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ZANUBRUTINIB PLUS OBINUTUZUMAB IN PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL) OR RELAPSED/REFRACTORY (R/R) FOLLICULAR LYMPHOMA (FL)

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Introduction: Bruton Tyrosine Kinase (BTK) plays a critical role in B cell receptor (BCR) signaling. Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK preclinically, with minimal inhibition of other kinases; it has minimal effect on interleukin-2 inducible tyrosine kinase (ITK) and does not inhibit ITK-mediated rituximab-induced antibody-mediated cytotoxicity. **Methods:** This is a phase 1b study of the combination of zanubrutinib with obinutuzumab in patients with B-cell malignancies. Eligible

TABLE 1

	37 CLL (n=37) / SLL (n=8) (20 TN & 25 RR) n = 45	R/R FL n = 36
Demographics		
Median (range) age, y	68 (38, 82)	59 (34, 86)
Median (range) prior therapies	1 (0, 4)	2 (1, 9)
Safety, n (%)		
Grade ≥3 AEs	32 (71)	18 (50)
Serious AEs	22 (49)	12 (33)
AEs leading to zanubrutinib discontinuation	2 (4)	2 (6)
Fatal AEs	1 (2)	0
Efficacy (Evaluable)	**n = 45**	**n = 36**
Median (range) follow-up, mo	25 (8, 34)	18 (2, 34)
ORR, n/N (%)	43/45 (96) CLL: 15/15 TN, 20/22 RR SLL: 5/5 TN, 3/3 RR	26/36 (72)
Best response		
CR	12 (27) CLL: 5/15 TN, 6/22 RR SLL: 1/5 TN, 0/3 RR	13 (36)
PR	31 (69)	13 (36)
Stable disease	2 (4)	5 (14)
Progressive disease	0	5 (14)

patients had ECOG status of 0-2, neutrophil count >1000/μL, platelets >40,000/μL, adequate renal and hepatic function and no significant cardiac disease. Growth factors, transfusion and anticoagulation were allowed. The primary efficacy endpoint was objective response using 2007 International Working Group criteria.

Results: As of 16Nov2018, enrollment was complete with 45 CLL/SLL patients (20 treatment-naïve [TN] and 25 R/R) and 36 R/R FL patients. Median follow-up was 25.5 mo (range: 7.9-33.5) for CLL/SLL and 17.8 mo (range: 2.3-33.8) for R/R FL. One fatal adverse event (AE) occurred: squamous cell carcinoma in a CLL patient with prior squamous cell carcinoma. Serious AEs were reported in 22 (49%) CLL/SLL and 12 (33%) R/R FL patients. Common (>20%) any-grade AEs reported in CLL/SLL patients were upper respiratory tract infection (URTI; 49%), neutropenia (42%), contusion (33%), diarrhea (27%), cough (27%), fatigue (27%), and pyrexia (22%); and in FL patients were URTI (39%), contusion (28%), fatigue (25%), and cough (22%). AEs lead to zanubrutinib discontinuation in 2 (4%) CLL/SLL (disseminated cryptococcusand squamous cell carcinoma) and 2 (6%) R/R FL patients (lethargy, ascites). There were no AEs of atrial fibrillation. All patients completed baseline and ≥1 response assessment. Overall response rates [complete response+partial response] were 96% in CLL/SLL (100% for TN, 92% for R/R) and 72% in R/R FL. There were 6 CRs in patients with TN CLL/SLL, 6 in R/R CLL/SLL and 13 in R/R FL.

Conclusions: The combination of zanubrutinib plus obinutuzumab was generally well tolerated and active in patients with CLL/SLL and R/R FL. Few patients discontinued due to AEs. A Phase 2 trial comparing zanubrutinib plus obinutuzumab against obinutuzumab alone in R/R FL is ongoing.

Keywords: B-cell receptor inhibitors; chronic lymphocytic leukemia (CLL); follicular lymphoma (FL).

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