Improved depth of response with increased follow-up for patients (pts) with Waldenström Macroglobulinemia (WM) treated with Bruton's tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111)

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Background: Zanubrutinib (zanu) is a potent, specific and irreversible oral BTK inhibitor. In Phase 1 testing, we have demonstrated that high plasma concentrations can be safely achieved, resulting in complete and sustained BTK inhibition in blood and lymph nodes. Early clinical data from an ongoing Phase 1 trial has shown single-agent zanu to be safe and efficacious for the treatment of pts with chronic lymphocytic leukemia (Seymour 2017), WM (Trotman 2017), and other non-Hodgkin lymphomas (Tam 2017).

Aims: Report updated safety and efficacy data from WM pts with a median follow-up of >1 year in this Phase 1 trial.

Methods: This is an open-label, multi-center, dose-finding Phase I study of zanu in pts with B-cell malignancies, with indication-specific expansion cohorts: reported here are data from 67 WM pts enrolled as of 3 Nov 2017. Pts received doses of zanu ranging from 40 mg once daily to the final RP2D of 160 mg twice daily until disease progression (PD) or unacceptable toxicity. Pts were assessed by IgM monthly with full assessment of extramedullary disease every 3 months.

Results: 67 pts with WM were enrolled and evaluable for safety; 51 pts were evaluable for efficacy, excluding those with <12 weeks follow-up (n=13) or IgM <5 g/L at baseline (n=3). The 67 pts included 21 treatment-native (TN) and 46 relapsed/refractory (R/R; 1-8 prior therapies) and median follow-up 15.5

months (range, 0.1-37.6). The most frequent AEs (≥15%, all Gr 1-2 but 1) were petechia/purpura/contusion (37%), upper respiratory tract infection (34%), constipation (18%) and diarrhea (18%). Gr 3-4 AEs included anemia (8%), headache (2%), and diarrhea (2%). Serious AEs (SAEs) were seen in 22 pts (33%) with 5 individual pts (8%) considered related to zanu; febrile neutropenia, colitis, atrial fibrillation, hemothorax (spontaneous), and headache. There was 1 fatal event from worsening pre-existing bronchiectasis in a pt with VGPR. Atrial fibrillation/flutter was experienced by 4 pts (6%), all Gr 1-2, and major hemorrhage seen in 2 pts (3%). Discontinuation of zanu due to adverse events was seen in 3 pts (5%): the previously mentioned fatal bronchiectasis, prostate adenocarcinoma, and gastric adenocarcinoma. Two pts (3%) discontinued study treatment due to PD as assessed by investigator, 1 pt remains on treatment post PD. The objective response rate was 92% (47/51), with a major response rate of 80% (41/51); rate of VGPR increased with increasing follow-up (Table). Median time to response was 88 days (range, 77-279). Of 22/51 (43%) efficacy evaluable pts with hemoglobin <10 g/dL at baseline, the median increased from 8.7 g/dL (range, 6.3-9.8) to 13.8 g/dL (range, 7.7-15.8). For all efficacy evaluable pts, median IgM decreased from 32.5 g/L (range, 5.3-88.5) at baseline to 4.9 g/L (range, 0.1-57). For the 21/51 pts with baseline extramedullary disease, median of maximum post-baseline SPD decrease was 46% (range, 18-81%). Median PFS has not been reached; 91% progression-free at 1 year (Figure).

Conclusion: Zanu is generally well tolerated and highly active in WM with VGPR rates improving over time. A Phase 3 study comparing zanu with ibrutinib in WM is ongoing.

Efficacy per Investigator Assessment

Best Response, n (%)	Best Overall Response (n=51)	Response Over Time for Pts Reaching 1 Year Follow-Up		
		Up to Week 12 (n=39)	Up to Week 24 (n=39)	Up to 1 year (n=39)
VGPR	22 (43.1)	3 (7.7)	6 (15.4)	14 (35.9)
PR	19 (37.3)	23 (59.0)	23 (59.0)	17 (43.6)
MR	6 (11.8)	10 (25.6)	8 (20.5)	6 (15.4)
SD	4 (7.8)	3 (7.7)	2 (5.1)	2 (5.1)

Figure