Treatment of Waldenstrom Macroglobulinemia with the Highly Specific BTK Inhibitor BGB-3111

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Introduction: The BTK inhibitor ibrutinib (IB)is highlyactive inWM, achieving major responsesin 70% of pts.However, VGPR is infrequent,with rates ≤15% in reported series.BGB-3111 is a potent, highly-specific and irreversible BTK inhibitor, withgreater selectivity than IB for BTK vs. other TEC- and HER-family kinases, and superior bioavailability. We previously reported that the recommended phase 2 dose of BGB-3111 is 320mg daily (in single or split dose) in pts with advanced B cell malignancies. This achieves plasma levels equivalent to 6-10 fold that of IB, and at the dose of 160mg BID, complete and continuous inhibition of BTK in lymph node biopsies (Figure 1).

Methods: We present the results of BGB-3111 in patients with WM treated on a phase I study, including patients enrolled in dose escalation (n=6), and in WM specific expansion cohorts (n=20). Responses were determined according to the modified Sixth International Workshopon WM (IWWM) criteria. The data cut-off is 10 June 2016.

Results: Twenty-four pts are included in this analysis; 2 pts accrued at a single site were excluded because of insufficient documentation at baseline. Median age was 66 years, and 96% were previously treated with a median 2 lines of therapies. BGB-3111 was well tolerated with 71% reporting no drug related AE>Gr 1 severitywithin the first 12 weeks of therapy. The most frequent AEs (≥20%) of any attribution (all Gr 1/2) were

upper respiratory infection (25%), diarrhea (25%),and nausea (21%). There were 2SAEs assessed as possibly related to BGB-3111 (Gr 2 atrial fibrillation, Gr 3 cryptococcal meningitis); in both cases, BGB-3111 was temporarily held but safely resumed.In total, 2 pts developed AF (one Gr 1, one Gr 2).No serious hemorrhage (≥Gr 3 or CNS hemorrhage of any grade) was reported. After a median follow-up of 7.6 months (2-21 months), the response rate was 92% (22/24). The major response rate was 83% (20/24), with VGPR (>90% reduction in IgM and reduction in extramedullary disease) in 33% (8/24) and PR (50-90% reduction in IgM and reduction in extramedullary disease) in 50% (12/24) pts (Figure 2).Median time to initial response and major response were 29 days and 34 days, respectively. IgM decreased from a median of 29.9g/l at baseline to 3.0g/l; hemoglobin increased from a median of 10.1g/dl at baseline to 13.5g/l. Only one patient discontinued BGB-3111, due to exacerbation of pre-existing bronchiectasis while in VGPR. There have been no cases of disease progression. Analysis of response by genomic characteristics (including MYD88 and CXCR4 mutational status) is ongoing.

Conclusions:BGB-3111 is well-tolerated and highly active in WM. The depth and quality of responses, as reflected by the VGPR rate of 33%,warrant a randomized comparison againstibrutinib in pts with WM.

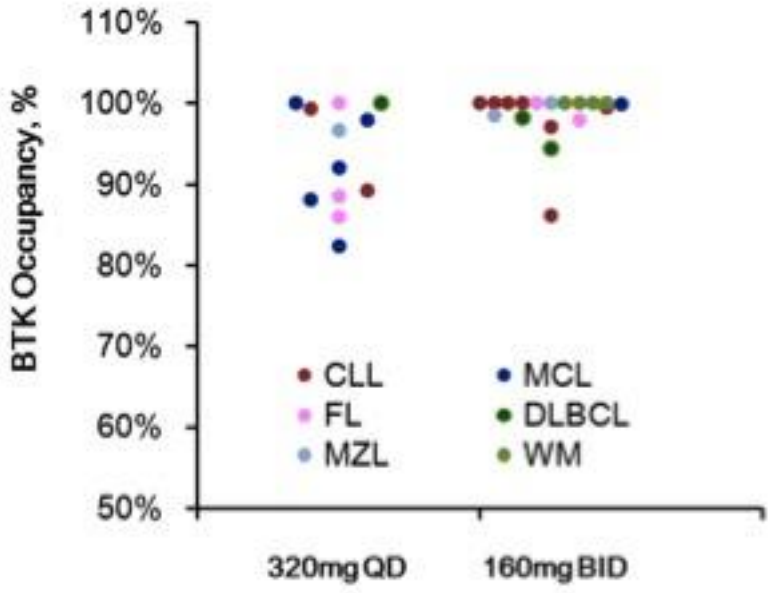

Figure 1: Trough BTK occupancy in lymph node biopsies

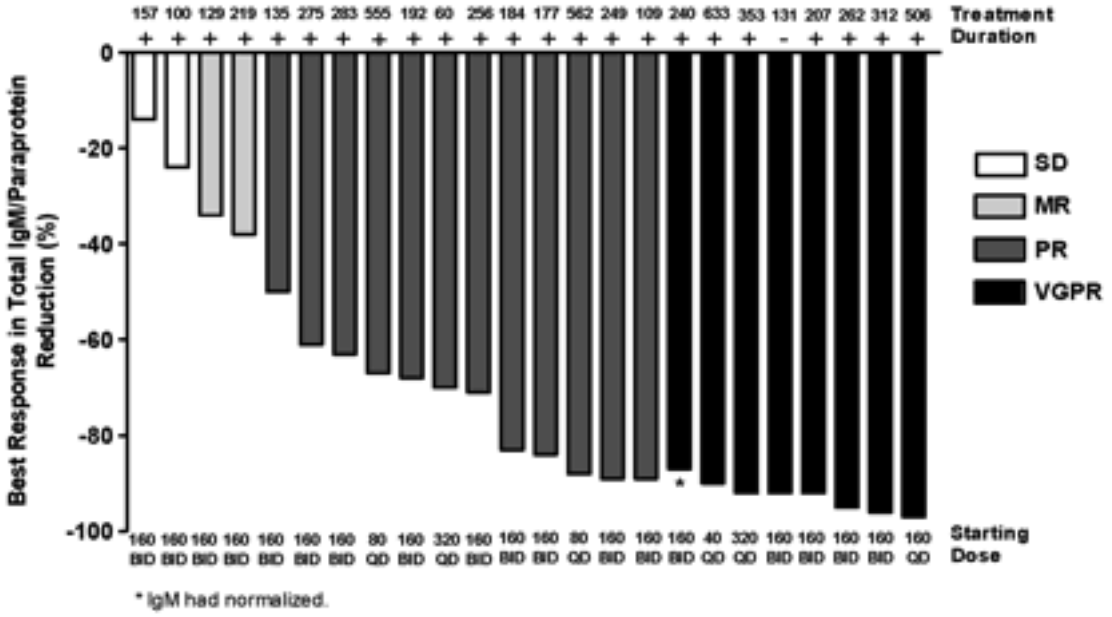

Figure 2: IgM Responses to BGB-3111