***Title (Italian)*:** ZANUBRUTINIB PIÙ OBINUTUZUMAB VERSO OBINUTUZUMAB IN PAZIENTI CON LINFOMA FOLLICOLARE RECIDIVATO/REFRATTARIO: ANALISI AGGIORNATA DELLO STUDIO ROSEWOOD

Title (English): ZANUBRUTINIB PLUS OBINUTUZUMAB VS OBINUTUZUMAB IN PATIENTS WITH RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA: UPDATED ANALYSIS OF THE ROSEWOOD STUDY

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Background: In an early-phase study, the combination of zanubrutinib plus obinutuzumab (ZO) was well tolerated and showed an early signal of efficacy in patients with follicular lymphoma (FL) (Tam et al. *Blood Adv.* 2020). ROSEWOOD (NCT03332017) is a phase 2, randomized study designed to assess the efficacy and safety of ZO vs obinutuzumab (O) in patients with relapsed/refractory (R/R) FL. Here, we present an updated analysis with a median follow-up of 20.2 months.

Methods: Patients with R/R FL (grade 1-3a) who received ≥2 lines of therapy including an anti-CD20 antibody and alkylating agent were randomized 2:1 to receive ZO or O. Zanubrutinib was given at 160 mg twice daily until progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) by independent central review. Other endpoints included duration of response (DOR), progression-free survival (PFS), time to next treatment, overall survival, and safety.

Results: A total of 217 patients were randomized (ZO, n=145; O, n=72). Median age was 64 years. Median number of prior lines of therapy was 3 (range, 2-11). Most patients (52.5%) were refractory to rituximab; 98.6% of patients had received prior immunochemotherapy. The ORR was 69.0% (ZO) vs 45.8% (O) (*P*=.0012). DOR rate at 18 months was 69.3% (ZO) vs 41.9% (O), and median PFS was 28.0 months (ZO) vs 10.4 months (O) (hazard ratio, 0.50; 95% CI, 0.33-0.75; *P*=.0007). Additional efficacy results are shown in the **Table**. Nonhematologic treatment-emergent adverse events of any grade that occurred more frequently with ZO vs O (>5% difference) were petechiae and herpes zoster infection (6.3% vs 0% for both); pyrexia

(13.3 % vs 19.7%) and infusion-related reactions (2.8% vs 9.9%) occurred more frequently in patients receiving O. When adjusted for duration of treatment exposure, incidences of infection and cytopenia were similar, and the incidence of all grades of hemorrhage was 2.4 (ZO) vs 1.3 (O) persons per 100 person-months.

Conclusion: ZO demonstrated meaningful efficacy and a manageable safety profile in patients with heavily pretreated R/R FL and represents a potential novel therapy.

Table. Efficacy Results

	ZO	O	HR (95% CI)	2-sided *P* value
Primary endpoint				
ORR by ICR, %	69.0	45.8	-	.0012
Other endpoints				
Complete response rate by ICR, %[a]	39.3	19.4	-	.0035
DOR rate by ICR at 18 months, %[a]	69.3	41.9	-	
PFS by ICR, median, months[a]	28.0	10.4	0.50 (0.33-0.75)	.0007
TTNT, median, months	NE	12.2	0.34 (0.22-0.52)	<.0001
OS rate at 24 months, %[a]	77.3	71.4	-	-
OS, median, months[a]	NE	34.6	0.62 (0.35-1.07)	.0845

DOR, duration of response; HR, hazard ratio; ICR, independent central review; NE, not evaluable; O, obinutuzumab; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; TTNT, time to next treatment; ZO, zanubrutinib plus obinutuzumab.
[a] Secondary endpoint.