Zanubrutinib for Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia

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Introduction: Zanubrutinib is a selective and irreversible BTK inhibitor that has demonstrated potent inhibition of BTK preclinically, with minimal, off-target inhibition of other kinases. Complete and sustained BTK occupancy in both blood and lymph node biopsies from patients treated with zanubrutinib at 160 mg twice daily (BID) was observed in a phase 1 clinical trial.

Methods: In this single-arm, multicenter phase 2 study (clinicaltrials.gov NCT03206918), zanubrutinib was given by mouth, 160 mg BID to patients with relapsed or refractory CLL/SLL until disease progression (PD) or unacceptable toxicity. Efficacy endpoints were assessed by independent review (IRC) in accordance with IWCLL guidelines (IWCLL, 2008) or the Lugano Classification (Cheson, 2014) for CLL and SLL, respectively.

Results: As of 14 December 2018, 91 pts (82 with CLL; 9 with SLL) were enrolled and treated at 11 centers in China. Baseline disease characteristics are summarized in the table. Median follow-up was 15.1 mo (range, 0.8-21.2 mo) with treatment discontinuation in 16 (17.6%) pts (8 due to AEs, 7 due to PD, and 1 due to pt withdrawal). A total of 83 pts (91.2%, 95% CI: 83.4, 91.6) achieved a best response of partial response with lymphocytosis (PR-L) or better according to investigators' assessment. Patients with del(17p) or TP53 mutation achieved a high ORR (95.5%). Median time for achieving first response was 2.79 mo (range, 2.6-5.6 mo) among responders. Estimated PFS rate at 12 months was 80.9% (95% CI: 67, 89). The most frequently reported AEs are summarized in the table below. Major hemorrhage was reported in 2 patients (Gr 3, gastrointestinal hemorrhage and Gr 2 intracranial hemorrhage), which led to discontinuation of zanubrutinib. Four (4.4%) pts died within 30 days of their last dose of

study drug, 2 due to PD and 2 due to AEs (pulmonary infection; cardiopulmonary failure).

Conclusions: Zanubrutinib was generally well-tolerated and resulted in a high response rate, including in patients with del(17p) or TP53 mutation.

Baseline Disease Characteristics	**N=91**	
Median age, y (range)	61.0 (35-87)	
Male, n (%)	52 (57.1)	
Binet stage B or C (CLL pts), n (%)	77 (93.9)	
Stage IV (SLL pts), n (%)	7 (77.8)	
Del(17p), n (%)	17 (18.7)	
TP53 mutation, n (%)	20 (22.0)	
Del(17p) or TP53 mutation, n (%)	22 (24.2)	
Del(13q), n (%)	41 (45.1)	
Del(11q), n (%)	20 (22)	
Trisomy 12, n (%)	21 (23.1)	
IGHV unmutated, n (%)	51 (56.0)	
Lines of prior therapy, median (range)	1 (1-9)	
Efficacy[a]		
Complete response (CR), n (%)	4 (4.4)	
Nodular partial response (nPR), n (%)	2 (2.2)	
Partial response (PR), n (%)	60 (65.9)	
Partial response with lymphocytosis (PR-L), n (%)	17 (18.7)	
Stable disease (SD), n (%)	4 (4.4)	
Progressive disease (PD), n (%)	1 (1.1)	
Discontinued prior to 1st assessment, n (%)	3 (3.3)	
Safety		
Any TEAE, n (%)	91 (100)	
Serious AE, n (%)	30 (33.0)	
AE leading to treatment discontinuation, n (%)	8 (8.8)	
AE leading to death[c], n (%)	3 (3.3)	
Common Adverse Event	**Any Grade**	**Grade ≥3**
Neutrophil count decreased, n (%)	62 (68.1)	40 (44.0)
Upper respiratory tract infection, n (%)	41 (45.1)	9(9.9)
Purpura, n (%)	31 (34.1)	0 (0)
Platelet count decreased, n (%)	30 (33.0)	8 (8.8)
Haematuria, n (%)	27 (29.7)	0 (0)
Anaemia, n (%)	25 (27.5)	8 (8.8)
Hypokalaemia, n (%)	23 (25.3)	6 (6.6)

[a] Best response as assessed by the investigator. IRC-assessed efficacy outcomes are on-going and will be presented.
[b] 'Not evaluable' were due to missing anatomy imaging of 2 patients, and lacking evidence of maintenance for at least 2 months of 1 patient.
[c] One of the patients with primary reason of death due to PD also reported a fatal AE of multiple organ dysfunction syndrome.