Long-term impact of dose interruptions (DIs) of Bruton tyrosine kinase inhibitors (BTKis) on change in IgM levels and clinical Outcomes in Waldenström macroglobulinemia (WM)

Authors: Judith Trotman,[1] Katherine Rankin,[2] Ibrahim Tohidi-Esfahani,[1] Alessandra Tedeschi,[3] Constantine S. Tam,[4] Christian Buske,[5] Roger G. Owen,[6] Véronique LeBlond,[7] Meletios A. Dimopoulos,[8] Peter Smallwood,[9] Heather Allewelt,[10] Wai Y. Chan,[10] Radha Prathikanti,[10] Jingjing Schneider,[10] Remus Vezan,[10] Stephen Opat[11]

Affiliations: [1]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [2]Calvary Mater Newcastle Hospital, Waratah, NSW, Australia; [3]ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy; [4]Alfred Hospital and Monash University, Melbourne, VIC, Australia; [5]Institute of Experimental Cancer Research, Comprehensive Cancer Center Ulm, University Hospital Ulm, Ulm, Germany; [6]St. James's University Hospital, Leeds, UK; [7]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [8]National and Kapodistrian University of Athens, School of Medicine, Alexandra Hospital, Athens, Greece; [9]Patient author, Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [10]BeiGene USA, Inc, San Mateo, CA, USA; [11]Lymphoma Research Group, School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia

Introduction: BTKis are a mainstay of therapy for patients with WM, with most receiving continuous oral monotherapy for several years. While dosing is commonly interrupted, data on the impact of BTKi DIs on disease control remain limited. The phase 1/2 BGB-3111-AU-003 study (NCT02343120) evaluated zanubrutinib monotherapy in patients with B-cell malignancies. The subsequent phase 3 ASPEN study (NCT03053440) evaluated zanubrutinib vs ibrutinib in patients with *MYD88* mutated WM and zanubrutinib in patients with *MYD88* wild-type WM. At the end of each study, eligible patients (including those in the ibrutinib arm) could enroll in a zanubrutinib long-term extension study, BGB-3111-LTE1 (NCT04170283). Here, data is presented from a large cohort of patients with WM across all 3 studies, with consistent criteria for BTKi DI for adverse events (AEs) and surgery/procedures.

Methods: This was an ad hoc analysis of data from all patients with WM enrolled in AU-003 and ASPEN, and their continued treatment in LTE1, if applicable. Response assessments were based on modified IWWM-6 response criteria (Owen 2013). IgM flare was defined as a rise in serum IgM level or in known extramedullary disease meeting progressive disease (PD) criteria after DI of ≥7 consecutive days. DI impacts were assessed at the event and patient levels. Loss of disease control was indicated by IgM flare or hemoglobin (Hgb) decrease of >20 g/L immediately following DI. Patient level impact was assessed by recovery rates (IgM, Hgb, and categorical response returning to pre-DI level or better) and PD. Summary statistics are reported; for ASPEN data, a joint modeling method was used for the recurrent event of dose holds and longitudinal IgM and Hgb values, with adjustments for treatment effect, stratification factors (prior therapy lines and CXCR4 mutation status), age group (≤65, >65), and baseline IgM or Hgb values.

Results: Data from 301 patients was included (ASPEN, n=227 [zanubrutinib, n=129; ibrutinib, n=98]; AU-003, n=74 zanubrutinib). Median treatment duration was 45 months (IQR, 14-56) and the overall PD rate during study was 24%. Of 225 patients, 75% had a total of 806 DI (73% due to AEs; 64% for procedures). The median duration of DI was 7 days (IQR, 4-11) with 56 DIs ≥28 days in duration. Recurrent DIs ≥7 days were associated with Hgb decrease (HR, 0.987; *P*=.002); no significant relationship was seen between DIs ≥7, ≥14, or ≥28 days and increase in IgM. Eleven (1%) of DI events were immediately followed by PD. IgM flare occurred following 12% of DI events (by DI duration: 20% [≥7 days], 34% [≥14 days], 41% [≥28 days], 10% [<28 days]). Median changes in IgM were 1.6 g/L (IQR, −0.4-6), 2.7 g/L (IQR, 0-9), and 4.3 g/L (IQR, 0.4-11.1) following DIs of ≥7, ≥14, and ≥28 days in duration, respectively. IgM flare in the context of DIs of <28 days and ≥28 days were followed by IWWM-6 categorical response recovery in 77% and 74% of events, and IgM recovery to ≤ pre-DI level in 61% and 57%. The median time from treatment reinitiation to complete IgM recovery was 154 days (IQR, 78-280). The probability of IgM non-recovery from IgM flare was 46% for patients after DI ≥28 days vs 29% for patients with no DI ≥28 days; however, rates of subsequent PD were 10% and 30%. The PD rates for patients without IgM recovery were 25% vs 5% with ≥1 occurrence of IgM recovery following DI (*P*=.026).

The proportions of DI events with a subsequent ≥20-g/L decrease in Hgb were 15% (≥7 days), 24% (≥14 days), 33% (≥28 days), and 11% (<28 days); Hgb recovery occurred after 33% of these events; the median time from treatment reinitiation to Hgb recovery was 84 days (IQR, 49-156). Patients with DI in the first 12 months of treatment had a higher PD rate (29%) than those without (13%, *P*=.017); the difference in PD rates for those with DI in the first 6 months vs those without was not significant (28% vs 21%, *P*=.209).

Conclusions: This analysis of 806 DIs in 301 patients with WM with a median BTKi treatment duration of almost 4 years, provides practice-relevant information on the short- and long-term impacts of BTKi DI. IgM flare or Hgb decrease >20 g/L occurred more frequently with increased DI duration. Most patients with IgM flare following DI returned to their prior level of disease control, and DIs after the first year of therapy conferred lower risk of PD than those within the first year. Taken together, these data may help patients and clinicians weigh the risks and benefits of BTKi DI, including the relative timing and duration of DI.