Pooled Analysis of Safety Data from Zanubrutinib (BGB-3111) Monotherapy Studies in Haematologic Malignancies

Abstract PF445

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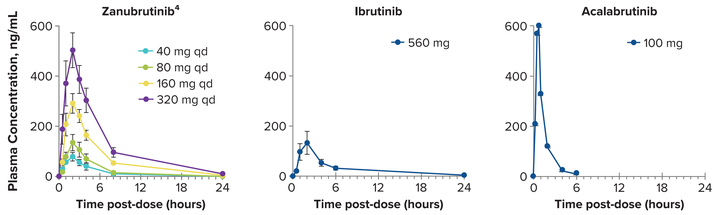
INTRODUCTION

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor (BCR) signaling, which mediates B-cell proliferation, migration, and adhesion[1–3]
- Based on preclinical data, zanubrutinib (BGB-3111) was shown to be a potent, highly selective, and irreversible BTK inhibitor with advantageous pharmacokinetics, designed to minimize off-target inhibition of TEC- and EGFR-family kinases (**Figure 1**)[4]
  - Complete and sustained BTK occupancy in peripheral blood mononuclear cells AND lymph nodes (**Figure 2**)
  - Scientific rationale for reduced toxicity profile or perhaps enhanced efficacy compared with less specific and potent BTK inhibitors

Figure 1. Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



Adapted from Advani RH, et al. *J Clin Oncol.* 2013[5]

Adapted from Byrd JC, et al. *N Engl J Med.* 2015[6]

Figure 2. Sustained BTK Inhibition in Peripheral Blood and Lymph Nodes

Complete and sustained BTK occupancy is seen in paired PMBC (left figure) and lymph node biopsy samples (right figure) collected pre-dose on day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg). Note, 100% median trough occupancy at a dose of 160 mg bid with 94% of patients having > 90% occupancy in lymph nodes across malignancies.

METHODS

- Safety data from patients in 4 ongoing zanubrutinib monotherapy studies were analysed (**Table 1**)

Table 1. Zanubrutinib Monotherapy Studies Included in Pooled Analysis

ClinicalTrials.gov Identifier	Study Number	Phase	Malignancies	Patients (n)
NCT03189524	BGB-3111-1002	1	B-cell lymphoma	44
NCT03206918	BGB-3111-205	2	R/R CLL/SLL	91
NCT03206970	BGB-3111-206	2	R/R MCL	86
NCT02343120	BGB-3111-AU-003	1	B-Cell lymphoid malignancies	255

CLL/SLL, chronic lymphocytic leukaemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; MCL, mantle cell lymphoma; R/R, relapsed/refractory.;

- All patients have been treated with ≥1 dose of oral (po) zanubrutinib at 40 mg once-daily (qd) to 160 mg twice-daily (bid)
- The analysis included frequency and severity of adverse events (AEs), AEs of interest, and AEs leading to treatment discontinuation

RESULTS

- A total of 476 patients were included in the pooled analysis
- Median age was 63 years and 70% were male (**Table 2**)
  - Majority of patients (92%) had relapsed/refractory disease

Table 2. Baseline and Disease Characteristics

	N=476
Age (years), median (range)	63 (20-87)
<65 years, n (%)	266 (56)
65 to <75 years, n (%)	146 (31)
≥75 years, n (%)	64 (13)
Male sex, n (%)	333 (70)
Female sex, n (%)	143 (30)
Eastern Cooperative Oncology Group performance status, n (%)	
0	236 (50)
1	218 (46)
2	22 (5)
Prior treatment status, n (%)	
Treatment-naïve	38 (8)
Relapsed/refractory	438 (92)
Prior lines of therapy, median (range)	2 (1-10)
Mean body mass index (range), kg/m²	25 (15-55)

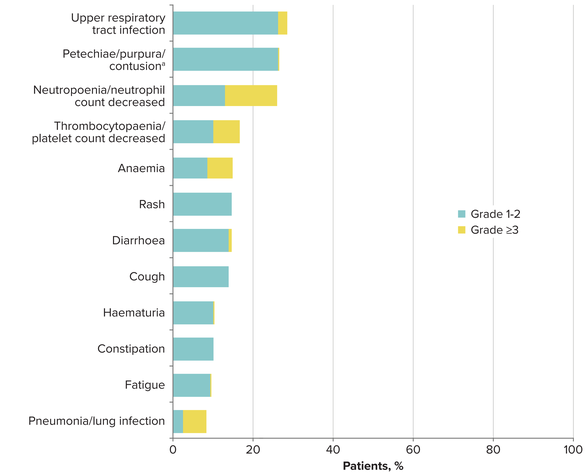
- Patients were treated with zanubrutinib for median of 7 months and a maximum of 36 months (**Table 3**)
  - 15% of patients were treated for ≥72 weeks
  - 35% of patients required dose modifications
  - 23% of patients had discontinued treatment, most commonly due to progressive disease (14%) or adverse events (5%)
    - 3% of patients discontinued zanubrutinib due to treatment-related AEs

Table 3. Exposure and Disposition

	N=476
Months of exposure, median (range)	7.0 (0.02-36.05)
<12 weeks, n (%)	119 (25)
12 to <36 weeks, n (%)	147 (31)
36 to <72 weeks, n (%)	142 (30)
72 to <120 weeks, n (%)	56 (12)
≥120 weeks, n (%)	12 (3)
Patients with dose modifications, n (%)	165 (35)
Dose interruptions	152 (32)
Dose reductions	52 (11)
Patients discontinued, n (%)	109 (23)
Due to progressive disease	66 (14)
Due to adverse event (regardless of relation to treatment)	26 (5)
Withdrawal by patient	9 (2)
Noncompliance	3 (<1)
Other	16 (3)

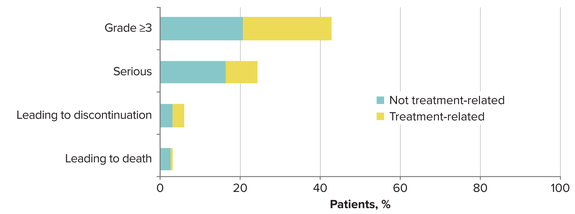
- The majority of patients experienced ≥1 AE (94%), primarily grade 1-2 (**Figures 3-4**)
  - The most common Grade ≥3 AEs were neutropoenia/neutrophil count decreased (14%), anaemia (7%), and thrombocytopaenia/platelet count decreased (7%)
- Serious AEs (SAEs) were reported in 116 patients (24%), including 8% assessed as related to zanubrutinib (**Figure 4**)
  - The most common SAEs were pneumonia/lung infection (6%), pleural effusion (1%), and febrile neutropoenia (1%)
  - The only treatment-related SAE reported in >1% of patients was pneumonia/lung infection (2%)
  - No cases of pneumocystis jirovecii pneumonia (PJP) or cytomegalovirus (CMV) reactivation were reported

Figure 3. Most Common Adverse Events (All Grade in ≥10% or Grade ≥3 in ≥2%) Regardless of Causality



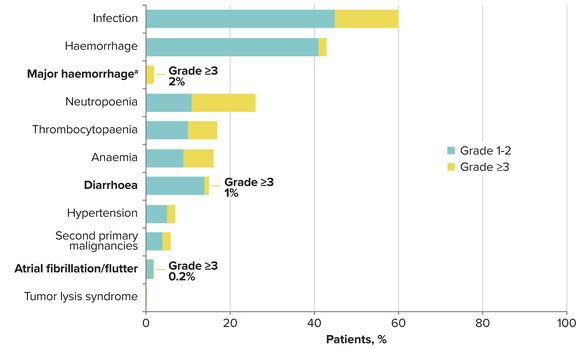
[a]Includes patients with any of the 3 preferred terms.

Figure 4. Safety Summary



- AEs of interest were reported in 396 patients (83%) (**Figure 5**)
- The most common bleeding events included petechiae/purpura/contusion (27%) and haematuria (11%)
  - Major haemorrhage (2%) included gastrointestinal haemorrhage/melena (n=3), intraparenchymal CNS haemorrhage Gr 5, haematuria, purpura, haemorrhagic cystitis, renal haematoma, and haemothorax (each n=1)
    - Among these 8 patients with major haemorrhage, only 1 had thrombocytopaenia AEs or medical history of thrombocytopaenia
    - The median time to first major haemorrhage was 1.2 months (range, 0.1-8.6)
- Amongst patients with emergent atrial fibrillation/flutter (n=8), a majority had known risk factors including hypertension (n=2), pre-existing cardiovascular disease (n=2), and concurrent infection (n=1)
- The cumulative rates of Grade ≥3 infections were 14% at month 6, 19% at month 12, and 21% at month 18
  - Exposure-adjusted incidence rate of 1.82 per 100 person-months
- The most frequent funcal infections were vulvovaginal candidiasis, bronchopulmonary aspergillosis, and oral candidiasis (<1%)
- The most common second primary malignancies included basal cell carcinoma (3%) and squamous cell carcinoma of skin (2%)
  - Other Grade ≥3 second primary malignancies included breast cancer, colon cancer, sqamous cell carcinoma, invasive ductal breast carcinoma, lentigo maligna, lung neoplasm malignant, malignant melanoma, metastases to central nervous system, and prostate cancer

Figure 5. Adverse Events of Interest, by Category, Regardless of Causality



[a]Includes serious or Grade ≥3 bleeding of any site, or central nervous system bleeding of any grade.
AEs of interest chosen based on warnings and precautions for other BTK inhibitors.

CONCLUSIONS

- Zanubrutinib has been generally well-tolerated in patients with various B-cell malignancies
- In zanubrutinib's cumulative safety experience, events of interest with BTK inhibitors, such as atrial fibrillation/flutter (2%), major haemorrhage (2%), and grade 3 and above diarrhoea (1%), have been infrequent
- Treatment discontinuation due to zanubrutinib-related AEs was uncommon (3%)
- Data suggest that exposure levels of zanubrutinib resulting in complete and sustained BTK inhibition can be achieved with tolerability

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DISCLOSURES

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