MAJOR RESPONSES IN MYD88 WILDTYPE (MYD88WT) WALDENSTRÖM MACROGLOBULINEMIA (WM) PATIENTS TREATED WITH BRUTON TYROSINE KINASE (BTK) INHIBITOR ZANUBRUTINIB (BGB-3111)

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Background

BTK inhibitors have been shown to be highly active in patients with WM harboring *the MYD88^{L265P}* mutation, however lower response rates and shorter survival have been reported in patients that lack such mutations (i.e *MYD88^{WT}*; N Engl J Med 2015;372:1430-1440). Zanubrutinib is a potent, specific, and irreversible oral investigational BTK inhibitor with a favorable pharmacokinetic profile resulting in complete and sustained BTK inhibition in blood and lymph nodes. Preliminary studies have identified a high response rate with 41.4% of unselected patients achieving a very good partial response [VGPR]) or better (Tam et al, IWWM-10, 2018). Zanubrutinib is currently being evaluated in several ongoing international Phase 3 studies, including two head-to head studies comparing to ibrutinib.

Aims

Assess the safety and efficacy of zanubrutinib in WM patients with *MYD88^{WT}*.

Methods

Reported here are data from an exploratory cohort of patients with treatment-naïve (TN) or relapsed/refractory (R/R) WM in an open-label, multicenter, randomized phase 3 study. Bone marrow *MYD88* and *CXCR4* mutations were assessed centrally at study entry (NeoGenomics Laboratory). The MYD88 mutation assay used in this study detects all mutations in the region encompassing amino acid Ala^{260}- Pro^{278}, which includes the predominant mutation in WM, *MYD88^{L265P}*. Mutation detection in the *MYD88* amplicon includes a wildtype-allele-blocking approach resulting in enhanced sensitivity (limit of Detection [LOD] 0.5%; *Int J Lab Hematol* 2016;38:133-140]); compared to a standard polymerase chain reaction/bi-directional Sanger sequencing assay used to detect *CXCR4* mutations (LOD 10-15%). Patients were assigned to Cohort 1 (*MYD88* mutated; randomized) or Cohort 2 (*MYD88^{WT}*; non-randomized) based on the MYD88 mutation assay results. All Cohort 2 patients were assigned zanubrutinib 160 mg twice daily until disease progression. Responses were assessed monthly by IgM with extramedullary disease assessment every 3 months, according to response criteria in the NCCN WM guidelines and modified Owen criteria (*Br J Haematol* 2013;160:171-176).

Results

A total of 26 *MYD88^{WT}* WM **patients (5 TN**, 21 R/R) **were enrolled into Cohort 2; 23 *CXCR4^{WT}*, 1** *CXCR4^{WHIM}* **and 2 with unknown** *CXCR4^{WHIM}* **mutation status. The median duration of follow-up (cut-off 30Nov2018) was 9.5 months** (range, 2.3-18.8). The overall response rate was 76.9% (20/26), with a major response rate of 53.8% (14/26) including 15.4% (4/26) with VGPR; one patient achieved normalized IgM and was negative by immunofixation (CR by IgM) but extramedullary disease persisted. Median time to first major response was 2.9 months (range, 1.9-7.4). Median PFS has not been reached. Most frequent adverse events (AEs in ≥15%) were diarrhea (19.2%, grade 3: 7.7%); constipation, contusion, muscle spasm, and upper respiratory tract infection (each 15.4%). Serious AEs occurred in 8 patients (30.8%), all single cases except for pyrexia (n=2, 7.7%). No fatal events or atrial fibrillation were reported. Major hemorrhage was reported in 2 patients (7.7%). Zanubrutinib discontinuations occurred due to AE (n=1, 3.8%), and disease progression (n=4, 15.4%).

Table: Efficacy per Investigator Assessment* in patients with MYD88 unmutated (WT) WM

	Modified Owen, 6th IWWM, n (%)		
Best Overall Response*	TN	R/R	Overall
	n=5	n=21	n=26
Median follow-up (months)	11.56	8.84	9.51
Complete response	0	0	0
Very good partial response	0	4 (19.0)	4 (15.4)
Partial response	2 (40.0)	8 (38.1)	10 (38.5)
Minor response	2 (40.0)	4 (19.0)	6 (23.1)
Stable disease	1 (20.0)	4 (19.0)	5 (19.2)
Progressive disease	0	1 (4.8)	1 (3.8)

*Responses assessed per NCCN WM guidelines, modified Owen criteria (*Br J Haematol*. 2013;160:171-176)

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Conclusion

Zanubrutinib was generally well tolerated and demonstrated single-agent major response activity (including VGPR) in over 50% of patients with *MYD88^{WT}* WM. The depth and durability of response in patients with MYD88^{WT} WM will be further assessed in this ongoing Phase 3 study