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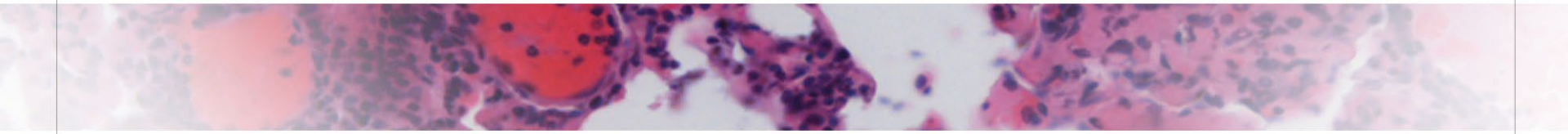


Final Analysis of the Randomized Phase 2 ROSEWOOD Study of Zanubrutinib + Obinutuzumab vs Obinutuzumab Monotherapy in Patients With Relapsed/Refractory Follicular Lymphoma

Pier Luigi Zinzani,[1] Jiří Mayer,[2] Christopher R. Flowers,[3] Fontanet Bijou,[4] Ana C. De Oliveira,[5] Yuqin Song,[6] Qingyuan Zhang,[7] Marco Brociner,[8] Krimo Bouabdallah,[9] Peter S. Ganly,[10] Huilai Zhang,[11] Sam Yuen,[12] Marek Trněný,[13] Rebecca Auer,[14] Sha Huang,[15] Jiayi Shen,[16] Jamie Hirata,[16] Judith Trotman[17]

[1]Institute of Hematology "Seràgnoli," University of Bologna, Bologna, Italy; [2]Masaryk University and University Hospital, Brno, Czech Republic; [3]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Institut Bergonié, Bordeaux, France; [5]Institut Català d'Oncologia (ICO) - Hospital Duran i Reynals, Barcelona, Spain; [6]Peking University Cancer Hospital and Institute, Beijing, China; [7]Harbin Medical University Cancer Hospital, Harbin, China; [8]Hematology, University Hospital "Ospedale di Circolo e Fondazione Macchi" - ASST Sette Laghi, University of Insubria, Varese, Italy; [9]Hôpital Haut-Lévêque, CHU Bordeaux, Pessac, France; [10]Department of Haematology, Christchurch Hospital, Christchurch, New Zealand; [11]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [12]Calvary Mater Newcastle, Waratah, NSW, Australia; [13]Charles University, General Hospital, Prague, Czech Republic; [14]St Bartholomew's Hospital, Barts Health NHS Trust, London, UK; [15]BeOne Medicines, Ltd, Shanghai, China; [16]BeOne Medicines, Ltd, San Carlos, CA, USA; [17]Department of Hematology, Concord Repatriation General Hospital, Sydney, NSW, Australia

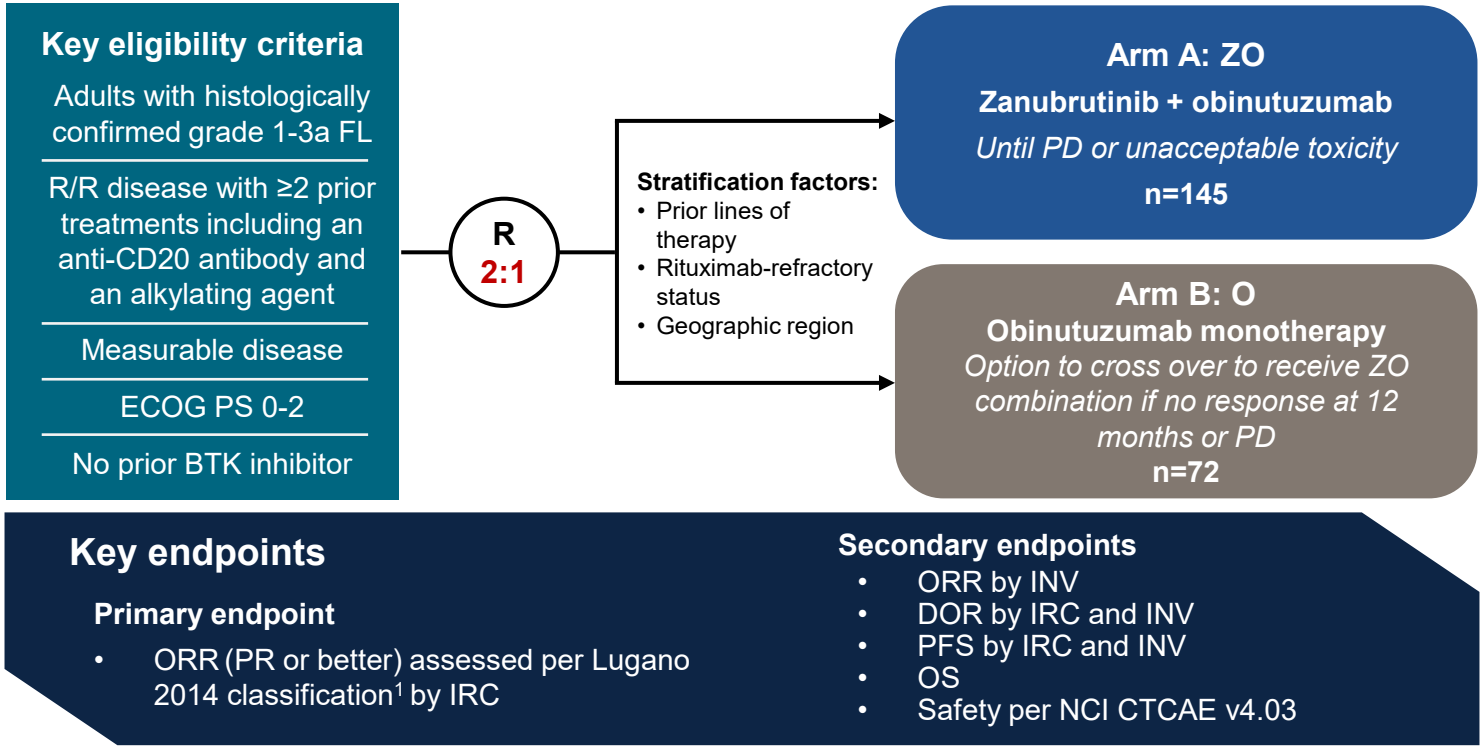
Introduction

- Treatment advances have improved outcomes in FL; however, many patients experience multiple relapses, highlighting a need for new therapies[1]
- Zanubrutinib, a potent and selective, next-generation BTK inhibitor designed for complete and sustained BTK occupancy, is approved in multiple countries for various B-cell malignancies[2-4]
- ROSEWOOD (NCT03332017) is a phase 2 study of zanubrutinib and obinutuzumab (ZO) combination therapy vs obinutuzumab monotherapy (O) in patients with R/R FL who had received ≥2 prior lines of therapy[5]
- A previous analysis (median follow-up of 20.2 months) showed a significantly improved ORR per independent review committee (IRC) with ZO vs O[5]
- Here, we report the final analysis of ROSEWOOD with a median follow-up of 34.6 months

BTK, Bruton tyrosine kinase; FL, follicular lymphoma; IRC, independent review committee; O, obinutuzumab monotherapy; ORR, overall response rate; R/R, relapsed/refractory; ZO, zanubrutinib + obinutuzumab.

1. Ghione P, et al. *Haematologica.* 2023;108(3):822-832; 2. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940; 3. Brukinsa (zanubrutinib). Prescribing information. BeOne Medicines, Ltd; 2023; 4. Brukinsa (zanubrutinib). Summary of product characteristics. BeOne Medicines, Ltd; 2024; 5. Zinzani PL, et al. *J Clin Oncol.* 2023;41(33):5107-5117.

ROSEWOOD: A Global, Randomized, Open-Label, Phase 2 Study



BTK, Bruton tyrosine kinase; CD, cluster of differentiation; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; INV, investigator; IRC, independent review committee; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; R, randomized; R/R, relapsed/refractory; ZO, zanubrutinib + obinutuzumab.

1. Cheson BD, et al. *J Clin Oncol.* 2014;32(27):3059-3068.

Baseline Characteristics

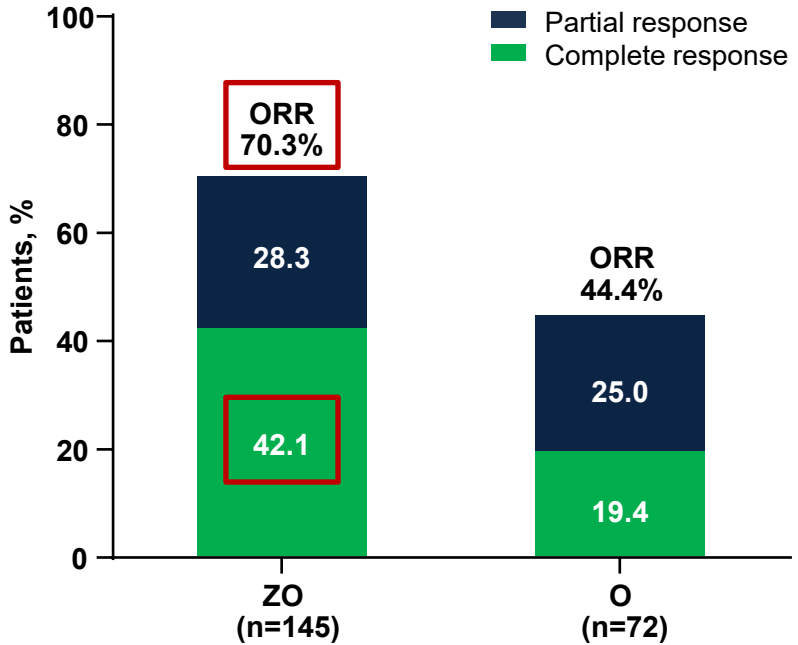
- 217 patients from 127 sites in 17 countries/regions were randomized between November 2017 and June 2021
  - 214 received treatment with ZO (n=143) or O (n=71)
- As of December 31, 2024, median study follow-up was 34.6 months (range, 0.1-69.7 months)

Characteristic	ZO n=145	O n=72
Age, median (range), years	63.0 (31-84)	65.5 (32-88)
Male, n (%)	75 (51.7)	33 (45.8)
Race, n (%)		
White	92 (63.4)	47 (65.3)
Asian	30 (20.7)	17 (23.6)
Not reported	23 (15.9)	8 (11.1)
ECOG PS ≥1, n (%)	59 (40.6)	41 (57.0)
High 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)
Bone marrow involvement at screening, n (%)	39 (26.9)	26 (36.1)
High tumor burden per GELF criteria, n (%)	83 (57.2)	40 (55.6)
High LDH level (>ULN), n (%)	49 (33.8)	29 (40.3)

Characteristic	ZO n=145	O n=72
No. of lines of prior therapy, median (range)	3 (2-11)	3 (2-9)
2-3, n (%)	104 (71.7)	54 (75.0)
>3, n (%)	41 (28.3)	18 (25.0)
Refractory to rituximab, n (%)	78 (53.8)	36 (50.0)
Refractory to most recent line of therapy, n (%)	47 (32.4)	29 (40.3)
POD24, n (%)	51 (35.2)	30 (41.7)
Prior therapy, n (%)		
Anti-CD20 mAb	145 (100)	72 (100)
Prior immunochemotherapy	143 (98.6)	71 (98.6)
Cyclophosphamide	136 (93.8)	68 (94.4)
Anthracyclines	118 (81.4)	57 (79.2)
Bendamustine	79 (54.5)	40 (55.6)
Prior stem cell transplant	32 (22.1)	13 (18.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; FLIPI, Follicular Lymphoma International Prognostic Index; GELF, Groupe d'Etude des Lymphomes Folliculaires; LDH, lactate dehydrogenase; mAb, monoclonal antibody; O, obinutuzumab; POD24, progression of disease ≤24 months after starting frontline therapy; ULN, upper limit of normal; ZO, zanubrutinib + obinutuzumab.

ORR per IRC With ZO Was Higher Compared With O



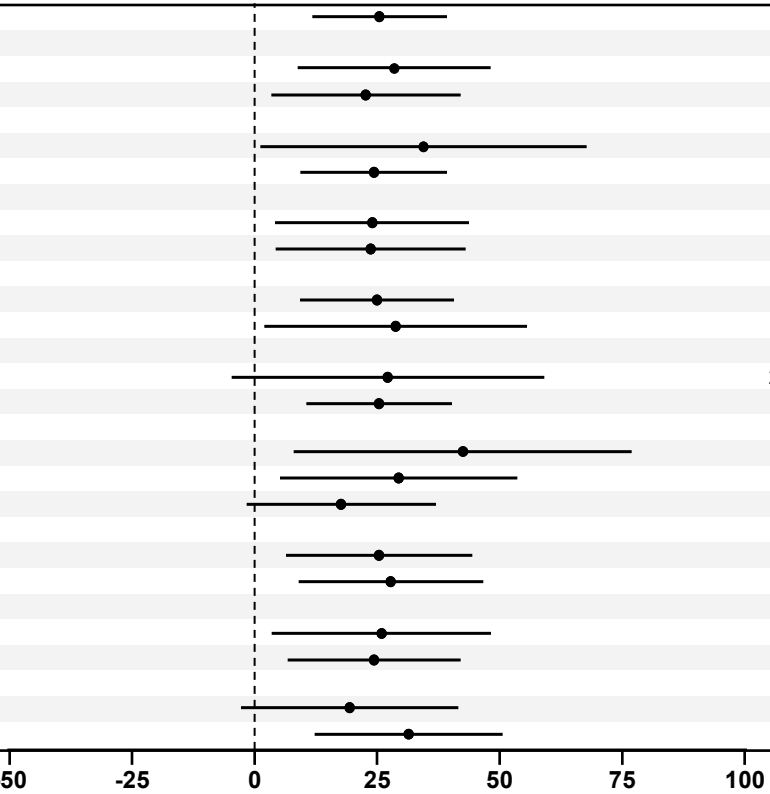
- ORRs per INV were similar to ORRs per IRC (ZO, 68.3%; O, 43.1%)

	ZO (n=145)	O (n=72)
Overall response rate, n (%)	102 (**70.3**)	32 (**44.4**)
95% CI	62.2-77.6	32.7-56.6
Risk difference (95% CI), %	25.5 (11.8-39.3)	
2-sided *P* value[a]	.0003	
Complete response rate, n (%)	61 (**42.1**)	14 (**19.4**)
95% CI	33.9-50.5	11.1-30.5
2-sided *P* value[a]	.0009	
Other responses, n (%)		
Stable disease	21 (14.5)	14 (19.4)
Indeterminate due to zanubrutinib hold	1 (0.7)	0
Non-progressive disease[b]	6 (4.1)	9 (12.5)
Progressive disease	13 (9.0)	16 (22.2)
Discontinued prior to first assessment/NE	2 (1.4)	1 (1.4)

[a]*P* value is descriptive. [b]Defined as PET assessment missing or not evaluable, and CT assessment showed no progressive disease.
CT, computed tomography; INV, investigator; IRC, independent review committee; O, obinutuzumab; ORR, overall response rate; PET, positron emission tomography; ZO, zanubrutinib + obinutuzumab.

ORR Benefit With ZO Over O Consistent Across Subgroups

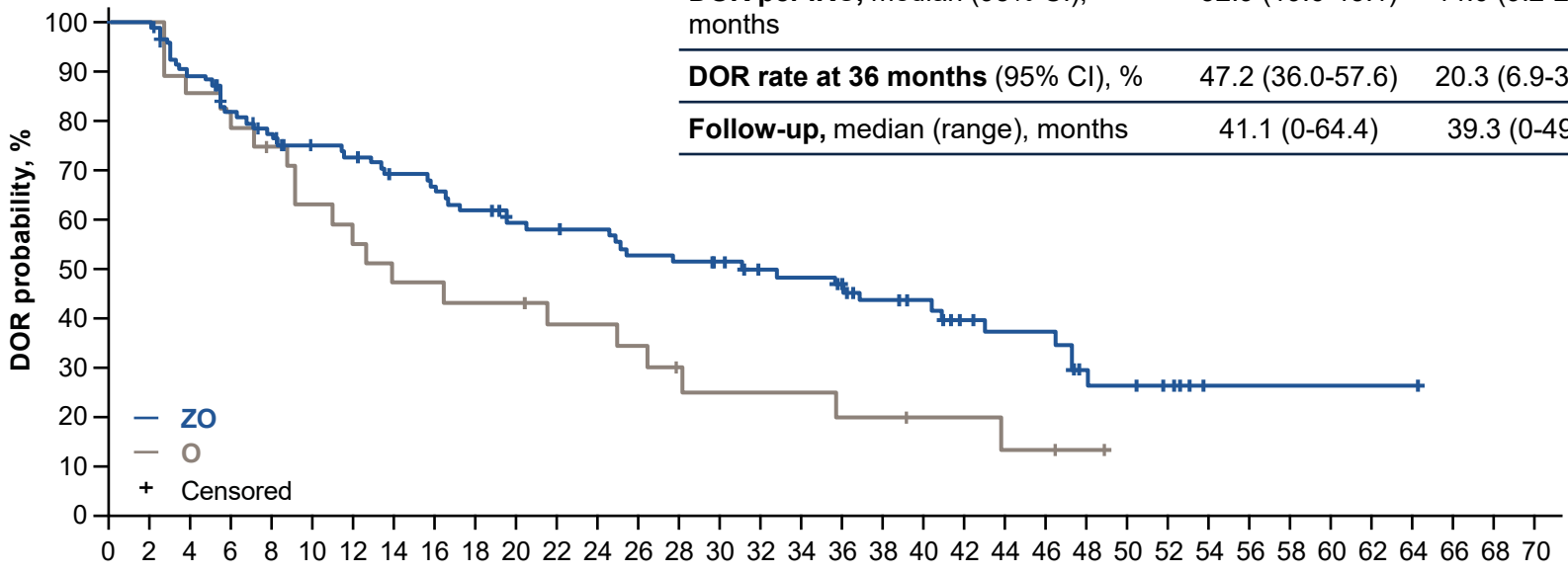
Subgroup	Responders/Patients O	Responders/Patients ZO	Risk difference (95% CI), %
All patients	32/72	102/145	25.5 (11.8-39.3)
Age, years			
<65	14/32	60/83	28.5 (8.8-48.2)
≥65	18/40	42/62	22.7 (3.4-42.1)
Geographic region			
China	5/12	16/21	34.5 (1.2-67.8)
Ex-China	27/60	86/124	24.4 (9.4-39.3)
Baseline ECOG PS			
0	16/31	65/86	24.0 (4.2-43.8)
≥1	16/41	37/59	23.7 (4.3-43.1)
No. of prior lines of therapy			
2-3	26/54	79/108	25.0 (9.3-40.7)
>3	6/18	23/37	28.8 (2.0-55.6)
Bulky disease (≥7 cm)			
Yes	3/12	12/23	27.2 (-4.7 to 59.1)
No	29/60	90/122	25.4 (10.6-40.3)
FLIPI risk category			
Low (0-1)	3/9	22/29	42.5 (8.0-77.0)
Intermediate (2)	12/24	27/34	29.4 (5.2-53.6)
High (≥3)	17/37	49/77	17.7 (-1.6 to 37.0)
Refractory to rituximab			
Yes	13/36	48/78	25.4 (6.4-44.5)
No	19/36	54/67	27.8 (9.0-46.7)
Refractory to most recent line of therapy			
Yes	11/29	30/47	25.9 (3.5-48.3)
No	20/42	67/93	24.4 (6.8-42.1)
POD24 (PD ≤24 months after starting frontline therapy)			
Yes	13/30	32/51	19.4 (-2.7 to 41.6)
No	15/35	55/74	31.5 (12.3-50.6)



FLIPI, Follicular Lymphoma International Prognostic Index; O, obinutuzumab; PD, progressive disease; ZO, zanubrutinib + obinutuzumab.

Duration of Response Was Longer in the ZO Arm

	ZO	O
DOR per IRC, median (95% CI), months	32.9 (19.6-43.1)	14.0 (9.2-26.5)
DOR rate at 36 months (95% CI), %	47.2 (36.0-57.6)	20.3 (6.9-38.6)
Follow-up, median (range), months	41.1 (0-64.4)	39.3 (0-49.0)



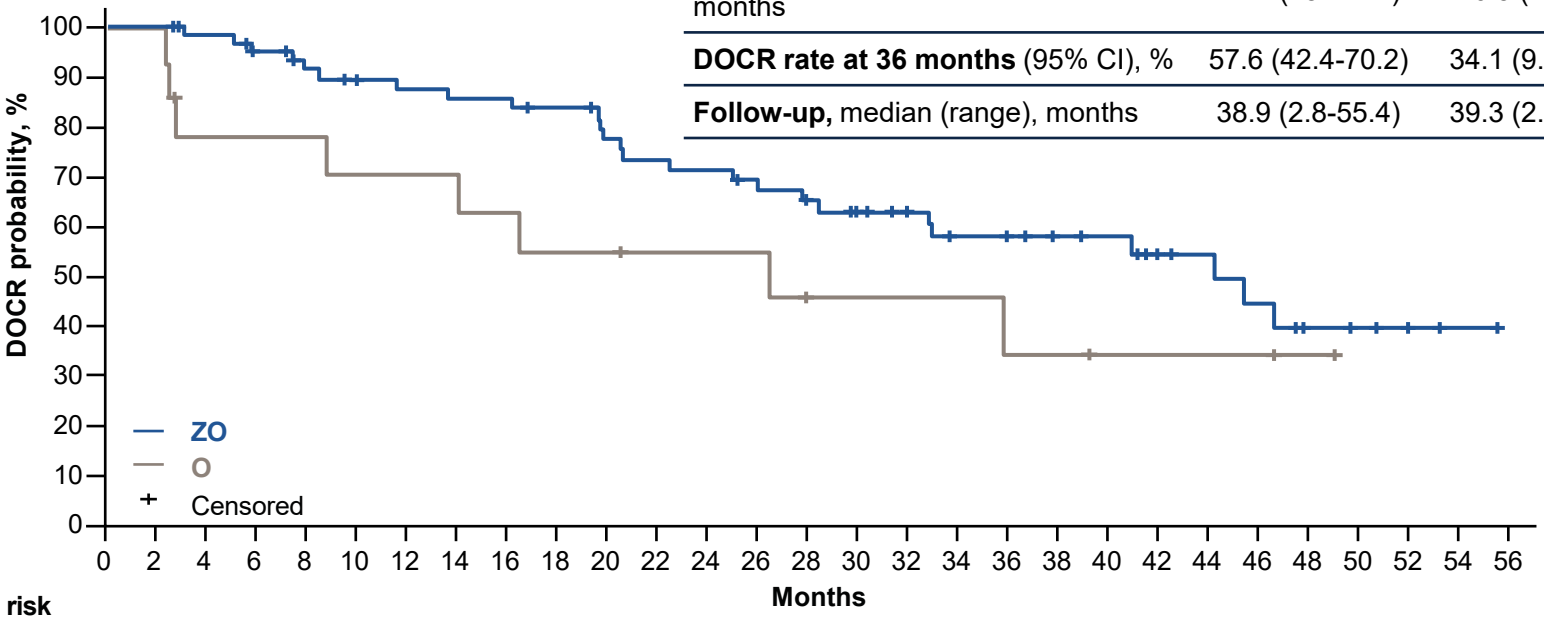
No. at risk

ZO	102	100	85	75	69	64	62	57	55	51	46	45	44	40	39	37	33	32	30	25	23	17	15	15	9	8	6	1	1	1	1	1	1	0
O	32	29	24	23	20	16	14	12	12	11	11	9	9	8	6	5	5	5	4	4	3	3	2	2	1	0								

DOR, duration of response; IRC, independent review committee; O, obinutuzumab; ZO, zanubrutinib + obinutuzumab.

Complete Responses Were Durable

	ZO	O
DOCR per IRC, median (95% CI), months	44.2 (28.4-NE)	26.5 (2.7-NE)
DOCR rate at 36 months (95% CI), %	57.6 (42.4-70.2)	34.1 (9.7-60.9)
Follow-up, median (range), months	38.9 (2.8-55.4)	39.3 (2.4-49.0)



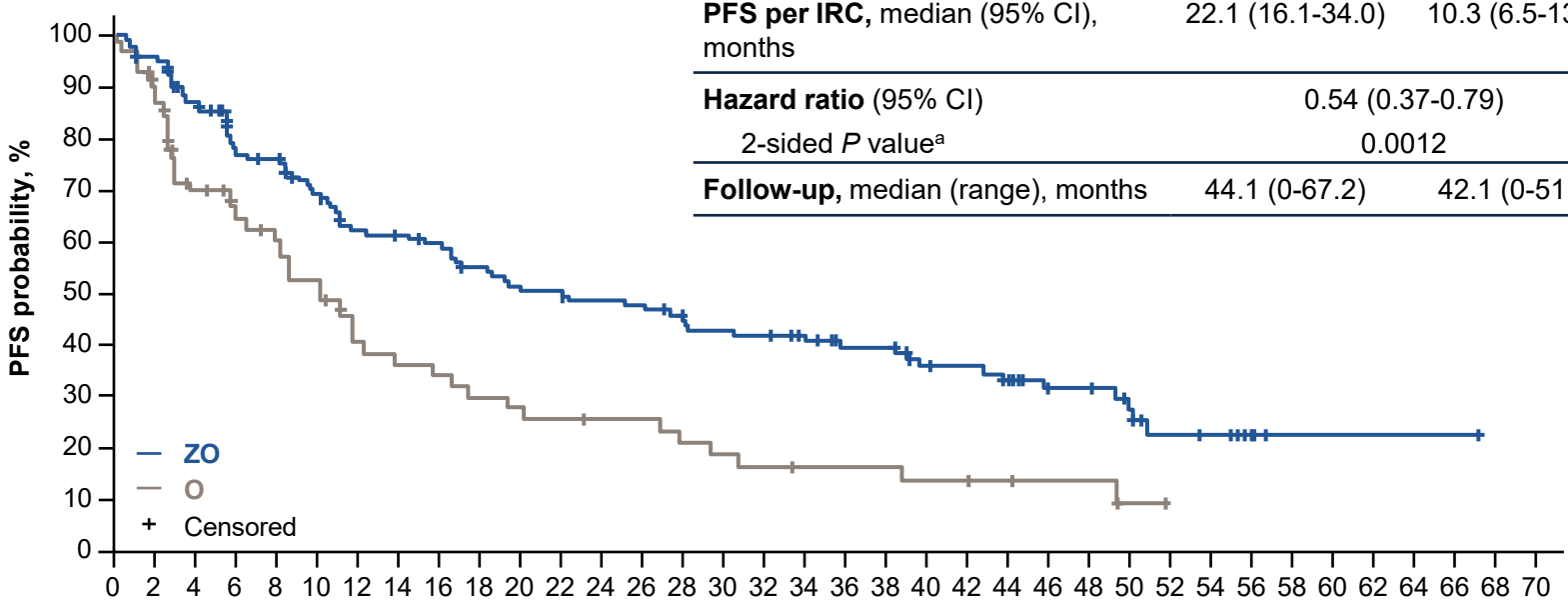
No. at risk

ZO	61	61	58	53	49	46	45	44	44	42	38	36	35	32	30	27	24	21	20	18	17	12	11	9	6	5	3	1	0
O	14	14	10	10	10	9	9	8	8	7	7	6	6	6	4	4	4	4	3	3	2	2	2	2	1	0			

DOCR, duration of complete response; IRC, independent review committee; O, obinutuzumab; NE, not estimable; ZO, zanubrutinib + obinutuzumab.

PFS per IRC Was Longer in the ZO Arm

	ZO	O
PFS per IRC, median (95% CI), months	22.1 (16.1-34.0)	10.3 (6.5-13.8)
Hazard ratio (95% CI)	0.54 (0.37-0.79)	
2-sided *P* value[a]	0.0012	
Follow-up, median (range), months	44.1 (0-67.2)	42.1 (0-51.8)



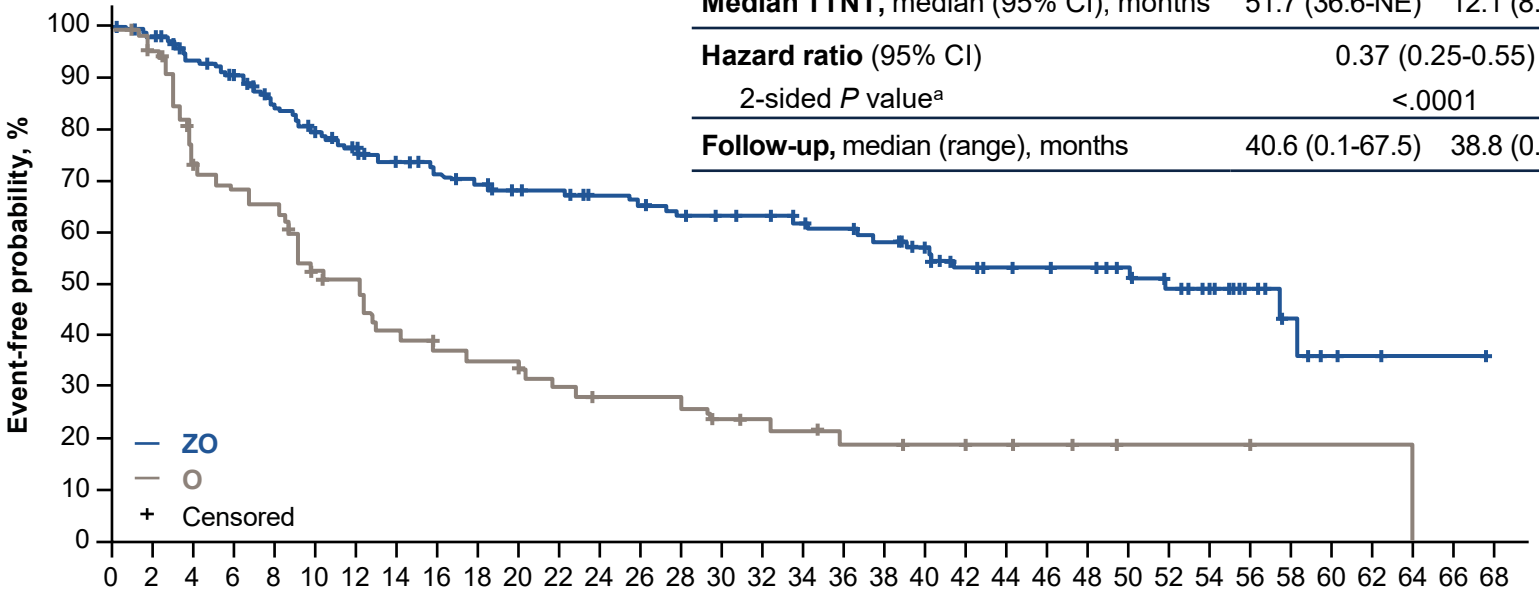
No. at risk

ZO	145	135	117	95	93	80	70	68	65	59	55	54	51	50	44	43	42	39	34	34	28	27	24	17	17	13	8	7	3	1	1	1	1	1	0
O	72	61	41	35	31	27	19	17	16	14	13	12	11	11	9	8	7	6	6	6	5	5	4	3	3	1	0								

[a]*P* value is descriptive.
IRC, independent review committee; O, obinutuzumab; PFS, progression-free survival; ZO, zanubrutinib + obinutuzumab.

Time to New Anticancer Therapy Was Longer in the ZO Arm vs the O Arm

	ZO	O
Median TTNT, median (95% CI), months	51.7 (36.6-NE)	12.1 (8.3-15.9)
Hazard ratio (95% CI)	0.37 (0.25-0.55)	
2-sided *P* value[a]	<.0001	
Follow-up, median (range), months	40.6 (0.1-67.5)	38.8 (0.1-63.9)



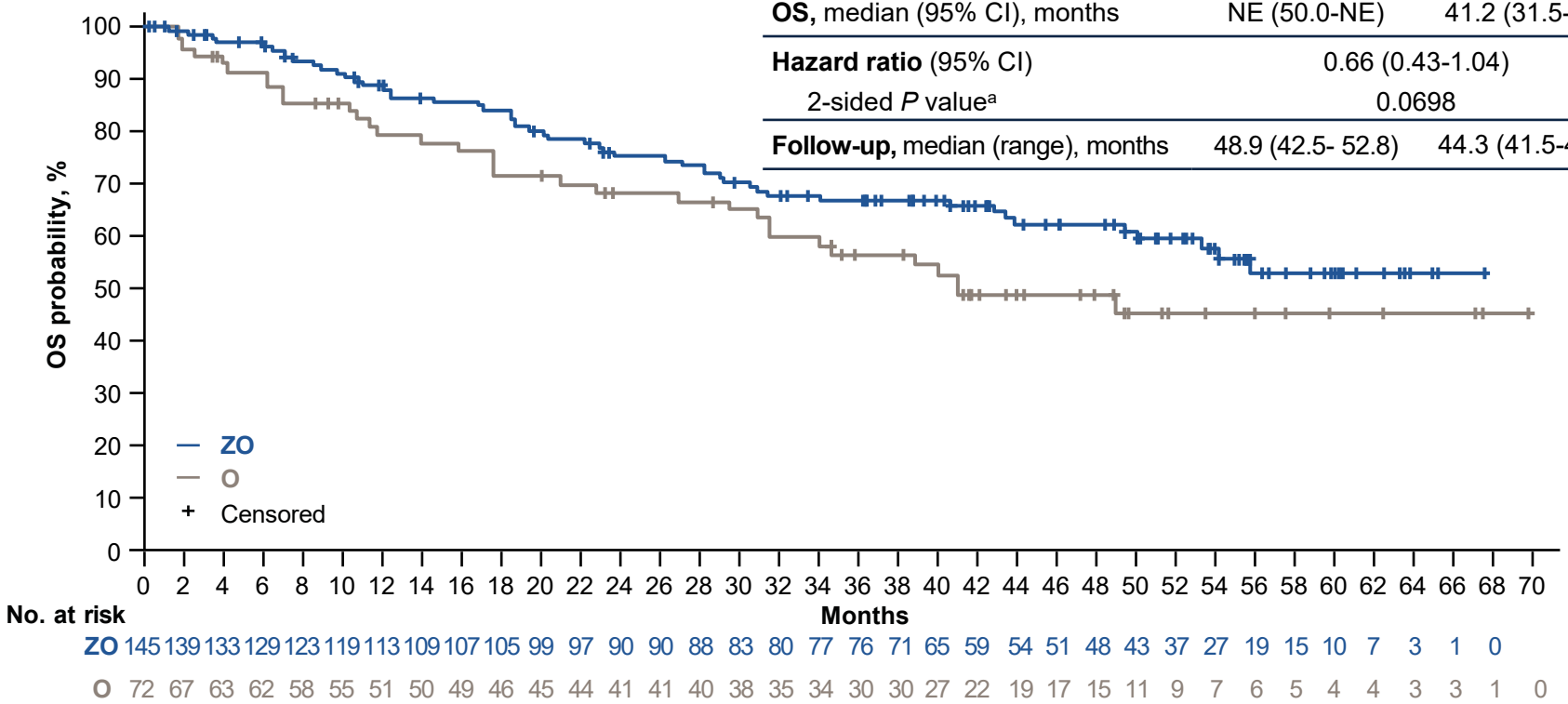
No. at risk

ZO	145	137	126	118	107	99	91	84	80	76	71	70	66	64	61	58	57	54	52	49	43	37	34	33	31	27	22	16	11	6	3	2	1	1	0
O	72	65	49	44	42	32	30	24	21	20	18	16	14	14	13	11	10	9	7	7	6	6	5	4	3	2	2	2	1	1	1	1	0		

[a]*P* value is descriptive.
TTNT, time to new anticancer therapy or crossover; NE, not estimable; O, obinutuzumab; ZO, zanubrutinib + obinutuzumab.

Overall Survival

	ZO	O
OS, median (95% CI), months	NE (50.0-NE)	41.2 (31.5-NE)
Hazard ratio (95% CI)	0.66 (0.43-1.04)	
2-sided *P* value[a]	0.0698	
Follow-up, median (range), months	48.9 (42.5- 52.8)	44.3 (41.5-49.6)



[a]*P* value is descriptive.

NE, not estimable; O, obinutuzumab; OS, overall survival; ZO, zanubrutinib + obinutuzumab.

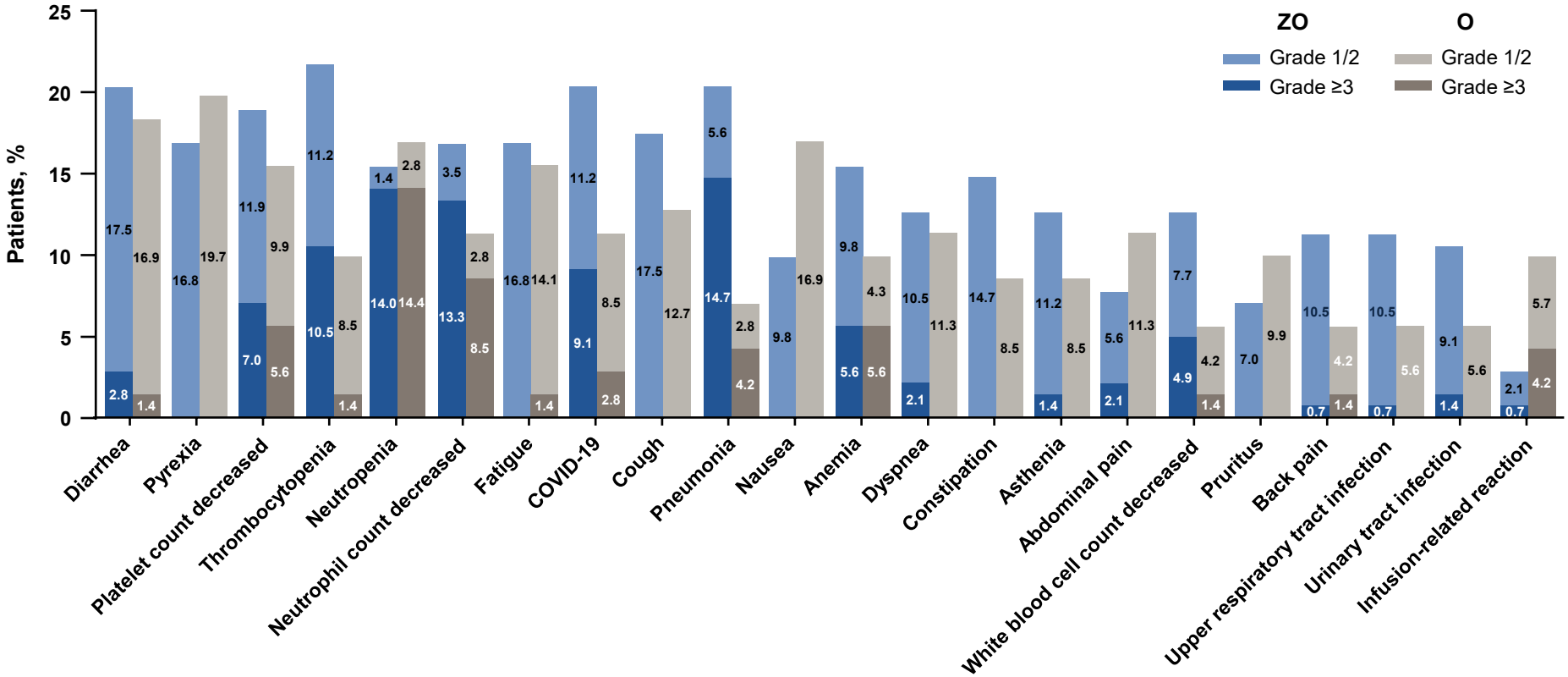
Safety Summary

- With a longer median duration of exposure (ZO, 12.4 months; O, 6.5 months), the incidence of TEAEs and treatment-related TEAEs was generally higher in the ZO arm vs the O arm

n (%)	ZO n=143	O n=71
Any TEAE	137 (95.8)	65 (91.5)
Any treatment-related TEAE	110 (76.9)	49 (69.0)
Grade ≥3	103 (72.0)	34 (47.9)
Treatment-related grade ≥3	62 (43.4)	19 (26.8)
Serious	75 (52.4)	22 (31.0)
Treatment-related serious	29 (20.3)	8 (11.3)
Leading to death	15 (10.5)	7 (9.9)
Treatment-related leading to death	2 (1.4)	1 (1.4)
Leading to treatment discontinuation	31 (21.7)	9 (12.7)
Treatment-related leading to treatment discontinuation	14 (9.8)	3 (4.2)

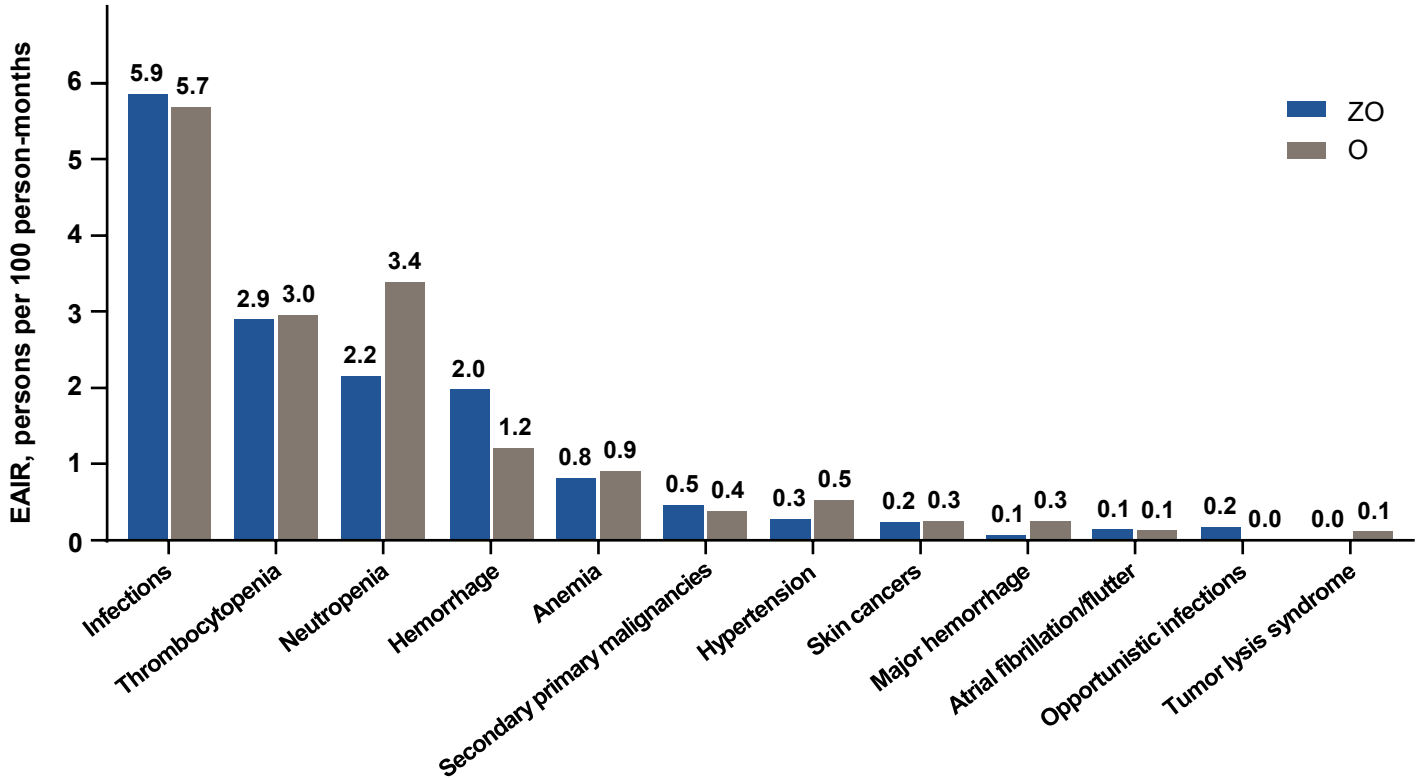
O, obinutuzumab; TEAE, treatment-emergent adverse event; ZO, zanubrutinib + obinutuzumab.

TEAEs Were Generally Consistent With the Known Safety Profiles of Zanubrutinib and Obinutuzumab



O, obinutuzumab; TEAE, treatment-emergent adverse event; ZO, zanubrutinib + obinutuzumab.

Exposure-Adjusted Incidence Rates (EAIRs)[a] for TEAEs of Special Interest Were Comparable Between Arms



[a]EAIR is calculated as the number of patients experiencing the event divided by the total exposure time from the first dose date to the first event date, or from the first dose date to the treatment-emergent period end date if there was no event.

EAIR, exposure-adjusted incidence rate; O, obinutuzumab; TEAE, treatment-emergent adverse event; ZO, zanubrutinib + obinutuzumab.

Final Analysis of ROSEWOOD: Conclusions

- The favorable risk-benefit profile of ZO in heavily pretreated patients with R/R FL was sustained
- Compared with O monotherapy, combination treatment with ZO demonstrated substantially
  - higher ORR and CR rate
  - longer DOR and PFS
- ZO had a manageable, consistent safety profile, with no new safety signals
- With a long median follow-up (34.6 months), these data support the potential benefit of ZO as a novel combination therapy for patients with R/R FL
- To further evaluate ZO in patients with R/R FL with ≥1 prior line of therapy, the phase 3 MAHOGANY study (NCT05100862) comparing ZO vs lenalidomide + rituximab is ongoing

CR, complete response; DOR, duration of response; FL, follicular lymphoma; O, obinutuzumab; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory; Z, zanubrutinib; ZO, zanubrutinib + obinutuzumab.

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Corresponding author: Pier Luigi Zinzani, pierluigi.zinzani@unibo.it