Zanubrutinib plus obinutuzumab versus obinutuzumab monotherapy in patients with relapsed or refractory follicular lymphoma: primary analysis of the phase 2 randomized ROSEWOOD trial

Abstract 7510

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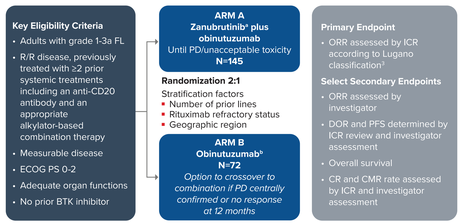
BACKGROUND

- 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 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% 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 plus obinutuzumab vs obinutuzumab in patients with R/R FL who have received 2 or more lines of therapy

METHODS

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

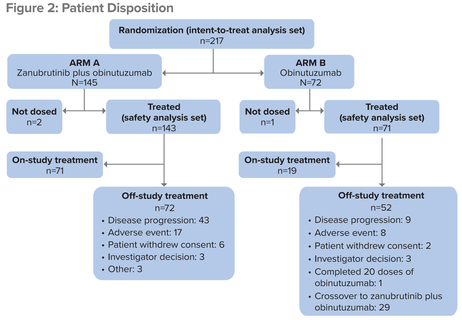
Figure 1: Study Design



ClinicalTrials.gov: NCT03332017

[a]Zanubrutinib was given orally at 160 mg twice a day; [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.

Figure 2: Patient Disposition



- In the zanubrutinib plus obinutuzumab arm, 50% of patients were still on treatment at the data cutoff date (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.

RESULTS

- Baseline characteristics were balanced between the 2 arms (**Table 1**)

Table 1. 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 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 microglobulin at screening, %	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 completion of the first line of therapy, %	34.5	41.7

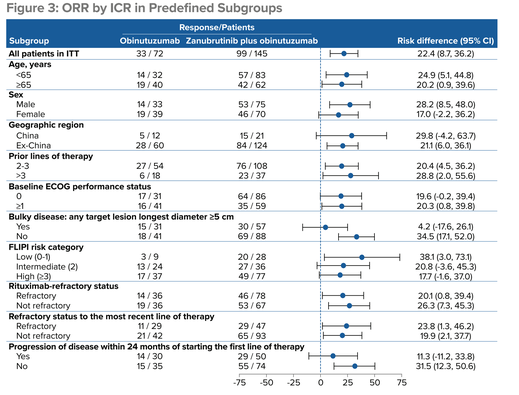
- The study met its primary endpoint with 68.3% ORR per ICR in the zanubrutinib plus obinutuzumab arm vs 45.8% in the obinutuzumab arm (**Table 2**)

Table 2. Disease Response by ICR

Response by ICR	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	
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 tumor 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	

- Benefit of zanubrutinib plus obinutuzumab over obinutuzumab was consistent across prespecified subgroups (**Figure 3**)

Figure 3: ORR by ICR in Predefined Subgroups



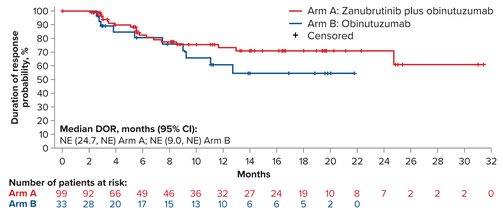
- After receiving obinutuzumab monotherapy, 29 patients crossed over to zanubrutinib plus obinutuzumab; ORR was 24.1% including 2 patients with CR (**Table 3**)

Table 3. Disease Response After Crossover (Investigator Assessment)

	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 tumor assessment after crossover	2 (6.9)
NE	5 (17.2)

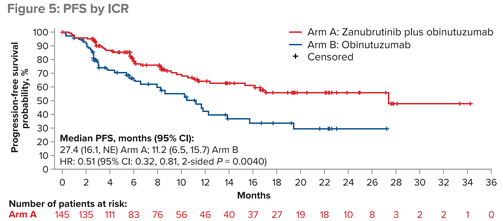
- The 18-month duration of response rate was 70.9% in the zanubrutinib plus obinutuzumab arm vs 54.6% in the obinutuzumab arm (**Figure 4**)

Figure 4: Duration of Response by ICR



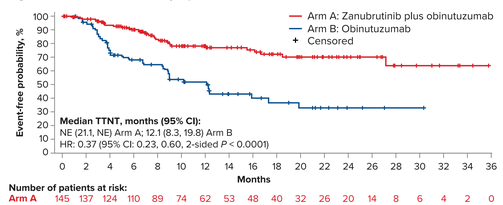
- Zanubrutinib plus obinutuzumab was associated with a 49% reduction of risk of progression or death compared to obinutuzumab (**Figure 5**)

Figure 5: PFS by ICR



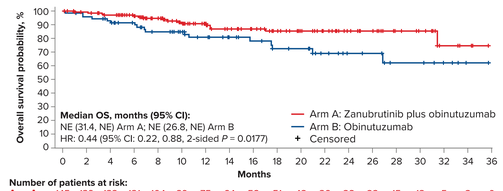
- Time to next antilymphoma treatment was significantly prolonged for patients randomized in the zanubrutinib plus obinutuzumab arm (**Figure 6**)

Figure 6: Time to Next Antilymphoma Treatment



- Although not powered to detect OS difference, OS results favored combination of zanubrutinib plus obinutuzumab (**Figure 7**)

Figure 7: OS



- Good tolerability of zanubrutinib led to prolonged treatment exposure (**Table 4**)

Table 4. Summary of Treatment Exposure

Treatment exposure	Zanubrutinib plus obinutuzumab		
	Zanubrutinib N=143	Obinutuzumab N=143	Obinutuzumab N=71
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 actual zanubrutinib dose intensity, mg/day (min, max)	318.29 (98.2, 320.0)	-	-
Median relative zanubrutinib dose intensity, % (min, max)	99.47 (30.7, 100.0)	-	-

- Most common any-grade and grade ≥3 toxicities in the zanubrutinib plus obinutuzumab arm were heme toxicities; other toxicities were similar between the 2 arms (**Table 5**)
- There were no unexpected safety findings associated with the zanubrutinib plus obinutuzumab arm

Table 5: 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
Neutrophil count decreased or neutropenia	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
Second primary malignancies	6.3	3.5	2.8	0.0
Tumor lysis syndrome	0.0	0.0	1.4	1.4

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)
  - Improvement of ORR was consistent across prespecified subgroups
- Zanubrutinib plus 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 plus obinutuzumab was associated with improved PFS 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)
  - 18-month OS rate was 85.4% in the zanubrutinib plus 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

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DISCLOSURES

PL2: 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
JM: research funding from BeiGene
RA: consulting role with BeiGene, Incyte; research funding from Janssen
FB: advisory board for AstraZeneca, AbbVie
ACO: consulting role with Janssen, Alexion; travel expenses from Janssen
CRF: consulting role with Bayer, Gilead Sciences, Spectrum Pharmaceuticals, AbbVie, Celgene, Denovo Biopharma, BeiGene, Karyopharm Therapeutics, Pharmacyclics/Janssen, Genentech/Roche, Epizyme; research funding from Acerta Pharma, Janssen Oncology, Gilead Sciences, Celgene, TG Therapeutics, Genentech/Roche, Pharmacyclics, AbbVie, Millennium, Alimera Sciences, Xencor
KB: consulting role with Roche, Takeda, Kite/Gilead; travel expenses from Roche, Takeda; honoraria from Roche, Takeda Science Foundation, AbbVie, Kite/Gilead
RJ: honoraria from Kite/Gilead, Novartis, Takeda; consulting role from Kite/Gilead; speakers' bureau for Kite/Gilead, Novartis
EK: employment with Comprehensive Cancer Centers of Nevada
SA: consulting role with Roche/Genentech, BeiGene; travel expenses from Roche Canada; stock ownership with Knight Pharmaceuticals; honoraria with Janssen Oncology, Pfizer, AbbVie, Novartis Canada Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb; research funding from Roche Canada, Takeda, Astex Pharmaceuticals, BeiGene, Novartis
EI: stock ownership with and honoraria from BeiGene
PK, RD: employment and stock ownership with BeiGene
JH: employment with BeiGene; leadership role with BeiGene, Protera; stock ownership with BeiGene, Roche; research funding and patents from BeiGene
JT: research funding from BeiGene, Bristol-Myers Squibb, Roche, Cellectar, Janssen
MM, PSG, SY, GT: nothing to disclose

ABBREVIATIONS

3L+, third-line or later; BOR, best overall response; BTK, Bruton tyrosine kinase; CI, confidence interval; CMR, complete metabolic response; CR, complete response; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; ICR, independent central review; ITT, intent to treat; LDH, lactate dehydrogenase; NE, not evaluable; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PS, performance status; R/R, relapsed or refractory; SD, stable disease; TEAE, treatment-emergent adverse event; TTNT, time to next antilymphoma treatment.

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