SEQUOIA: Results of a Phase 3 Randomized Study of Zanubrutinib versus Bendamustine + Rituximab (BR) in Patients with Treatment-Naïve (TN) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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Objectives: Zanubrutinib (zanu) is a selective next-generation Bruton tyrosine kinase (BTK) inhibitor designed to have high specificity for BTK and minimize off-target effects (Guo, *J Med Chem* 2019;62:7923-40). In a phase 1/2 study, zanu demonstrated complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes and was associated with durable clinical responses in patients (pts) with CLL/SLL (Tam, *Blood* 2019;134:851-9). Here, we present interim results for the phase 3 SEQUOIA (BGB-3111-304; NCT03336333) trial, which evaluated the efficacy and safety of zanu vs BR in TN pts with CLL/SLL.

Methods: SEQUOIA is an open-label, global phase 3 study that randomized TN pts with CLL/SLL without del(17p) to receive zanu 160 mg twice daily until progressive disease or unacceptable toxicity, or bendamustine 90 mg/m^2 on day 1 and 2 and rituximab 375 mg/m^2 in cycle 1, 500 mg/m^2 in cycles 2-6

for 6 × 28-day cycles. Adult pts with CLL/SLL who met International Workshop on CLL (iwCLL) criteria for treatment (Hallek, *Blood* 2008;111:5446-56) were eligible if they were either ≥65 y or unsuitable for treatment with fludarabine, cyclophosphamide and rituximab. Central verification of del(17p) status by fluorescence in situ hybridization was required. Pts were stratified by age (<65 y vs ≥65 y), Binet Stage (C vs A/B), IGHV mutational status, and geographic region. The primary endpoint was independent review committee (IRC)-assessed progression-free survival (PFS) for zanu vs BR. Secondary endpoints included PFS by investigator assessment (INV), overall response rate (ORR; by IRC and INV), overall survival (OS), and safety. Responses for CLL and SLL were assessed per modified iwCLL criteria (Hallek, *Blood* 2008;111:5446-56; *J Clin Oncol* 2012;30:2820-2) and Lugano criteria (Cheson, *J Clin Oncol* 2014;32:3059-68), respectively. Adverse events (AEs) were recorded until disease progression to support safety evaluation over an equivalent time period.

Results: From 31 Oct 2017–22 Jul 2019, 479 pts without del(17p) were randomized to zanu (n=241) and BR (n=238). Treatment groups were well balanced for demographic and disease characteristics (zanu vs BR): median age, 70.0 y vs 70.0 y; unmutated IGHV, 53.4% (125/234) vs 52.4% (121/231); and del(11q), 17.8% vs 19.3%. At median follow-up (26.2 mo), PFS by IRC was significantly prolonged with zanu vs BR (HR 0.42, 95% CI 0.28–0.63, 1-sided and 2-sided *P*<0.0001; **Figure**); similar results were observed by INV (HR 0.42, 95% CI 0.27–0.66, 1-sided *P*<0.0001, 2-sided *P*=0.0001). Treatment benefit for zanu was observed across subgroups for age, Binet stage, bulky disease, and del(11q) status. Treatment benefit was also observed for pts with unmutated IGHV (HR 0.24, 1-sided and 2-sided *P*<0.0001), but not for mutated IGHV (HR 0.67, 1-sided *P*=0.0929). Estimated 24-mo PFS (IRC) for zanu vs BR was 85.5% (95% CI 80.1%– 89.6%) vs 69.5% (95% CI 62.4%–75.5%). ORR by IRC for zanu vs BR was 94.6% (95% CI 91.0%–97.1%) vs 85.3% (95% CI 80.1%–89.5%). Complete response rate was 6.6% with zanu and 15.1% with BR. ORR by INV for zanu vs BR was 97.5% (95% CI 94.7%–99.1%) vs 88.7% (95% CI 83.9%–92.4%) Estimated 24-mo OS for zanu vs BR was 94.3% (95% CI 90.4%–96.7%) and 94.6% (95% CI 90.6%–96.9%).

The most common AEs are shown in the **Table**. AEs of interest occurring during the full reporting period (pooled terms, zanu vs BR) included atrial fibrillation (any grade [gr]: 3.3% vs 2.6%), bleeding (any gr/gr≥3: 45.0%/3.8% vs 11.0%/1.8%), hypertension (any gr: 14.2% vs 10.6%), infection (any gr/gr≥3: 62.1%/16.3% vs 55.9%/18.9%), and neutropenia (any gr/gr≥3: 15.8%/11.7% vs 56.8%/51.1%). Treatment discontinuation due to AEs occurred in 20 pts (8.3%) receiving zanu vs 31 pts (13.7%) receiving BR; 85.5% of pts receiving zanu remain on treatment. AEs leading to death occurred in 11 pts (4.6%) receiving zanu vs 12 pts (5.3%) receiving BR. No sudden deaths were reported.

Conclusions: In this global registrational trial, zanu demonstrated statistically significant improvement in PFS compared to BR as assessed by IRC. Superiority was also observed in PFS by INV as well as ORR by both IRC and INV. Zanu was generally well tolerated, with low rates of atrial fibrillation consistent with those observed in the phase 3 ASPEN (Tam, *Blood* 2020;136:2038-2050) and ALPINE studies (Hillmen, EHA 2021 #LB1900). These data support the potential utility of zanu in the frontline management of pts with TN CLL/SLL.

Figure: Progression Free Survival by Independent Review Committee Assessment

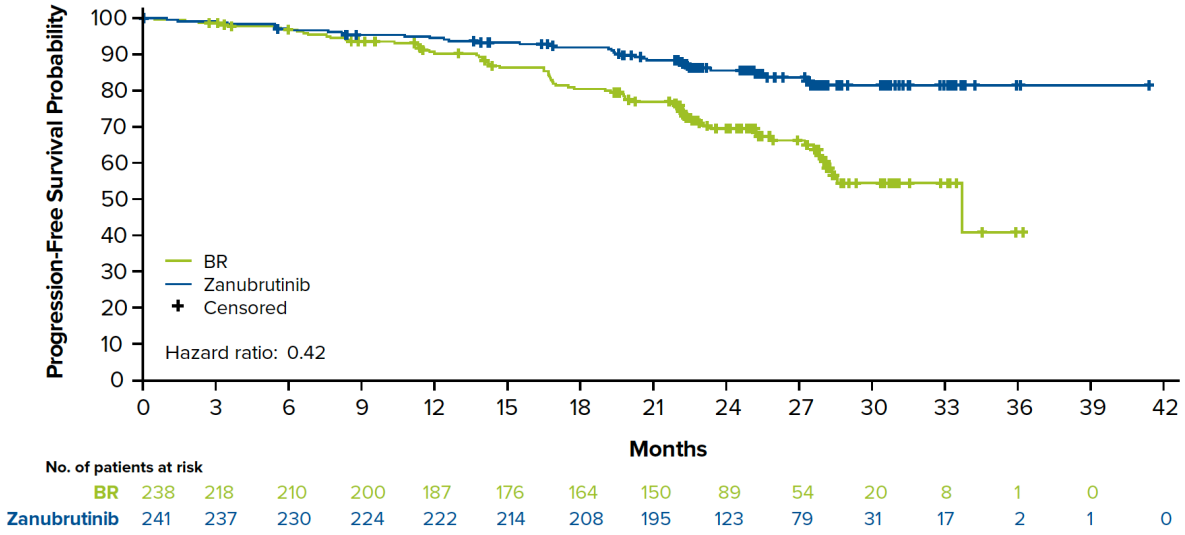

Table: Adverse Events Occurring at Any Grade (≥15% of Patients) or at Grade ≥3 (≥5% of Patients) in Zanubrutinib vs BR Arms

	Arm A, zanubrutinib (n = 240[a])		Arm B, BR (n = 227[b])	
	Any Grade	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Any, n (%)	224 (93.3)	126 (52.5)	214 (94.3)	169 (74.4)
Serious, n (%)	87 (36.3)		93 (41.0)	
Common AEs, n (%)				
Contusion	46 (19.2)	0 (0.0)	8 (3.5)	0 (0.0)
Upper respiratory tract infection	41 (17.1)	2 (0.8)	27 (11.9)	2 (0.9)
Neutropenia	31 (12.9)	22 (9.2)	104 (45.8)	94 (41.4)
Hypertension	29 (12.1)	15 (6.3)	20 (8.8)	11 (4.8)
Rash	26 (10.8)	0 (0.0)	44 (19.4)	6 (2.6)
Constipation	24 (10.0)	1 (0.4)	43 (18.9)	0 (0.0)
Nausea	24 (10.0)	0 (0.0)	74 (32.6)	3 (1.3)
Pyrexia	17 (7.1)	0 (0.0)	60 (26.4)	8 (3.5)
Anemia	11 (4.6)	1 (0.4)	43 (18.9)	4 (1.8)
Thrombocytopenia	9 (3.8)	4 (1.7)	31 (13.7)	16 (7.0)
Neutrophil count decreased	6 (2.5)	5 (2.1)	28 (12.3)	24 (10.6)
Febrile neutropenia	2 (0.8)	2 (0.8)	17 (7.5)	17 (7.5)
Infusion related reaction	1 (0.4)	0 (0.0)	43 (18.9)	6 (2.6)

AE, adverse event; BR, bendamustine + rituximab.
[a]1 patient did not receive zanubrutinib and is not included in the safety analysis.
[b]11 patients did not receive BR are not included in the safety analysis.