Zanubrutinib Plus Obinutuzumab Versus Obinutuzumab Monotherapy in Patients With Relapsed or Refractory Follicular Lymphoma: Primary Analysis of the Phase 2 Randomized ROSEWOOD Trial

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DISCLOSURES

Pier Luigi Zinzani has received honoraria from Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, Bristol Myers Squibb, and Janssen; has a consulting/advisory role in Roche, Gilead, Novartis, Servier, Incyte, Takeda, EUSA Pharma, Kyowa Kirin, BeiGene, Sanofi, Merck, Bristol Myers Squibb, and Janssen; and is in the Speakers' Bureau of Roche, Gilead, Novartis, Incyte, Takeda, Kyowa Kirin, Sanofi, Merck, and Janssen

Introduction

- Follicular lymphoma is the most common subtype of indolent non-Hodgkin lymphoma
- Approved treatment options are limited for patients with relapsed/refractory FL
- In the third-line setting or later, these treatments are often associated with low rates of long-term disease control[1]
- In a phase 1b trial, zanubrutinib plus obinutuzumab was generally well tolerated and associated with early signal of efficacy[2]
  - ORR was 72% and CRR was 39%
  - The estimated DOR rate at 18 months was 75.5% (95% confidence interval [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 phase 2, randomized study designed to assess efficacy and safety of zanubrutinib plus obinutuzumab vs obinutuzumab in patients with relapsed/refractory FL who have received ≥2 lines of therapy

1. Casulo et al. *Lancet Haematol* 2022;9:e289-300. 2. Tam et al. *Blood Adv* 2020;4(19):4802-4811.
CRR, complete response rate; DOR, duration of response; FL, folliculuar lymphoma; ORR, overall response rate; PFS, progression-free survival.

Study Design

Key Eligibility Criteria

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

ClinicalTrials.gov: NCT03332017

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

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

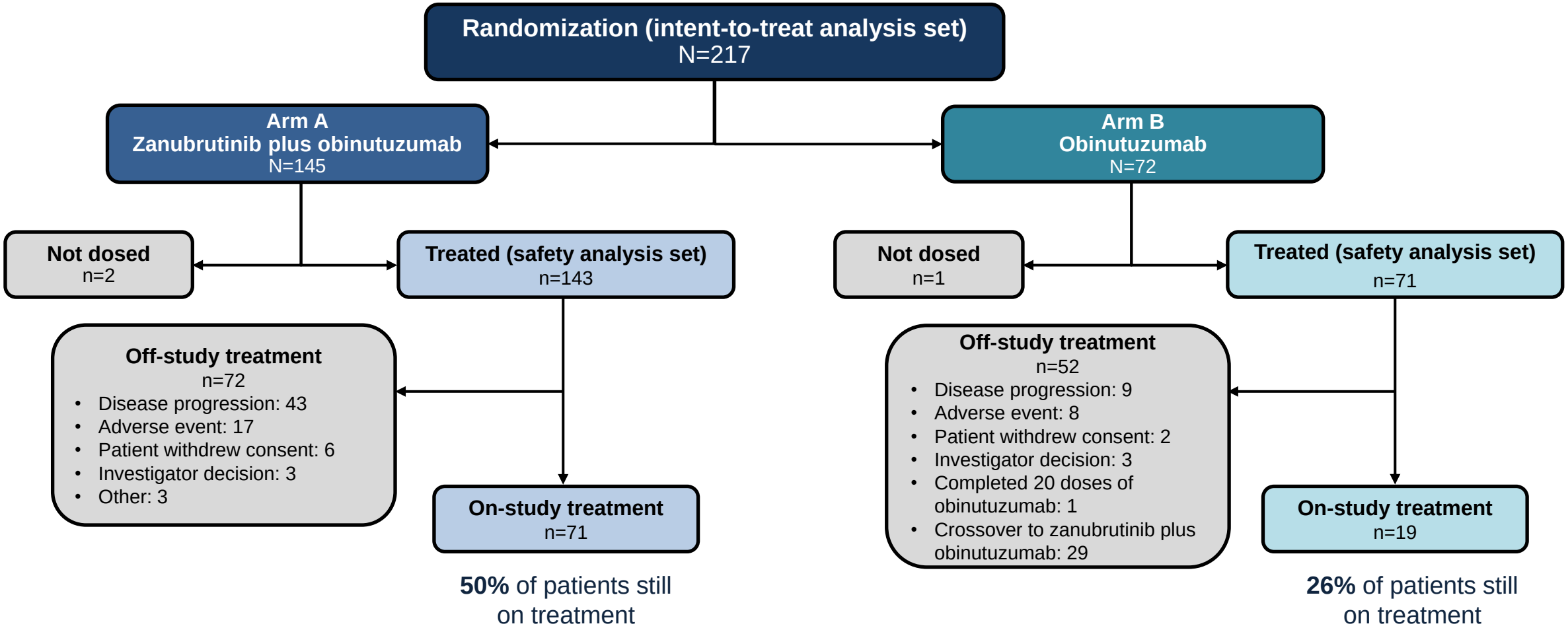
Primary Endpoint
- ORR assessed by ICR according to Lugano classification[1]

Select Secondary Endpoints
- ORR assessed by investigator
- DOR and PFS determined by ICR and investigator assessment
- Overall survival

- Patients were randomized between November 2017 and June 2021
- Median study follow-up: 12.5 months

1. Cheson et al. *J Clin Oncol* 2014;32(27):3059-68.
[a]Zanubrutinib was given orally at 160 mg twice a day; [b]Obinutuzumab 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; 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 or refractory~~; SD, stable disease~~.

Patient Disposition



Data Cutoff: 8 October 2021.

Baseline Patient Characteristics

Characteristic	Zanubrutinib plus obinutuzumab N=145	Obinutuzumab N=72
Male sex, %	51.7	45.8
Median age, years (min, max)	63.0 (31, 84)	65.5 (32, 88)
FLIPI, %		
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
Bulky disease (≥5 cm), %	39.3	43.1
Elevated LDH, %	34.5	40.3
Elevated beta-2 microglobulin, %	44.8	51.4
Median prior lines of therapy, n (min, max)	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 first 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 Independent Central Review (ICR)

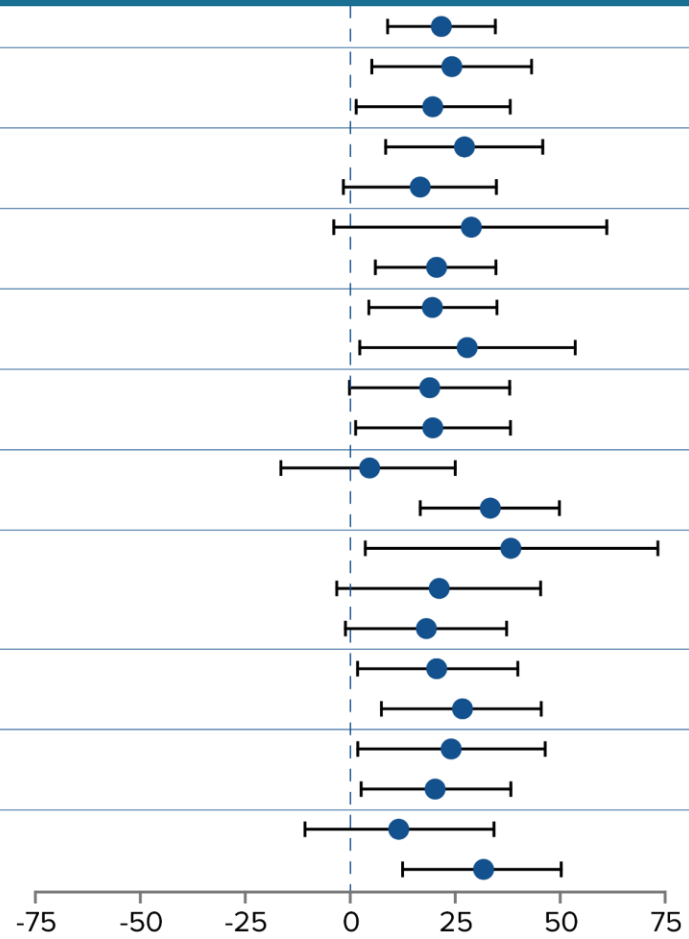
- The study met its primary endpoint
  - ORR per ICR was **68.3%** with zanubrutinib plus obinutuzumab vs **45.8%** with obinutuzumab

Response rate	Zanubrutinib plus 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**	
Best Response, 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)
CR rate, % (95% CI)	**37.2** (29.4, 45.7)	**19.4** (11.1, 30.5)
2-sided *P* value	**0.0083**	

CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Overall Response Rate by ICR in Predefined Subgroups

Subgroup		Response/Patients: Obinutuzumab	Response/Patients: Zanubrutinib plus 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 the first 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)



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

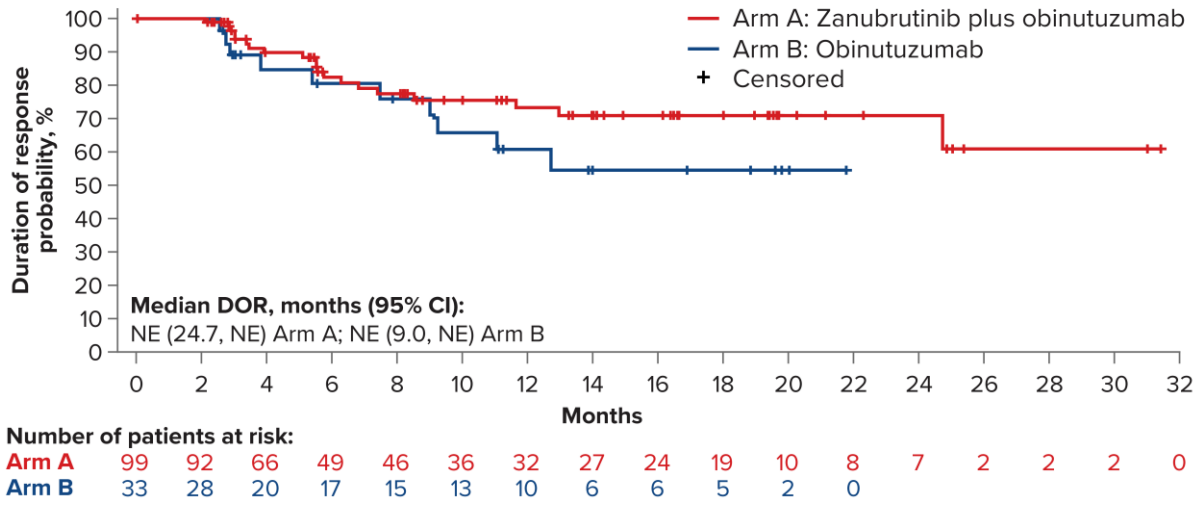
Disease Response After Crossover by Investigator Assessment

Response rate	Zanubrutinib plus 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; CR, complete response; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

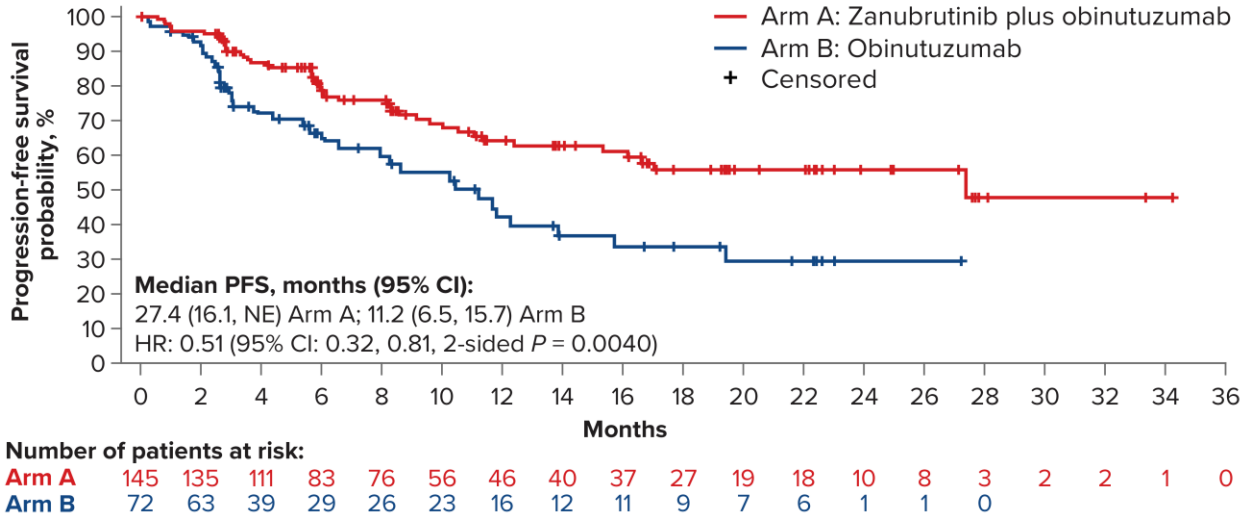
Duration of Response and Progression-Free Survival by ICR

Duration of Response



- The 18-month DOR rate was **70.9%** in the zanubrutinib plus obinutuzumab arm vs **54.6%** in the obinutuzumab arm

Progression-free survival

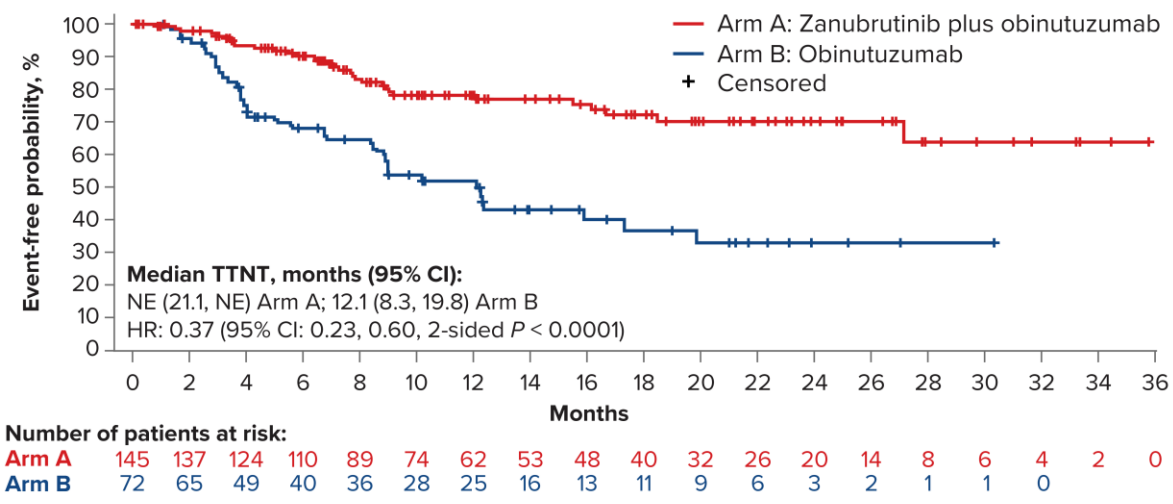


- Zanubrutinib plus obinutuzumab was associated with a **49%** reduction of risk of progression or death compared with obinutuzumab

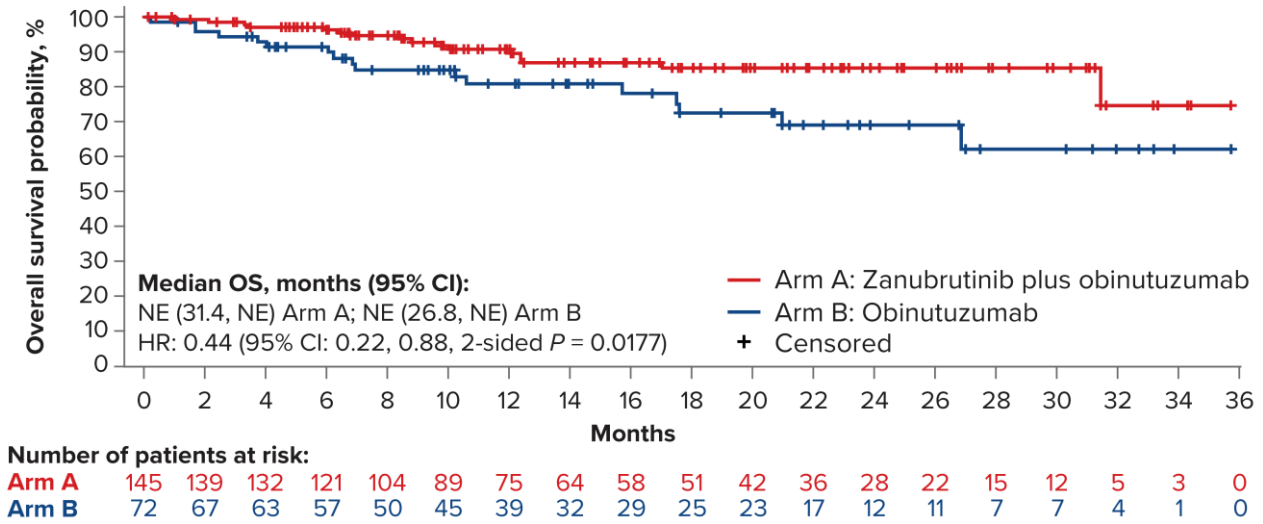
DOR, duration of response; ICR, independent central review; NE, not evaluable; PFS, progression-free survival.

Time to Next Antilymphoma Treatment and Overall Survival

Time to Next Antilymphoma Treatment



Overall Survival



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

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

NE, not evaluable; OS, overall survival; TTNT, time to next treatment.

Summary of Treatment Exposure

Treatment exposure	Zanubrutinib plus obinutuzumab		Obinutuzumab N=71
	Zanubrutinib N=143	Obinutuzumab N=143	
Duration of exposure			
Median, months (min, max)	**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, n (min, max)	**9.07** (0.5, 38.6)	**7.00** (1.0, 18.0)	**6.00** (1.0, 18.0)
Median number of obinutuzumab infusions, n (min, max)	-	**9** (3, 20)	**8** (3, 20)
Median relative dose intensity for zanubrutinib, % (min, max)	**99.47** (30.7, 100.0)	-	-

Most Common TEAEs (Safety Analysis Set)

TEAE, %	Zanubrutinib plus obinutuzumab N=143		Obinutuzumab N=71	
	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 plus obinutuzumab vs 45.8% with obinutuzumab (*P* = 0.0017)
- Zanubrutinib plus obinutuzumab was associated with a deep and durable response
- Zanubrutinib plus obinutuzumab was associated with improved PFS, TTNT, and OS vs obinutuzumab
  - Median PFS was 27.4 months in the zanubrutinib plus obinutuzumab arm vs 11.2 months in the obinutuzumab arm (HR: 0.51 [95% CI: 0.32, 0.81], *P* = 0.0040)
- The safety profile of the zanubrutinib plus obinutuzumab arm was generally comparable to the obinutuzumab arm, with no unexpected safety findings
- Zanubrutinib plus obinutuzumab has a favorable benefit-risk profile and represents a potential combination therapy for patients with R/R FL

FL, follicular lymphoma; ICR, independent central review; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R/R, relapsed/refractory; TTNT, time to next treatment.

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