Improved depth of response with increased follow-up in a phase 1 trial of patients with Waldenström macroglobulinemia (WM) treated with oral Bruton tyrosine kinase (BTK) inhibitor zanubrutinib (BGB-3111)

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Investigational BTK inhibitor zanubrutinib demonstrated greater selectivity versus other TEC- and EGFR-family kinases in biochemical assays and favorable pharmacokinetics/pharmacodynamics in preclinical studies. In phase 1 testing, high plasma concentrations were achieved, resulting in complete and sustained 24-hour BTK inhibition in blood and lymph nodes. Early clinical data demonstrated activity in CLL, WM, and other NHLs. Reported here are data from 67 WM patients (21 treatment-naïve, 46 relapsed/refractory [1–8 prior regimens]) in an open-label, multicenter, dose-finding phase 1 study in patients with B-cell malignancies, with indication-specific expansion cohorts. Patients received zanubrutinib 40mg qd to 160mg bid (RP2D) until disease progression or unacceptable toxicity. Patients were assessed monthly by IgM with extramedullary disease assessment every 3 months. Median follow-up (cutoff: 3Nov2017) was 15.5 months. 67 patients were evaluable for safety; 51 were evaluable for efficacy, excluding those with <12 weeks follow-up (n=13) or baseline IgM <5 g/L (n=3). Most frequent adverse events (AEs; ≥15%) were petechiae/purpura/contusion (37.3%), upper respiratory tract infection (34.3%), constipation (17.9%), and diarrhea (17.9%). Grade 3/4 AEs in ≥2 patients included anemia (7.5%), neutropenia (6.0%), basal cell carcinoma (3.0%), hypertension (3.0%), squamous cell carcinoma (3.0%), pyrexia (3.0%), pneumonia (3.0%), and actinic keratosis (3.0%). Serious AEs occurred in 22 patients (32.8%), 5 (7.5%) zanubrutinib-related: febrile neutropenia, colitis, atrial fibrillation, hemothorax (spontaneous), and headache.

Atrial fibrillation/flutter occurred in 4 patients (6.0%), all grade 1/2. Major hemorrhage occurred in 2 patients (3.0%). Four patients (6.0%) discontinued zanubrutinib because of AEs (n=1 each): fatal worsening bronchiectasis, prostate adenocarcinoma, gastric adenocarcinoma, and acute myeloid leukemia. Overall response rate was 92.2% (n=47/51), major response rate was 80.4% (n=41/51; **Table**). Median time to response was 88 days. For 22 patients (43.1%) with baseline hemoglobin <10 g/dL, the median increased from 8.7 to 13.8 g/dL. For all 51 patients, median IgM decreased from 32.5 to 4.9 g/L. Median progression-free survival was not reached; 1-year estimated progression-free survival was 91.0% (**Figure 1**). Zanubrutinib was generally well tolerated and highly active in WM in this phase 1 trial, with VGPR rates improving over time (**Figure 2**). A phase 3 study comparing zanubrutinib with ibrutinib in WM is ongoing.

Table. Efficacy per Investigator Assessment*

Best Response, n (%)	n=51
Very good partial response	22 (43.1)
Partial response	19 (37.3)
Minor response	6 (11.8)
Stable disease	4 (7.8)

*Responses assessed per NCCN WM guidelines.

Figure 1. Progression-Free Survival, Efficacy Analysis Set

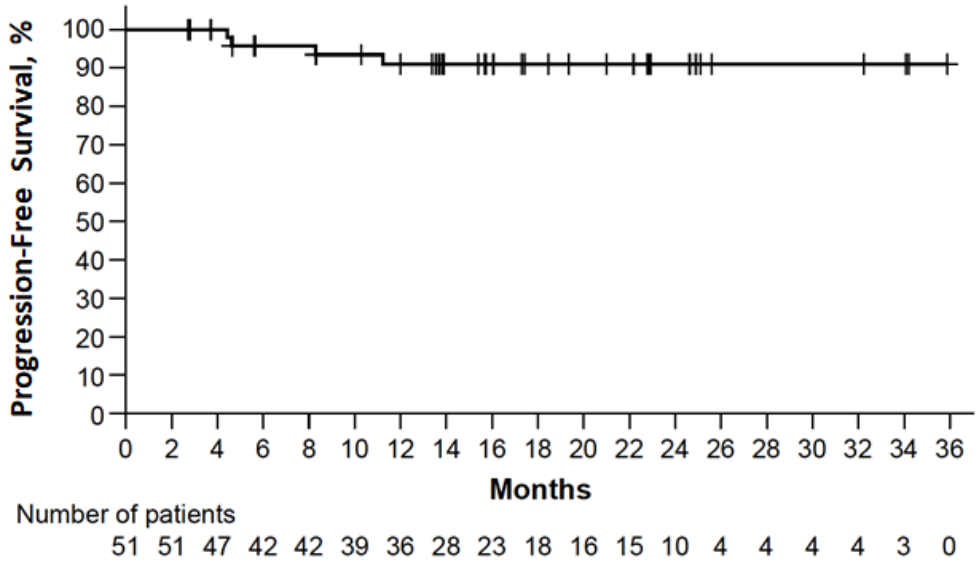
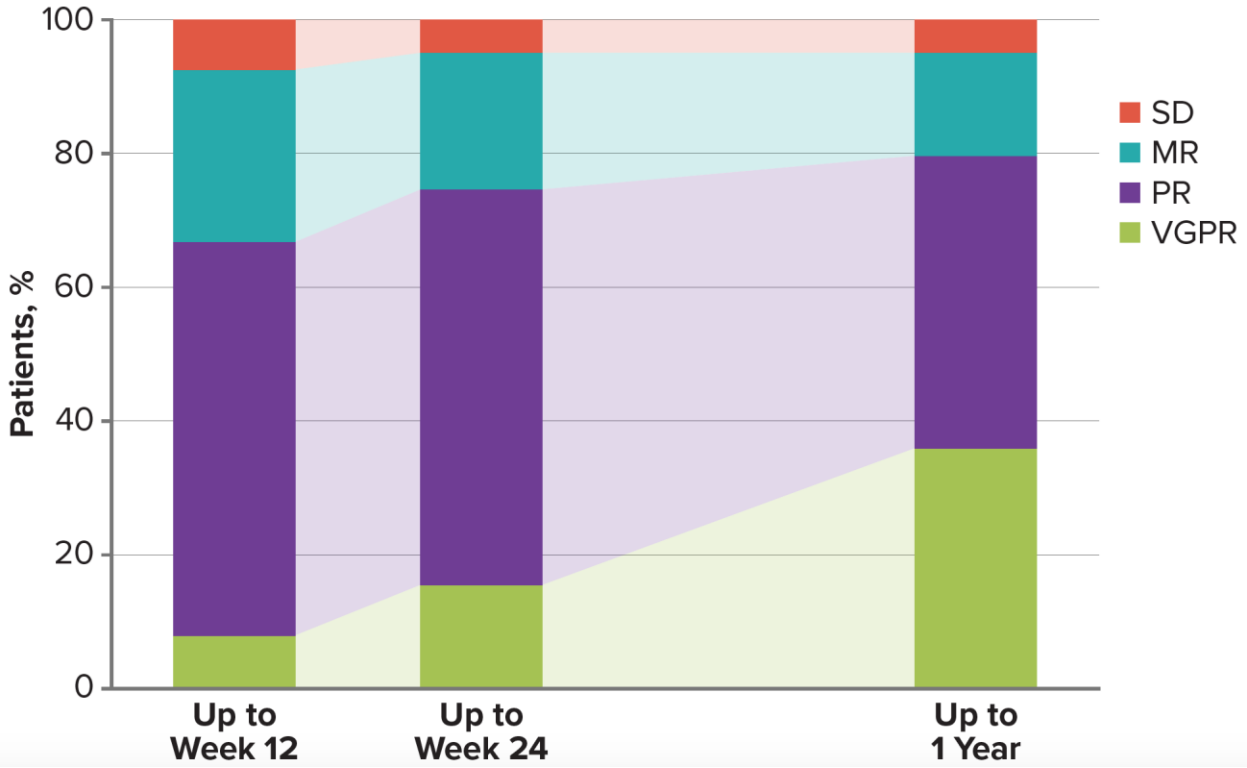
Figure 2. Best Response Over Time in Patients with ≥1 Year of Follow-Up (n=39)