Long-Term Impact of Dose Interruptions of Bruton Tyrosine Kinase Inhibitors on Change in IgM Levels and Clinical Outcomes in Waldenström Macroglobulinemia

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INTRODUCTION

- Bruton tyrosine kinase (BTK) inhibitors are a mainstay of therapy for WM, with most patients receiving continuous oral monotherapy for several years[1,2]
- While dosing is commonly interrupted, data on the impact of dose interruptions (DIs) on disease control remain limited[3]
- Here, data is presented from a large cohort of patients with WM across 3 studies, with consistent criteria for BTK inhibitor DIs for adverse events (AEs) and surgery/procedures:
  - The phase 1/2 BGB-3111-AU-003 study (NCT02343120) evaluated zanubrutinib monotherapy in patients with B-cell malignancies[4,5]
  - The phase 3 ASPEN study (NCT03053440) evaluated zanubrutinib vs ibrutinib in patients with *MYD88* mutated WM (Cohort 1) and zanubrutinib in patients with *MYD88* wild-type WM (Cohort 2)[6,7]
  - The study design, methods, and results of AU-003 and ASPEN have been described[4-7]
  - At the end of each study, eligible patients could enroll in a zanubrutinib long-term extension study, BGB-3111-LTE1 (LTE1; NCT04170283)[8]

METHODS

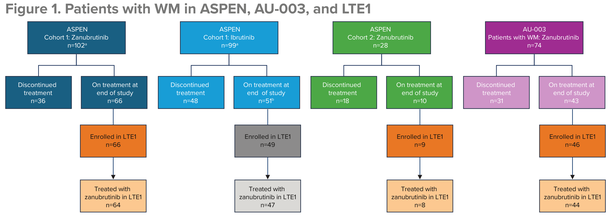
- Data from all patients with WM from AU-003 and ASPEN, were included in this ad hoc analysis; additional long-term follow-up data were included for patients who enrolled in LTE1 following AU-003 and ASPEN
- WM response assessments by the investigators, were per the modified IWWM-6 response criteria[9]
  - IgM flare was defined as a rise in serum IgM level, or in known extramedullary disease, meeting progressive disease 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 decrease of >20 g/L immediately following DI
  - Patient level impact was assessed by recovery rates (IgM, hemoglobin, and categorical response returning to pre-DI level or better) and progressive disease
- Summary statistics are reported
- For the ASPEN data, a joint modeling method was used for the recurrent event of dose holds and longitudinal IgM and hemoglobin values, with adjustments for treatment effect, stratification factors (prior therapy lines and chemokine receptor type 4 [*CXCR4*] mutation status), age group (≤65, >65), and baseline IgM or hemoglobin values, end of treatment is included as a terminal event

RESULTS

Patient Population

- Data from 301 patients from ASPEN (n=227 [zanubrutinib, n=129; ibrutinib, n=98]) and AU-003 (n=74 zanubrutinib) were included in this analysis (**Figure 1**)
- At data cutoff July 1, 2022, 225 patients (75%) had a total of 806 DIs:
  - Of these, 73% were due to AEs and 64% for procedures
- The overall progressive disease rate was 24% (73/301)
- Patient demographics, disease characteristics, and disposition in the AU-003 and ASPEN studies are shown (**Table 1**)

Figure 1. Patients with WM in ASPEN, AU-003, and LTE1



[a] In Cohort 1 of the ASPEN trial, one patient treated with zanubrutinib, and one patient treated with ibrutinib were randomized but not treated. [b] Dose interruptions in ibrutinib-treated patients after transition to zanubrutinib are not included in the analysis.
LTE1, BGB-3111-LTE1 study.

Table 1. Demographics, Disease Characteristics, and Disposition

	AU-003 (n=74)	ASPEN (n=227) Zanubrutinib Cohort 1 (n=101)	ASPEN (n=227) Ibrutinib Cohort 1 (n=98)	ASPEN (n=227) Zanubrutinib Cohort 2 (n=28)	Overall (N=301)
Median study follow-up time (IQR), months	57 (40-71)	52 (48-56)	48 (41-52)	48 (26-52)	50 (42-56)
Age at AU-003/ASPEN enrollment, median (IQR), years	67 (60-75)	70 (62-77)	71 (65-74)	72 (60-81)	70 (63-77)
Male, n (%)	58 (78)	68 (67)	64 (65)	14 (50)	204 (68)
Prior lines of therapy, n (%)					
0	24 (32)	19 (19)	18 (18)	5 (18)	66 (22)
1-3	40 (54)	75 (74)	73 (75)	20 (71)	208 (69)
>3	10 (14)	7 (7)	7 (7)	3 (11)	27 (9)
***CXCR4*^{MUT}, n (%)[a]**	11 (15)	33 (33)	20 (20)	1 (4)	65 (22)
Median treatment duration (IQR), months	56 (25-71)	50 (33-55)	45 (22-51)	30 (11-50)	49 (23-55)
Dose interruptions, n (%)	56 (76)	78 (77)	70 (71)	21 (75)	225 (75)
Progressive disease, n (%)	18 (24)	19 (19)	23 (24)	13 (46)	73 (24)

[a] *CXCR4* mutational status was assessed by next-generation sequencing (NGS), using the PredicineCARE panel, a Clinical Laboratory Amendments-certified NGS assay, which was validated to have a high sensitivity (limit of detection: ~0.1%-0.25%), representing 152 genes.
CXC chemokine receptor type 4; IQR, interquartile range; *MUT*, mutant.

Characteristics of Dose Interruptions

- The median duration of DI events was 7 days (IQR, 4-11) and 56 DIs were ≥28 days in duration (**Table 2**)
- Eleven (1%) of DI events were immediately followed by progressive disease
- The most common AE leading to DI was neutropenia (8% of all events); the most common AE leading to DI ≥28 days in duration was pneumonia (**Table 3**)
- Of DIs due to procedures, all but 6 (98%) were <28 days in duration

Table 2. Characteristics of Dose Interruptions

	Patients with DIs (n=225)	DI events (n=806)
Duration		
Days, median (Q1, Q3)	N/A	7 (4-11)
DI ≥7 days, n (%)	177 (79)	423 (52)
DI ≥14 days, n (%)	103 (46)	166 (21)
DI ≥28 days, n (%)	48 (21)	56 (7)
Recurrence, n (%)		
DI ≥7 days	99 (44)	N/A
DI ≥14 days	39 (17)	N/A
DI ≥28 days	8 (4)	N/A
Timing of first DIs of any duration, n (%)		
Within first 6 months of treatment	99 (44)	156 (19)
Within first year of treatment	157 (70)	292 (36)
Timing of first DIs ≥7 days in duration, n (%)		
Within first 6 months of treatment	65 (29)	91 (11)
Within first year of treatment	98 (44)	156 (19)
Timing of first DIs ≥14 days in duration, n (%)		
Within first 6 months of treatment	28 (12)	35 (4)
Within first year of treatment	45 (20)	59 (7)
Timing of first DIs ≥28 days in duration, n (%)		
Within first 6 months of treatment	6 (4)	9 (1)
Within first year of treatment	21 (9)	21 (3)
Reason for DI (806 events):		
AE	162 (72)	363 (43)
Procedure	141 (63)	383 (48)

AE, adverse event; DI, dose interruption; N/A, not applicable.

Table 3. Most Common TEAEs Leading to Dose Interruption by Duration[a]

DI due to AE[b,c], by SOC/PT n (%)	≥7 days (n=226)[d]	≥14 days (n=117)[d]	≥28 days (n=51)[d]	Any duration (n=363)[e]
Most comment PT				
Neutropenia	16 (57)	3 (11)	2 (7)	28 (8)
Diarrhoea	8 (53)	4 (27)	2 (13)	15 (4)
Pneumonia	8 (67)	5 (42)	4 (33)	12 (4)
Haematuria	7 (58)	3 (25)	1 (8)	12 (4)
Respiratory tract infection	6 (6)	3 (30)	0	10 (3)

[a] Study drug (zanubrutinib or ibrutinib) may be held for a maximum of 2 consecutive cycles and restarted upon resolution of toxicity and per investigator's discretion. If, in the investigator's opinion, it is in the patient's best interest to restart study drug after the dose has been held for more than 2 consecutive cycles, then written approval must be obtained from the Sponsor's Medical Monitor or designee. [b] Protocol recommendation: In the event of Grade 3/4 hematologic toxicity, at least grade 3 febrile neutropenia, or non-hematological toxicities that are at least grade 3, meeting dose hold criteria (as defined by the protocol), study drug will be held until recovery to ≤ grade 1 or baseline.
[c] Protocol recommendation: To minimize the risk of bleeding, patients will hold study drug for 3 to 7 days pre-and post- surgery, depending on the type of surgery, and the risk of bleeding. [d] Denominator of the percentage is the number of DI of any duration due to the specific PT (as in the last column). [e] Denominator of the percentage is the number of DI due to AE of any duration. There are 28 (8%) of missing PTs.
AE, adverse events; DI, dose interruption; PT, preferred term; SOC, system organ class.

Hemoglobin and Disease Progression Following Dose Interruptions

- The median change in hemoglobin was -2 g/L following DIs shorter than 14 days, and -5 g/L following DIs 28 days or longer (**Table 4**)
- The proportion of DI events with a subsequent >20 g/L decrease in hemoglobin was the lowest in DI events <14 days (**Table 4**)
- Hemoglobin recovery occurred after 33% of DI events associated with >20 g/L decrease in hemoglobin; the median time from treatment reinitiation to hemoglobin recovery was 84 days (IQR, 49-156)
- In patients with hemoglobin decrease >20 g/L following DI, no increase in PD rate was observed compared with the overall study population

Table 4. Hemoglobin and WM Response Following Dose Interruptions

Events	DI <14 days[a] (n=351)	DI ≥14 days (n=166)	DI ≥28 days (n=56)	All DIs (n=806)
Median Δ Hb (IQR), g/L	-2 (-7, 3)	-4 (-13, 1)	-5 (-13, 1.9)	-2 (-8, 3)
Hb decrease >20 g/L, n (%)	17 (5)	30 (18)	14 (25)	63 (8)
Hb recovery[b]	2 (11)	14 (47)	4 (27)	21 (33)
Patients	**DI <14 days[a] (n=122)**	**DI ≥14 days (n=103)**	**DI ≥28 days (n=48)**	**All DIs (n=225)**
Hb decrease >20 g/L, n (%)	14 (11)	26 (25)	13 (27)	48 (21)
Hb recovery[c]	2 (14)	12 (46)	4 (31)	15 (31)
Subsequent PD[c]	1 (7)	5 (19)	2 (15)	6 (13)

[a] Patients who had DI <14 days only. [b] Denominator of the percentage is the number of DI with Hgb decrease >20 g/L. [c] Denominator of the percentage is the number of patients with Hb decrease >20 g/L (as in the first row).
DI(s), dose interruption(s); Hb, hemoglobin; IQR, interquartile range; PD, progressive disease.

IgM Flare and Disease Progression Following Dose Interruption

- The median change in IgM was 0.03 g/L following DIs shorter than 14 days, and 4.3 g/L following DIs 28 days or longer (**Table 5**)
- The frequency of IgM flare following DI was increased with longer durations of DIs (**Table 5**)
- IgM flare was followed by IWWM-6 categorical response recovery or IgM recovery to ≤ pre-DI level in most cases
- The median time from treatment reinitiation to complete IgM recovery following IgM flare was 154 days (IQR, 78-280)
- In patients with IgM flare following DI, no increase in PD rate was observed compared with the overall study population, and the rate of IgM non-recovery was lowest in patients with DI <14 days

Table 5. IgM and WM Response Following Dose Interruptions

Events	DI <14 days[a] (n=351)	DI ≥14 days (n=166)	DI ≥28 days (n=56)	All DIs (n=806)
Median Δ IgM (IQR), g/L	0.03 (-0.87, 2.09)	2.70 (0.04, 9.00)	4.30 (0.04, 9.00)	0.42 (-0.80, 3.50)
IgM flare, n (%)	17 (5)	56 (34)	23 (41)	97 (12)
IgM recovery	13 (77)	30 (54)	13 (57)	58 (60)
WM response recovery	14 (82)	37 (66)	17 (74)	74 (76)
Patients	**DI <14 days[a] (n=122)**	**DI ≥14 days (n=103)**	**DI ≥28 days (n=48)**	**All DIs (n=225)**
IgM flare, n (%)	13 (11)	44 (43)	22 (46)	64 (28)
IgM recovery	10 (77)	25 (57)	12 (55)	44 (69)
WM response recovery	11 (85)	30 (68)	16 (73)	51 (78)
IgM non-recovery	2 (23)	19 (43)	10 (46)	20 (31)
Subsequent PD	0	5 (26)	1 (10)	5 (25)

[a] Patients who had DI <14 days only.
DI(s), dose interruption(s); IgM, Immunoglobulin M; IQR, interquartile range; PD, progressive disease.

CONCLUSIONS

- This analysis of 806 dose interruptions, in 301 patients with a median treatment duration of approximately 4 years, is the largest analysis of BTK inhibitor DIs in patients with WM
  - IgM flare and >20 g/L decrease in hemoglobin occured more frequently following DIs with longer durations of ≥14 days and ≥28 days
  - Most patients with IgM flare following DI returned to their prior level of disease control; no increase in PD rate was observed compared with the overall study population, and the rate of IgM non-recovery was lowest in patients with DI <14 days
  - DIs after the first year of therapy conferred lower risk of PD than those within the first year
- These data may help patients and clinicians weigh the risks and benefits of BTK inhibitor DIs, including the relative timing and duration

Timing of First Dose Interruption and Risk of Progressive Disease

- Patients with DI in the first 12 months of treatment had a higher rate of progressive disease (29%) than those without (13%, *P*=.017) (**Table 6**)

Table 6. Timing of First Dose Interruption and Risk of Progressive Disease

	Patients with DIs (N=225)	Patients with PD	*P* value[a]
Timing of first DIs of any duration, n (%)			
Within first 6 months of treatment	99 (44)	28 (28)	0.209
After 6 months	126 (56)	26 (21)	
Within first year of treatment	157 (70)	45 (29)	0.017
After 1 year	68 (30)	9 (13)	
Timing of first DIs ≥7 days in duration, n (%)			
Within first 6 months of treatment	65 (29)	15 (23)	
Within first year of treatment	98 (44)	25 (26)	
Timing of first DIs ≥14 days in duration, n (%)			
Within first 6 months of treatment	28 (12)	6 (21)	
Within first year of treatment	45 (20)	8 (18)	

DI, dose interruption; PD, progressive disease.
[a] Based on Fisher's exact test.

Relationship Between Recurrence of Dose Interruption and IgM, Hemoglobin, and Treatment Discontinuation

- In the ASPEN study, recurrent DIs ≥7 days (HR, 0.987; *P*=.002) and recurrent DIs ≥14 days (HR, 0.988; *P*=.037) were associated with hemoglobin decrease
- No significant relationship was observed between IgM increase and recurrent DIs ≥7, ≥14, or ≥28 days
- The risk of treatment discontinuation increases with the recurrence of DIs based on the joint modeling method (recurrent DIs ≥7 days [HR, 0.969; *P*<.0001] and recurrent DIs ≥14 days [HR, 0.961; *P*=.012])

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