POOLED ANALYSIS OF SAFETY DATA FROM MONOTHERAPY STUDIES OF THE BRUTON TYROSINE KINASE (BTK) INHIBITOR, ZANUBRUTINIB (BGB-3111) IN B-CELL MALIGNANCIES

Abstract PS1159

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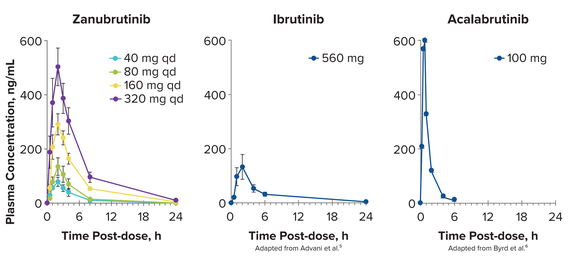
INTRODUCTION

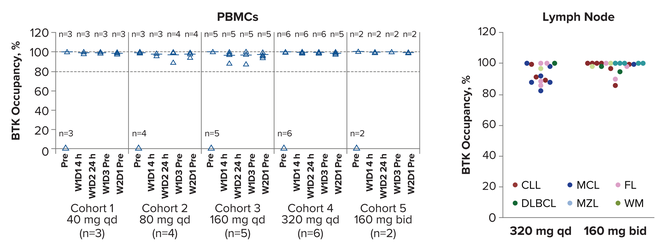
- Bruton tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
- Zanubrutinib (BGB-3111) is an investigational BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous pharmacokinetic/pharmacodynamic properties[4] (**Figure 1**)
  - Complete and sustained BTK occupancy in both peripheral blood mononuclear cells and lymph nodes[4] (**Figure 2**)
    - Provides a scientific rationale for a reduced toxicity profile and perhaps enhanced efficacy compared with less specific and potent BTK inhibitors
- Based on drug interaction studies:
  - Co-administration with strong or moderate CYP3A inhibitors (including agents such as azole anti-fungals, important in the management of patients with leukemia/lymphoma) is permitted at a reduced dose
  - Co-administration of proton pump inhibitors or other gastric acid-reducing agents does not affect zanubrutinib exposure
  - Patients have been allowed to receive anticoagulant and antiplatelet agents on zanubrutinib trials

Figure 1: Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib



qd, once daily.
Note: these data are from 3 separate analyses and differences in studies should be considered.

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



Complete and sustained BTK occupancy is seen in PBMC (left figure) and lymph node biopsy samples (right figure) collected predose 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 twice daily, with 94% of patients having >90% occupancy in lymph nodes across malignancies.
bid, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; D, day; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; Pre, predose; W, week; WM, Waldenström macroglobulinemia.

METHODS

- Safety data from patients in 6 ongoing zanubrutinib monotherapy studies were pooled and analyzed (**Table 1**)
- All patients were treated with ≥1 dose of oral zanubrutinib at doses of 40 to 320 mg once daily (qd); almost all received either 320 mg qd or 160 mg twice daily (bid)
- The analysis includes frequency/severity of adverse events (AEs), AEs of interest, and treatment discontinuation due to AEs

Table 1. Zanubrutinib Monotherapy Studies Included in Pooled Analysis

ClinicalTrials.gov Identifier	Study Number[a]	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
NCT03145064	BGB-3111-207	2	R/R, non-GCB DLBCL	41
NCT03332173	BGB-3111-210	2	R/R WM	44
NCT02343120	BGB-3111-AU-003	1/2	B-cell malignancies	376
TOTAL:				**682**

[a]Data cutoff dates: BGB-3111-207: Sep 2018; BGB-3111 AU-003, -1002, -205, and 210: Dec 2018; BGB-3111-206: Feb 2019.
CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; MCL, mantle cell lymphoma; R/R, relapsed/refractory; WM, Waldenström macroglobulinemia.

RESULTS

- A total of 682 patients were included in the pooled analysis (**Table 2**)
  - Median age was 64 years, and 68% were men
  - 15% were aged ≥75 years
  - Most patients (91%) had relapsed or refractory disease

Table 2. Baseline Demographic and Disease Characteristics

	N=682
Age, median (range), y	64 (20-90)
<65, n (%)	357 (52)
65 to <75, n (%)	224 (33)
≥75, n (%)	101 (15)
Men, n (%)	464 (68)
ECOG PS, n (%)	
0/1	639 (94)
2	43 (6)
Prior treatment status, n (%)	
Treatment-naïve	63 (9)
Relapsed/refractory	619 (91)
Prior lines of therapy (relapsed/refractory patients), median (range)	2 (1-12)
B-cell malignancy, n (%)	
Waldenström macroglobulinemia	124 (18)
CLL/SLL	226 (33)
Non-Hodgkin lymphoma	310 (46)
Other (hairy cell leukemia; Richter transformation)	22 (3)

ECOG PS, Eastern Cooperative Oncology Group performance status.

- Patients were treated with zanubrutinib for a median of 13.4 months (**Table 3**)
  - 57% of patients had ≥12 months of exposure
  - 5% of patients were treated for ≥36 months
  - Median (25th-75th percentile) relative dose intensity across all studies was 99.8% (99.1-100)
  - 38% of patients discontinued treatment, most commonly due to progressive disease (25%) or AEs (9%) as the primary reason

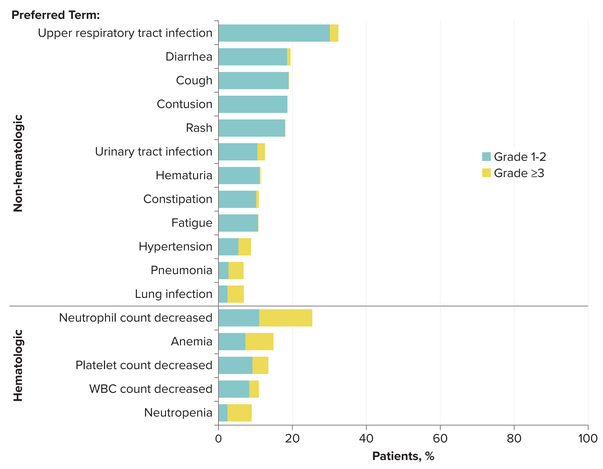
Table 3. Exposure and Patient Disposition

	N=682
Exposure, median (25th-75th percentile), mo	13.4 (6.1, 19.6)
Patients discontinued treatment, n (%)	259 (38.0)
Primary reason for treatment discontinuation[a], n (%)	
Progressive disease	169 (25)
Adverse event	62 (9)
Withdrawal by patient	14 (2)
Investigator discretion	8 (1)
Protocol deviation, other	6 (1)

[a]Based on study treatment discontinuation case report form.

- Almost all patients (97%) reported ≥1 AE, primarily grade 1-2 (**Figure 3**):
  - The most common grade ≥3 AEs were neutrophil count decreased (14%), anemia (8%), neutropenia (7%), pneumonia (5%), platelet count decreased (4%), lung infection (4%), and hypertension (3%)

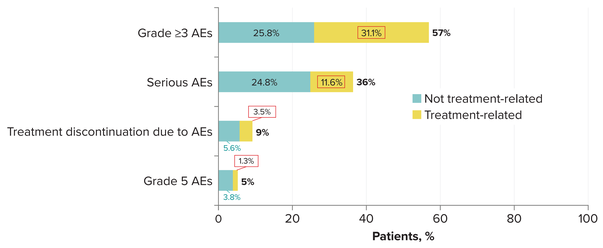
Figure 3. Most Common AEs (All Grade in ≥10% or Grade 3 or higher in ≥3%)[a]



[a]Regardless of causality.
AE, adverse event; WBC, white blood cell.

- Serious AEs (SAEs) were reported in 248 patients (36%), including 79 (12%) assessed as treatment-related (**Figure 4**):
  - The most common SAEs were pneumonia (5%), lung infection (3%), urinary tract infection (2%), pyrexia (2%), cellulitis (1%), anemia (1%), and pleural effusion (1%)
  - Treatment-related SAEs reported in >1% of patients were pneumonia and lung infection (each 2%)

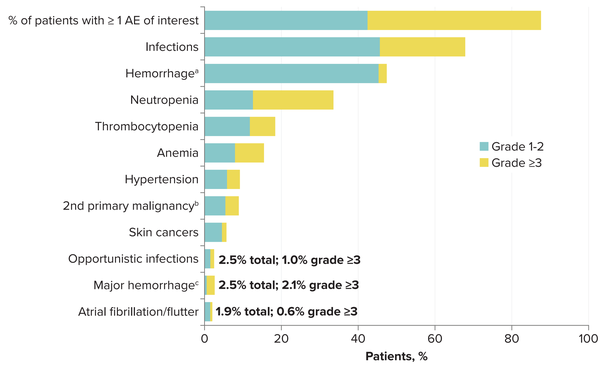
Figure 4. Safety Summary



AE, adverse event.

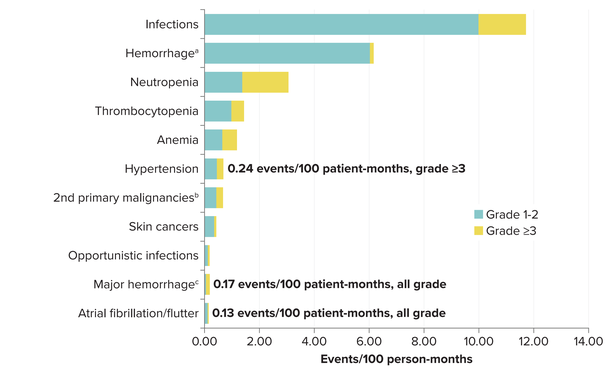
- Median (25th-75th percentile) time to treatment discontinuation due to AEs was 3.7 months (1.6, 7.7)
- Grade 5 AEs reported in >1 patient were pneumonia (n=6; <1%); septic shock (n=2; <1%); death, cause unspecified (n=5; <1%); fatigue (n=2; <1%); and multiorgan system failure (n=2; <1%)
  - Of 35 patients with grade 5 AEs, at least 7 occurred in the setting of disease progression
- At least 1 AE of interest was reported in 87.7% of patients (**Figure 5**)

Figure 5. AEs of Interest by Category



AE, adverse event.
[a]Inclusive of major hemorrhage; events consist primarily of grade 1-2 mucocutaneous bleeding.
[b]Inclusive of skin cancers (primarily basal cell [3.5%] and squamous cell carcinomas [2.2%]).
[c]Includes any serious or grade ≥3 bleeding event or central nervous system bleed of any severity grade.

Figure 6. Exposure-Adjusted Incidence Rates for AEs of Interest by Category



AE, adverse event.
[a]Inclusive of major hemorrhage.
[b]Inclusive of skin cancers.
[c]Includes any serious or grade ≥3 bleeding event or central nervous system bleed of any severity grade.

Hemorrhage

- The most common events included grade 1-2, mucocutaneous bleeding (ie, petechiae, purpura, contusion, hematuria, epistaxis)
- Major hemorrhages reported in >1 patient included:
  - Gastrointestinal (GI) hemorrhage/upper GI hemorrhage, n=3 (in 3 mantle cell lymphoma patients, hemorrhage was reported in the setting of GI tumor recurrence)
  - Hematuria, n=2
  - Intracranial hemorrhage, n=3
    - Grade 5 cerebral hemorrhage in a MCL patient with blastic histology and poor risk MIPI-b on study day 6
    - Grade 2, post-traumatic, right thalamic hemorrhage in a patient with chronic lymphocytic leukemia/small lymphocytic lymphoma on study day 369
    - Grade 3, bilateral subdural hematomas on study day 9 in a B-cell lymphoma patient with prestudy atrial fibrillation receiving rivaroxaban
- Exposure-adjusted incidence rate for major hemorrhage, 0.17 events/100 patient-months (**Figure 6**)

Atrial fibrillation/flutter

- Exposure-adjusted incidence rate for atrial fibrillation/flutter, 0.13 events/100 patient-months (**Figure 6**)
  - Among 13 (1.9%) patients with atrial fibrillation, 10 (77%) occurred in the first 12 months of study treatment
- Most patients had known risk factors including hypertension (n=4), pre-existing cardiovascular disease (n=7), hyperlipidemia (n=4), concurrent infection (n=4), and prior atrial fibrillation (n=1)

Infections

- Most infections involved the respiratory and urinary tracts
- At least 1 grade ≥3 infection was reported in 22.3% of patients; 14.7% reported a first grade ≥3 infection within the first 6 months of treatment; 18.8% reported a first grade ≥3 infection within the first 12 months of treatment
- Opportunistic infections (OIs) reported in >1 patient were herpes simplex (n=7), bronchopulmonary aspergillosis (n=4), and cryptococcal meningitis (n=2)
  - Other OIs included cerebral aspergillosis, listeria sepsis, esophageal candidiasis, cryptococcal pneumonia, scedosporium infection (each n=1)
  - All OIs were reported in the first 12 months of treatment

Second primary malignancies

- 60 patients (8.8%) reported at least 1 second primary malignancy
- Excluding ultraviolet light-mediated skin cancers (basal cell carcinomas, 3.5%; squamous cell carcinomas, 2.2%), second primary malignancies reported in >1 patient included head and neck squamous cell cancer (HNSCC; n=6), prostate cancer (n=4), breast cancer (n=2), colon cancer (n=2), and "malignant neoplasm of auricular cartilage" (n=2)
- Two patients had fatal second primary malignancies (gastric adenocarcinoma and HNSCC)

CONCLUSIONS

- In the cumulative safety experience with zanubrutinib monotherapy, AEs of interest associated with BTK inhibitors, such as atrial fibrillation/flutter (1.9%), major hemorrhage (2.5%), and grade ≥3 hypertension (3.4%) have been infrequent
- Treatment discontinuation due to AEs occurred in 9% of patients overall, including 3.5% of patients for whom the event(s) was treatment-related
- These data indicate that zanubrutinib was generally well tolerated at exposure levels resulting in complete and sustained BTK inhibition in patients with B-cell malignancies

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DISCLOSURES

CST: honoraria from Janssen, AbbVie, Roche, and BeiGene; travel expenses from Janssen and BeiGene; research funding from Janssen and AbbVie

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PM: consulting/advisory role with Roche, Janssen, Novartis, AbbVie, Astellas, and Amgen; travel expenses from Roche

AWR: research funding from AbbVie and Janssen; patents from Genentech, AbbVie

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CD, MJ: stock options with BeiGene

SF, LL, WN: employment and stock options with BeiGene

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