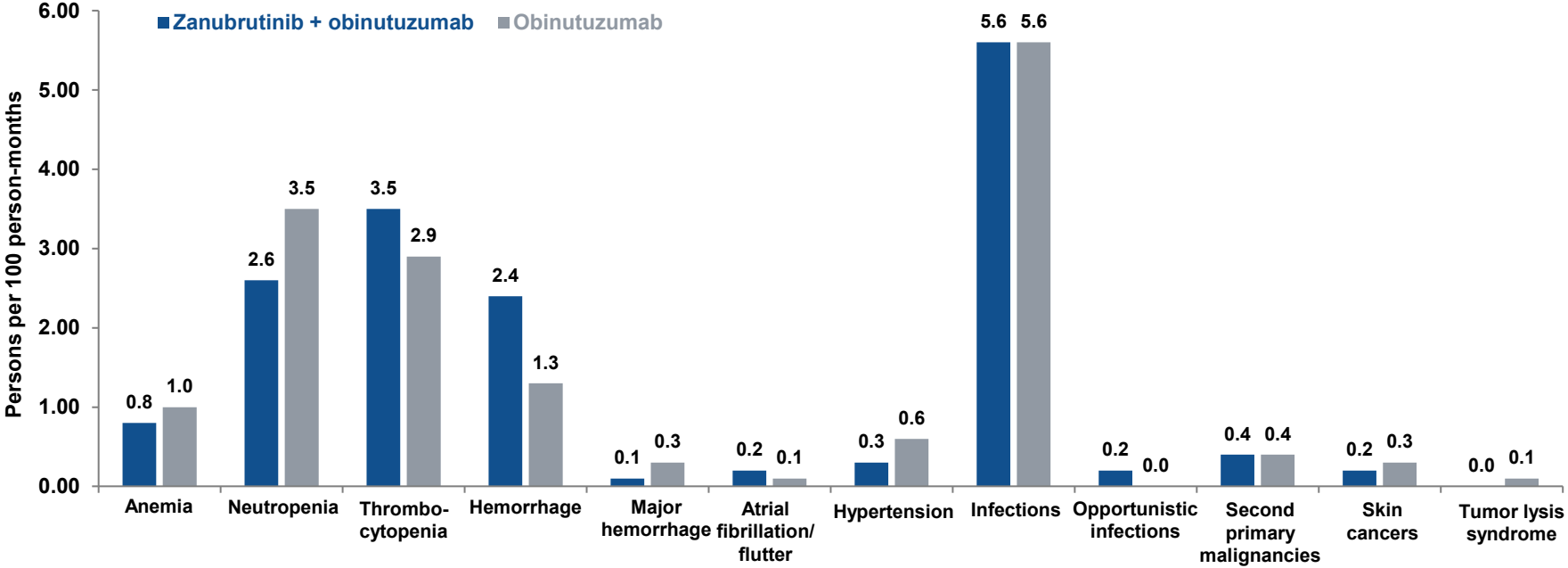
Grade ≥3 nonhematologic TEAEs

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
IRR	1 (0.7)	3 (4.2)
Hypertension	1 (0.7)	1 (1.4)

IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

EAIRs for TEAEs of special interest were similar in both arms, except for any grade hemorrhage

EAIRs for TEAEs of special interest



EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

Conclusions

- In the ROSEWOOD study, zanubrutinib + 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 + obinutuzumab vs obinutuzumab alone
  - A consistent benefit was observed across key prespecified subgroups
- Zanubrutinib + obinutuzumab demonstrated 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 + obinutuzumab in patients who previously received ≥1 line of systemic therapy is now underway (MAHOGANY; NCT05100862)

FL, follicular lymphoma; PFS, progression-free survival; R/R, relapsed or refractory; TTNT, time to next treatment.

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