Zanubrutinib + Obinutuzumab vs Obinutuzumab Monotherapy in Patients with Relapsed or Refractory Follicular Lymphoma: Primary Analysis of the Phase 2 Randomized ROSEWOOD Trial

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Disclosures for Pier Luigi Zinzani

Honoraria with Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, BMS, Janssen; consulting role with Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, BMS, Janssen; speakers' bureau for Roche, Gilead, Novartis, Incyte, Takeda, Kyowa Kirin, Sanofi, Merck, Janssen

Background

- FL is the most common subtype of indolent NHL
- Approved treatment options are limited for patients with R/R FL and are associated with significant toxicities precluding use in patients with advanced age and/or comorbidities
- In the 3L+ setting, these treatments are often associated with low rates of long-term disease control[1]
- In a phase 1b trial, zanubrutinib + obinutuzumab was generally well tolerated and associated with an early signal of efficacy[2]
  - ORR was 72% and CRR was 39%
  - The estimated DOR rate at 18 months was 75.5% (95% CI: 53.1, 88.3); median PFS was 25 months (range, 0.7-36)
- Here, we report the primary analysis of ROSEWOOD (BGB-3111-212; NCT03332017), a global phase 2, randomized study designed to assess efficacy and safety of zanubrutinib + obinutuzumab vs obinutuzumab in patients with R/R FL who have received ≥ 2 lines of therapy

3L+, third-line or later; CI, confidence interval; CRR, complete response rate; DOR, duration of response; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PFS, progression-free survival; R/R, relapsed/refractory.

1. Casulo C, et al. *Lancet Haematol* 2022;9:e289-300. 2. Tam CS, et al. *Blood Adv* 2020;4(19):4802-4811.

Study Design

- The first patient was randomized in November 2017, and the last patient was randomized in June 2021
- Median study follow-up: 12.5 months

Key Eligibility Criteria

- Adults with grade 1-3a FL
- R/R disease, previously treated with ≥ 2 prior systemic treatments including an anti-CD20 antibody and an appropriate alkylator-based combination therapy
- Measurable disease
- ECOG PS 0-2
- Adequate organ function
- No prior BTK inhibitor

Arm A
Zanubrutinib[a] plus obinutuzumab
Until PD/unacceptable toxicity
n = 145

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

Arm B
Obinutuzumab[b]
n = 72
Option to crossover to combination if PD centrally confirmed or no response at 12 months

Primary Endpoint

- ORR assessed by ICR according to Lugano classification[1]

Select Secondary Endpoints

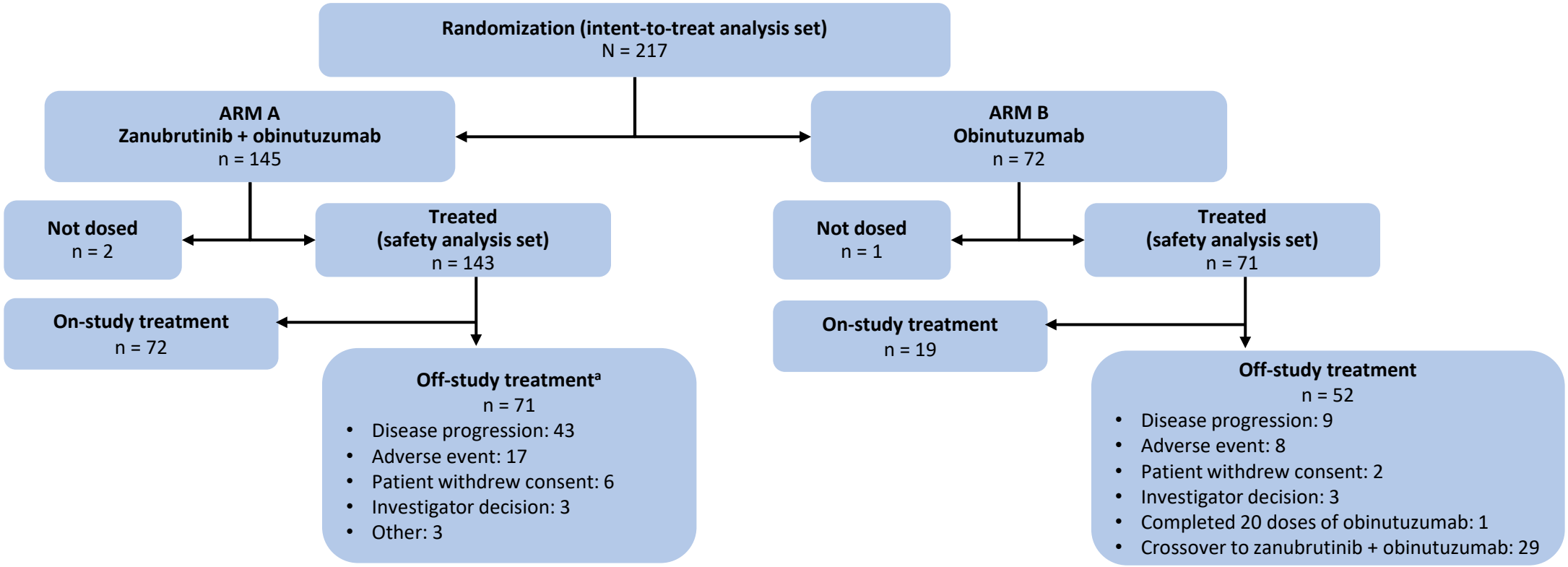
- ORR assessed by investigator
- DOR and PFS determined by ICR and investigator assessment
- Overall survival
- CR and CMR rate assessed by ICR and investigator assessment

ClinicalTrials.gov: NCT03332017

[a]Zanubrutinib was given orally at 160 mg twice daily; [b]Obinutuzumab (1000 mg) was given 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 20 doses maximum.
BTK, Bruton tyrosine kinase; CMR, complete metabolic response; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; ICR, independent central review; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory.

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

Patient Disposition



- In the zanubrutinib + obinutuzumab arm, 50% of patients were still on treatment at the data cutoff date of October 8, 2021
- In the obinutuzumab arm, 26% of patients were still on treatment; the major reason for treatment discontinuation was disease progression either followed by crossover to the zanubrutinib plus obinutuzumab arm or not

[a]For patients in zanubrutinib + obinutuzumab arm, both reasons for discontinuation are reported if the end-of-treatment reasons are different.

Patient Characteristics

- Baseline characteristics were balanced between the 2 arms

Characteristic	Zanubrutinib + obinutuzumab n = 145	Obinutuzumab n = 72
Sex, male, %	51.7	45.8
Age, median (range), years	63.0 (31, 84)	65.5 (32, 88)
FLIPI at screening, %		
Low (0-1)	19.3	12.5
Intermediate (2)	24.8	33.3
High (≥ 3)	53.1	51.4
Missing	2.8	2.8
ECOG performance status ≥ 1, %	40.7	56.9
Baseline bulky disease (≥ 5 cm), %	39.3	43.1
Elevated LDH at screening, %	34.5	40.3
Elevated beta-2 macroglobulin at screening, %	44.8	51.4
Prior lines of therapy, median (range)	3 (2, 11)	3 (2, 9)
Patients with > 3 lines of therapy, %	28.3	25.0
Patients refractory to rituximab, %	53.8	50.0
Patients refractory to the most recent line of therapy, %	32.4	40.3
Patients with PD within 24 months of starting the 1st line of therapy, %	34.5	41.7

ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; PD, progressive disease.

Disease Response by ICR

- The study met its primary endpoint with 68.3% ORR per ICR in the zanubrutinib + obinutuzumab arm vs 45.8% in the obinutuzumab arm

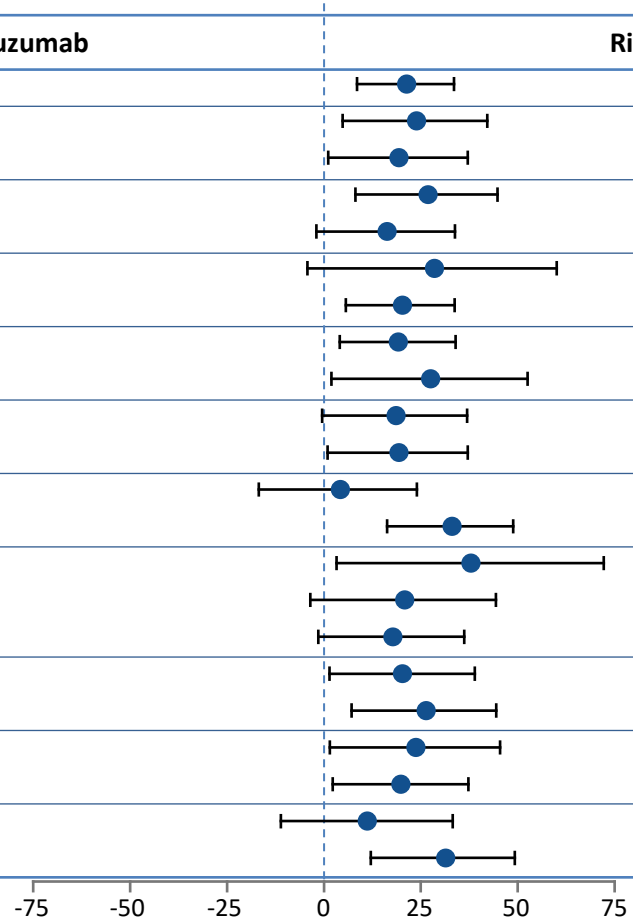
Response by ICR	Zanubrutinib + obinutuzumab n = 145	Obinutuzumab n = 72
ORR, % (95% CI)	68.3 (60.0, 75.7)	45.8 (34.0, 58.0)
Risk difference, % (95% CI)	22.0 (8.3, 35.8)	
2-sided *P* value	0.0017	
BOR, n (%)		
CR	54 (37.2)	14 (19.4)
PR	45 (31.0)	19 (26.4)
SD	25 (17.2)	14 (19.4)
Nonprogressive disease	3 (2.1)	4 (5.6)
PD	13 (9.0)	15 (20.8)
Discontinued prior to first assessment	4 (2.8)	6 (8.3)
NE	1 (0.7)	0 (0.0)
Complete response rate, % (95% CI)	37.2 (29.4, 45.7)	19.4 (11.1, 30.5)
2-sided *P* value	0.0083	

BOR, best overall response; CI, confidence interval; CR, complete response; ICR, independent central review; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

ORR by ICR in Predefined Subgroups

- Benefit of zanubrutinib + obinutuzumab over obinutuzumab was consistent across prespecified subgroups

Subgroup		Obinutuzumab	Zanubrutinib + obinutuzumab	Risk difference (95% CI)
All patients in ITT		33 / 72	99 / 145	22.4 (8.7, 36.2)
Age, years	< 65	14 / 32	57 / 83	24.9 (5.1, 44.8)
	≥ 65	19 / 40	42 / 62	20.2 (0.9, 39.6)
Sex	Male	14 / 33	53 / 75	28.2 (8.5, 48.0)
	Female	19 / 39	46 / 70	17.0 (-2.2, 36.2)
Geographic region	China	5 / 12	15 / 21	29.8 (-4.2, 63.7)
	Ex-China	28 / 60	84 / 124	21.1 (6.0, 36.1)
Prior lines of therapy	2-3	27 / 54	76 / 108	20.4 (4.5, 36.2)
	> 3	6 / 18	23 / 37	28.8 (2.0, 55.6)
Baseline ECOG performance status	0	17 / 31	64 / 86	19.6 (-0.2, 39.4)
	≥ 1	16 / 41	35 / 59	20.3 (0.8, 39.8)
Bulky disease: any target lesion longest diameter ≥5 cm	Yes	15 / 31	30 / 57	4.2 (-17.6, 26.1)
	No	18 / 41	69 / 88	34.5 (17.1, 52.0)
Baseline FLIPI risk category	Low (0-1)	3 / 9	20 / 28	38.1 (3.0, 73.1)
	Intermediate (2)	13 / 24	27 / 36	20.8 (-3.6, 45.3)
	High (≥ 3)	17 / 37	49 / 77	17.7 (-1.6, 37.0)
Rituximab-refractory status	Refractory	14 / 36	46 / 78	20.1 (0.8, 39.4)
	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	65 / 93	19.9 (2.1, 37.7)
Progression of disease within 24 months of starting 1st line of therapy	Yes	14 / 30	29 / 50	11.3 (-11.2, 33.8)
	No	15 / 35	55 / 74	31.5 (12.3, 50.6)



CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FLIPI, Follicular Lymphoma International Prognostic Index; ICR, independent central review; ITT, intent to treat; ORR, overall response rate.

Disease Response After Crossover (Investigator Assessment)

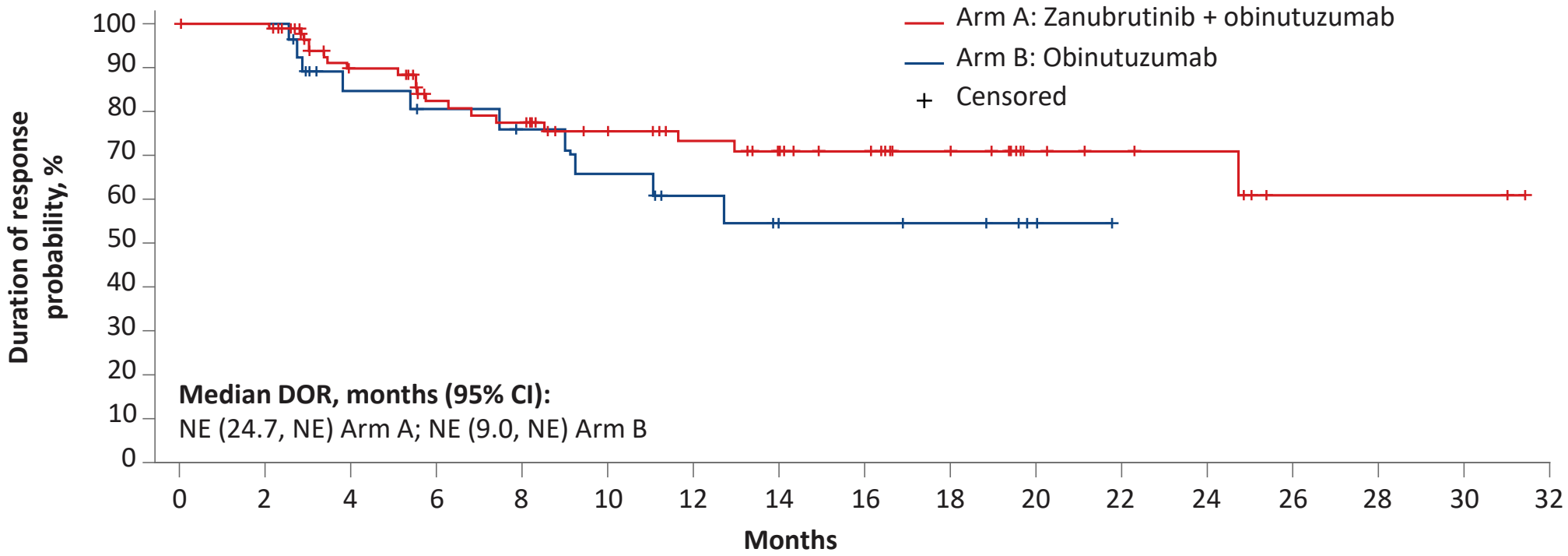
- After receiving obinutuzumab monotherapy, 29 patients crossed over to zanubrutinib + obinutuzumab; ORR was 24.1% including 2 patients with CR

	Zanubrutinib + obinutuzumab n = 29
ORR, % (95% CI)	24.1 (10.3, 43.5)
BOR, n (%)	
CR	2 (6.9)
PR	5 (17.2)
SD	6 (20.7)
PD	9 (31.0)
Discontinued prior to first assessment after crossover	2 (6.9)
NE	5 (17.2)

BOR, best overall response; CI, confidence interval; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Duration of Response by ICR

- The 18-month duration of response rate was 70.9% in the zanubrutinib + obinutuzumab arm vs 54.6% in the obinutuzumab arm



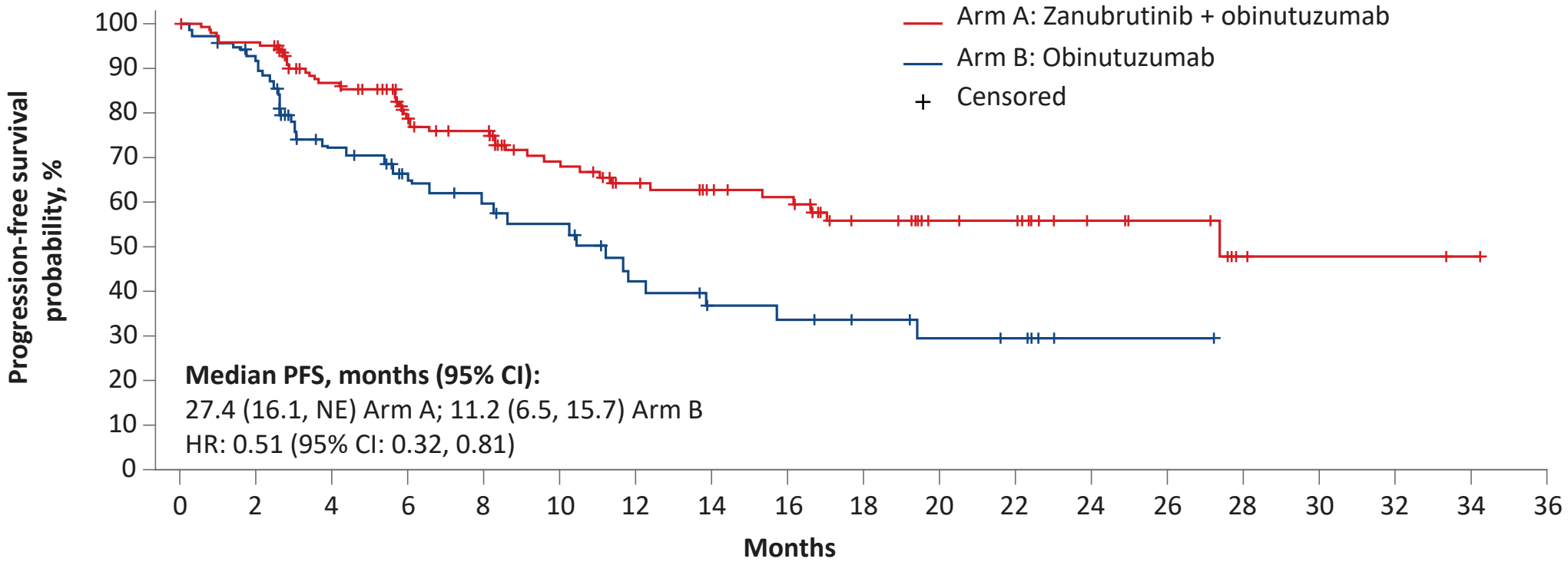
Number of patients at risk:

Arm A	99	92	66	49	46	36	32	27	24	19	10	8	7	2	2	2	0
Arm B	33	28	20	17	15	13	10	6	6	5	2	0					

CI, confidence interval; DOR, duration of response; ICR, independent central review; NE, not evaluable.

PFS by ICR

- Zanubrutinib + obinutuzumab was associated with a 49% reduction of risk of progression or death compared to obinutuzumab



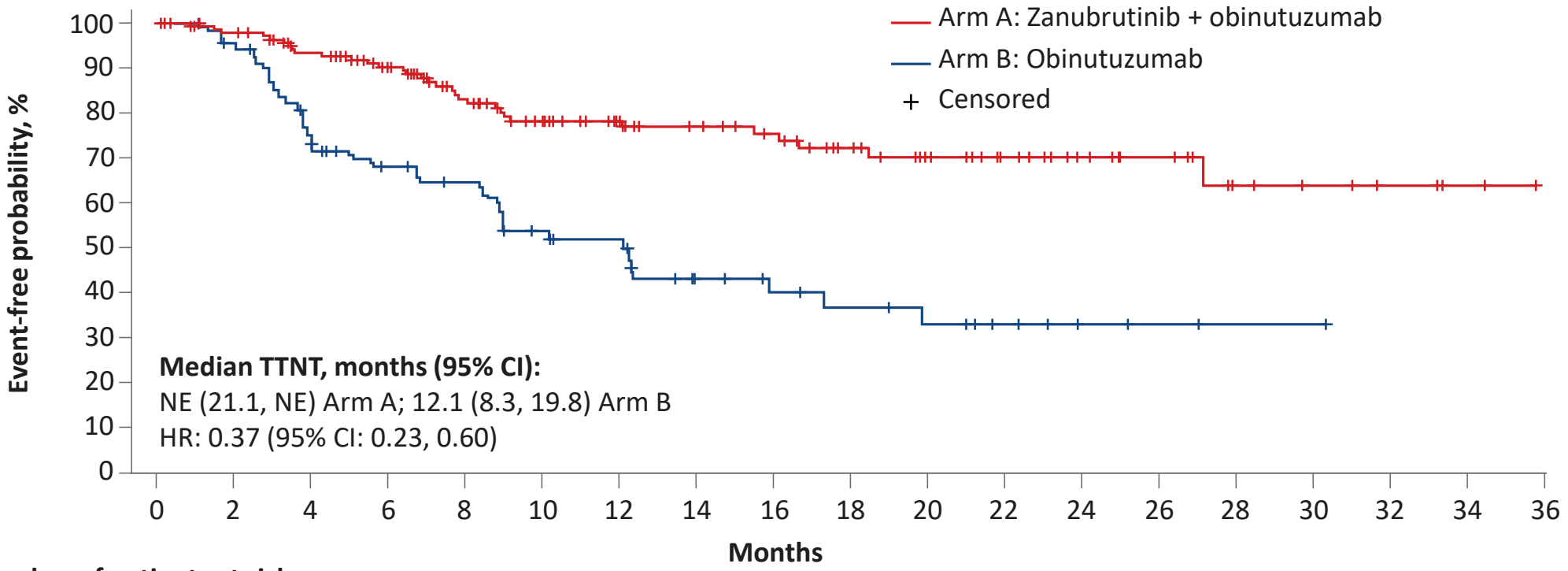
Number of patients at risk:

Arm A	145	135	111	83	76	56	46	40	37	27	19	18	10	8	3	2	2	1	0
Arm B	72	63	39	29	26	23	16	12	11	9	7	6	1	1	0				

CI, confidence interval; HR, hazard ratio; ICR, independent central review; NE, not evaluable; PFS, progression-free survival.

Time to Next Antilymphoma Treatment

- Time to next antilymphoma treatment was prolonged for patients randomized in the zanubrutinib + obinutuzumab arm



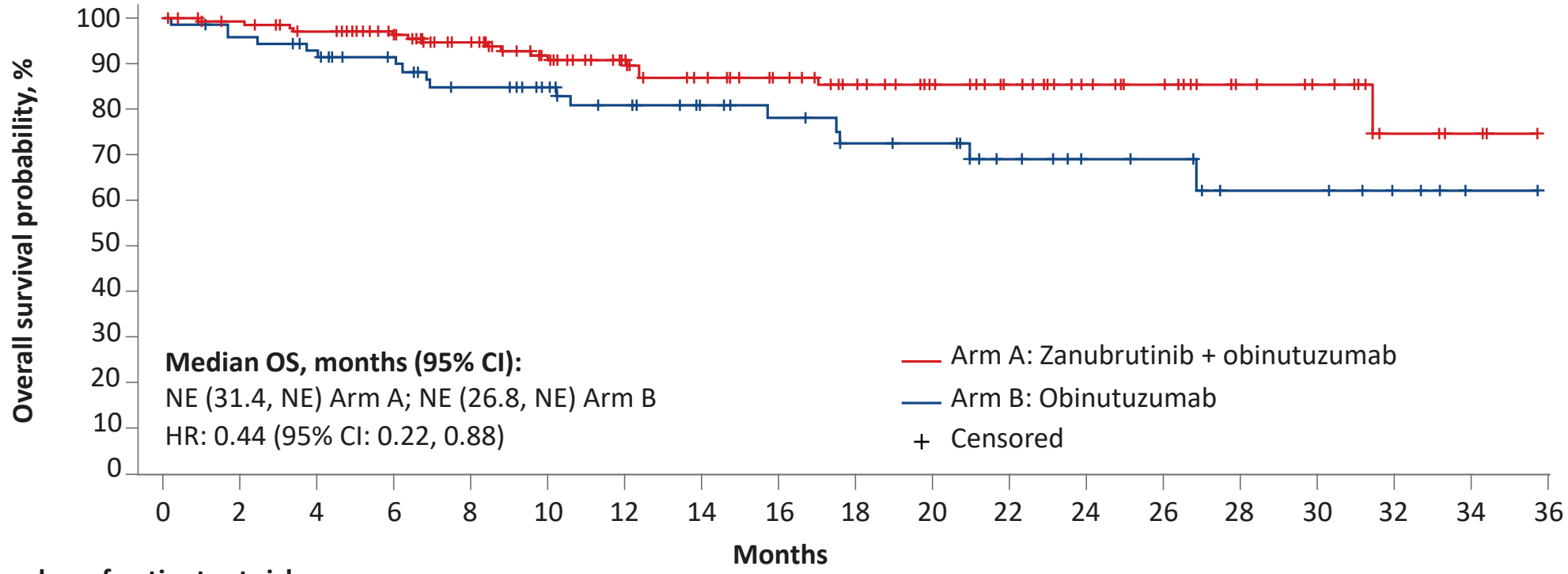
Number of patients at risk:

Arm A	145	137	124	110	89	74	62	53	48	40	32	26	20	14	8	6	4	2	0
Arm B	72	65	49	40	36	28	25	16	13	11	9	6	3	2	1	1	0		

CI, confidence interval; HR, hazard ratio; NE, not evaluable; TTNT, time to next treatment.

Overall Survival

- Although not powered to detect OS difference, OS results favored the combination of zanubrutinib + obinutuzumab



Number of patients at risk:

Arm A	145	139	132	121	104	89	75	64	58	51	42	36	28	22	15	12	5	3	0
Arm B	72	67	63	57	50	45	39	32	29	25	23	17	12	11	7	7	4	1	0

CI, confidence interval; HR, hazard ratio; NE, not evaluable; OS, overall survival.

Summary of Treatment Exposure

- Good tolerability of zanubrutinib led to prolonged treatment exposure

Treatment exposure	Zanubrutinib + obinutuzumab		Obinutuzumab n = 71
	Zanubrutinib n = 143	Obinutuzumab n = 143	
Duration of exposure			
Median (range), months	8.34 (0.5, 35.5)	8.31 (0.3, 35.5)	6.41 (0.1, 28.3)
≥ 12 months, %	35.0	33.6	23.9
Number of cycles			
Median (range)	9.07 (0.5, 38.6)	7.00 (1.0, 18.0)	6.00 (1.0, 18.0)
Obinutuzumab infusions, median (range)	-	9 (3, 20)	8 (3, 20)
Zanubrutinib dose intensity, median (range), mg/day	318.29 (98.2, 320.0)	-	-
Relative dose intensity for zanubrutinib, median (range), %	99.47 (30.7, 100.0)	-	-

Most Common TEAEs (Safety Analysis Set)

- Most common any-grade and Grade ≥ 3 toxicities in the zanubrutinib + obinutuzumab arm were heme toxicities; other toxicities were similar between the 2 arms
- There were no unexpected safety findings associated with the zanubrutinib + obinutuzumab arm

	Zanubrutinib + obinutuzumab n = 143		Obinutuzumab n = 71	
TEAE, %	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Patients with at least 1 TEAE	92.3	53.8	88.7	47.9
Thrombocytopenia or platelet count decreased	34.3	14.0	23.9	7.0
Neutropenia or neutrophil count decreased	27.3	22.4	25.4	19.7
Diarrhea	16.1	2.8	16.9	0.0
Fatigue	14.0	1.4	11.3	0.0
Constipation	13.3	0.0	7.0	0.0
Cough	11.9	0.0	11.3	0.0
Pyrexia	11.2	0.0	19.7	0.0
Dyspnea	10.5	1.4	9.9	0.0
Anemia	9.1	4.2	9.9	5.6
Nausea	8.4	0.0	12.7	0.0
Pruritus	7.0	0.0	9.9	0.0
Infusion-related reaction	2.8	0.7	9.9	4.2
TEAEs of special interest				
Atrial fibrillation and flutter	2.1	0.7	1.4	0.0
Hypertension	3.5	0.7	4.2	1.4
Hemorrhage	26.6	1.4	8.5	0.0
Major hemorrhage	1.4	1.4	1.4	0.0
Infections	47.6	18.9	36.6	12.7
Secondary primary malignancies	6.3	3.5	2.8	0.0

TEAE, treatment-emergent adverse event.

Conclusions

- The ROSEWOOD (BGB-3111-212) trial met its primary endpoint, with significant improvement of ORR by ICR
  - ORR was 68.3% with zanubrutinib + obinutuzumab vs 45.8% with obinutuzumab (*P* = 0.0017)
  - Improvement of ORR was consistent across prespecified subgroups
- Zanubrutinib + obinutuzumab was associated with a deep and durable response
  - CRR was 37.2% vs 19.4% with obinutuzumab alone
  - 18-month DOR rate was 70.9% vs 54.6% with obinutuzumab
- Zanubrutinib + obinutuzumab was associated with improved PFS and OS vs obinutuzumab
  - Median PFS was 27.4 months in the zanubrutinib + obinutuzumab arm vs 11.2 months in the obinutuzumab arm (HR: 0.51 [95% CI: 0.32-0.81])
  - 18-month OS rate was 85.4% in the zanubrutinib + obinutuzumab arm vs 72.6% in the obinutuzumab arm (HR: 0.44 [95% CI: 0.22-0.88])
- Zanubrutinib plus obinutuzumab has a favorable benefit-risk profile and represents a potential combination therapy for patients with R/R FL

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in this study.

This study was sponsored by BeiGene.

Editorial support was provided by Medical Expressions and funded by BeiGene.

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