Preliminary Safety and Efficacy of Zanubrutinib in Combination With Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma

Abstract 1627

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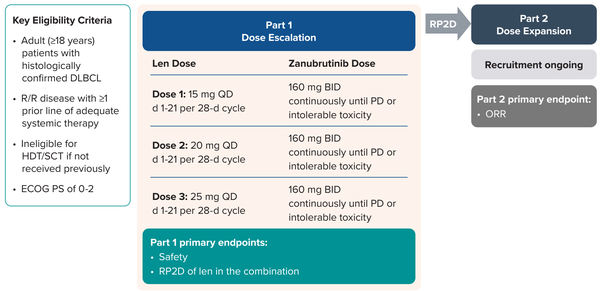
INTRODUCTION

- Despite overall improvements in outcomes of DLBCL, about one-third of patients will develop R/R disease, which remains a major cause of mortality[1]
- Effective therapies for R/R DLBCL are limited in China, especially for those patients not eligible for HDT/SCT[2]
- Zanubrutinib, a potent and selective inhibitor of Bruton tyrosine kinase, is approved for various B-cell malignancies, and preclinical data suggest potential synergy when combined with lenalidomide[3]
- Here, we present preliminary results from the dose-escalation part of an ongoing phase 1, open-label, multicenter, dose-escalation and -expansion study of zanubrutinib plus len combination in Chinese patients with R/R DLBCL (BGB-3111-110; NCT04436107)

METHODS

Figure 1. BGB-3111-110 Study Design



RESULTS

Patients

- As of June 6, 2022, a total of 27 patients were enrolled and treated in the dose-escalation part (6 at dose level 1, 10 at dose level 2, and 11 at dose level 3)
- Median age was 58 years (range 29-77), 74% of patients had stage III-IV disease, 52% had refractory disease, and 63% had non-GCB disease
- Median number of prior systemic therapies was 1 (range 1-5)
- Baseline characteristics are summarized in **Table 1**
- Median treatment exposure was 5.6 months (range 0.4-19.8) for both zanubrutinib and len, and the median follow-up was 8.3 months (range 0.5-20.4)

Safety

- Twenty-six (96%) patients experienced at least 1 TEAE, and the incidence of any-grade TEAEs did not increase significantly with increasing dose (**Table 2**)
- Grade ≥3 TEAEs occurred in 63% of patients, were most commonly hematologic toxicities, and were generally manageable across all dose levels (**Table 3**)
- No patients experienced dose-limiting toxicity at any tested dose level, and maximum tolerated dose was not reached
- Three patients experienced TEAEs leading to treatment discontinuation
  - Two (20%) at dose level 2: grade 3 platelet count decreased, related to both drugs, n=1; grade 5 cardiopulmonary failure, related to disease under study, n=1
  - One (9%) at dose level 3: grade 3 pulmonary embolism, related to len
- One TEAE leading to death was reported at dose level 2 (cardiopulmonary failure related to disease under study) and was assessed as not related to the study treatment

Efficacy and RP2D

- The ORR was 51.9%, with the best ORR of 90.9% observed at dose level 3 (**Table 4**)
- The overall CR rate was 22.2%, and patients treated with dose level 3 displayed the highest CR rate at 36.4% (**Table 4**)
- Treatment duration with response per patient is shown in **Figure 2**
- The median duration of response was not reached (overall 95% CI: 3.02-NE **Table 5**)
- At data cutoff, 11 of the 14 responders are still progression free, with the longest PFS of >14.8 months observed in 1 patient at dose level 1; 2 patients at dose level 2 have PFS >11 months
- Median PFS was 2.79 months, 2.89 months, and not reached for dose levels 1, 2, and 3, respectively (**Table 6**)
- Based on the strong efficacy and manageable safety demonstrated, the RP2D of len in the combination was determined to be dose level 3 (len 25 mg once daily on days 1-21 of each 28-day cycle with zanubrutinib 160 mg twice daily continuously)

RESULTS (cont.)

Table 1. Patient Demographics and Baseline Disease Characteristics

Characteristics, n (%)	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 6)	Len 20 mg QD (Dose level 2) (n = 10)	Len 25 mg QD (Dose level 3) (n = 11)	Total (N=27)
Sex				
Male	4 (67)	6 (60)	5 (45)	15 (56)
Female	2 (33)	4 (40)	6 (55)	12 (44)
Age				
Median (range), years	52 (29-65)	57 (31-77)	60 (32-77)	58 (29-77)
>60 years	1 (17)	2 (20)	5 (45)	8 (30)
ECOG PS				
0	3 (50)	4 (40)	3 (27)	10 (37)
1	3 (50)	6 (60)	7 (64)	16 (59)
2	0	0	1 (9)	1 (4)
Disease stage at study entry				
Stage I-II	1 (17)	2 (20)	4 (36)	7 (26)
Stage III-IV	5 (83)	8 (80)	7 (64)	20 (74)
Number of prior systemic therapies				
1	2 (33)	6 (60)	6 (55)	14 (52)
2	3 (50)	4 (40)	2 (18)	9 (33)
≥3	1 (17)	0	3 (27)	4 (15)
Disease status				
Refractory	4 (67)	7 (70)	3 (27)	14 (52)
Relapsed	2 (33)	3 (30)	8 (73)	13 (48)
DLBCL subtype				
Non-GCB	3 (50)	6 (60)	8 (73)	17 (63)
GCB	3 (50)	3 (30)	3 (27)	9 (33)
Unknown	0	1 (10)	0	1 (4)
Prior radiotherapy	1 (17)	2 (20)	3 (27)	6 (22)
Prior transplant	0	0	0	0

Table 2. TEAEs

Preferred term, n (%)	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 6)	Len 20 mg QD (Dose level 2) (n = 10)	Len 25 mg QD (Dose level 3) (n = 11)	Total (N=27)
Patients with ≥1 TEAE[a]	6 (100)	10 (100)	10 (91)	26 (96)
White blood cell count decreased	3 (50)	6 (60)	9 (82)	18 (67)
Neutrophil count decreased	2 (33)	6 (60)	9 (82)	17 (63)
Platelet count decreased	1 (17)	7 (70)	7 (64)	15 (56)
Lymphocyte count decreased	4 (67)	5 (50)	4 (36)	13 (48)
Anemia	2 (33)	5 (50)	5 (45)	12 (44)
Aspartate aminotransferase increased	0	4 (40)	4 (36)	8 (30)
Hypokalemia	2 (33)	3 (30)	3 (27)	8 (30)
Rash	2 (33)	4 (40)	2 (18)	8 (30)
Hypoalbuminemia	1 (17)	4 (40)	2 (18)	7 (26)
Blood lactate dehydrogenase increased	1 (17)	5 (50)	1 (9)	7 (26)
Serious	0	3 (30)	3 (27)	6 (22)
Leading to death	0	1 (10)	0	1 (4)
Leading to treatment discontinuation	0	2 (20)	1 (9)	3 (11)
Leading to dose modification	2 (33)	6 (60)	6 (55)	14 (52)
Leading to dose interruption	2 (33)	6 (60)	5 (45)	13 (48)
Leading to dose reduction	0	0	2 (18)	2 (7)

[a]TEAEs are defined as adverse events that had an onset date on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib or len (whichever comes later), or the start of new anticancer therapy; whichever comes first. Any-grade TEAEs occurring in ≥25% of patients are shown.

Table 3. Grade ≥3 TEAEs

Preferred term, n (%)	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 6)	Len 20 mg QD (Dose level 2) (n = 10)	Len 25 mg QD (Dose level 3) (n = 11)	Total (N=27)
Grade ≥3 TEAEs[a]	3 (50)	6 (60)	8 (73)	17 (63)
Neutrophil count decreased	1 (17)	6 (60)	5 (45)	12 (44)
White blood cell count decreased	0	4 (40)	3 (27)	7 (26)
Lymphocyte count decreased	2 (33)	1 (10)	1 (9)	4 (15)
Platelet count decreased	0	2 (20)	2 (18)	4 (15)
Anemia	0	2 (20)	0	2 (7)
Neutropenia	0	0	2 (18)	2 (7)
Pneumonia	0	1 (10)	1 (9)	2 (7)
Hypokalemia	0	0	2 (18)	2 (7)

[a]TEAEs are defined as adverse events that had an onset date on or after the first dose of study drug and up to 30 days after the last dose of zanubrutinib or len (whichever comes later), or the start of new anticancer therapy; whichever comes first. Grade ≥3 TEAEs occurring in ≥5% of patients are shown.

Table 4. Disease Response by Investigator Based on the Lugano 2014[4] Classification

Response	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 6)	Len 20 mg QD (Dose level 2) (n = 10)	Len 25 mg QD (Dose level 3) (n = 11)	Total (N=27)
Best overall response, n (%)				
CR	1 (16.7)	1 (10.0)	4 (36.4)	6 (22.2)
PR	0	2 (20.0)	6 (54.5)	8 (29.6)
SD	0	2 (20.0)	1 (9.1)	3 (11.1)
PD	4 (66.7)	5 (50.0)	0	9 (33.3)
Discontinued prior to first assessment	1 (16.7)	0	0	1 (3.7)
ORR,[a] n (%) [95% CI[b]]	1 (16.7) [0.4, 64.1]	3 (30.0) [6.7, 65.2]	10 (90.9) [58.7, 99.8]	14 (51.9) [31.9, 71.3]
CR rate, n (%) [95% CI[b]]	1 (16.7) [0.4, 64.1]	1 (10.0) [0.3, 44.5]	4 (36.4) [10.9, 69.2]	6 (22.2) [8.6, 42.3]

[a]ORR is defined as achieving at least a best overall response of PR or better.
[b]Two-sided Clopper-Pearson 95% CI.

Figure 2. Swimlane Plot of Treatment Duration With Response per Overall Assessment by Investigator

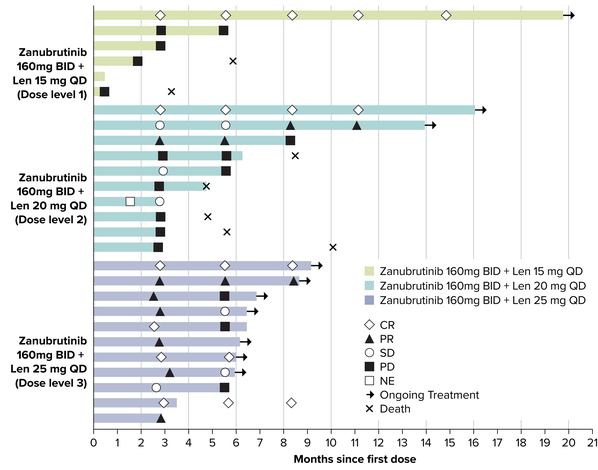


Table 5. DOR by Investigator Based on the Lugano 2014[4] Classification

	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 1)	Len 20 mg QD (Dose level 2) (n = 3)	Len 25 mg QD (Dose level 3) (n = 10)	Total (N=14)
Follow-up time, months[a]				
Median	12.06	8.34	4.16	5.42
Range	(12.06, 12.06)	(2.79, 8.34)	(0.03, 5.68)	(0.03, 12.06)
Duration of response, months[b]				
Median (95% CI)	NE (NE, NE)	NE (5.55, NE)	NE (3.02, NE)	NE (3.02, NE)
Range	(12.06+, 12.06+)	(2.79+, 8.34+)	(0.03+, 5.68+)	(0.03+, 12.06+)
Event-free rate, % (95% CI)[c]				
3 months	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)	100.0 (NE, NE)
6 months	100.0 (NE, NE)	50.0 (0.6, 91.0)	NE (NE, NE)	60.0 (19.5, 85.2)
9 months	100.0 (NE, NE)	NE (NE, NE)	NE (NE, NE)	60.0 (19.5, 85.2)

Percentages are based on number of responders (patients with best overall response of at least PR).
DOR for responders (CR or PR) is defined as the time from the date of the earliest qualifying response (PR or better) to the date of PD or death for any cause, whichever occurs earlier.
[a]Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
[c]Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.

Table 6. PFS by Investigator Based on the Lugano 2014[4] Classification

	Zanubrutinib 160 mg BID: Len 15 mg QD (Dose level 1) (n = 6)	Len 20 mg QD (Dose level 2) (n = 10)	Len 25 mg QD (Dose level 3) (n = 11)	Total (N=27)
Follow-up time, months[a]				
Median	14.82	11.04	5.68	8.34
Range	(0.03, 14.82)	(2.69, 11.10)	(2.73, 8.41)	(0.03, 14.82)
Progression-free survival, months[b]				
Median (95% CI)	2.79 (0.43, NE)	2.89 (2.69, NE)	NE (5.49, NE)	5.52 (2.79, NE)
Range	(0.03+, 14.82+)	(2.69, 11.10+)	(2.73+, 8.41+)	(0.03+, 14.82+)
Event-free rate, % (95% CI)[c]				
3 months	20.0 (0.8, 58.2)	45.7 (14.3, 73.0)	100.0 (NE, NE)	63.2 (41.0, 79.0)
6 months	20.0 (0.8, 58.2)	34.3 (8.2, 63.3)	66.7 (28.2, 87.8)	44.1 (23.4, 63.1)
9 months	20.0 (0.8, 58.2)	22.9 (3.5, 52.2)	NE (NE, NE)	37.8 (17.8, 57.9)

PFS is defined as the time from study treatment start to PD or death of any cause, whichever occurs first.
[a]Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b]Medians were estimated by Kaplan-Meier method with 95% CIs estimated using the Brookmeyer and Crowley method.
[c]Event-free rates were estimated by Kaplan-Meier method with 95% CIs estimated using the Greenwood formula.

CONCLUSIONS

- Zanubrutinib and len combination treatment showed an acceptable safety profile and promising preliminary efficacy data in patients with R/R DLBCL
- Dose-dependent increase in response was observed across the 3 dose levels
- The dose-expansion part of the study, which uses dose level 3 as the RP2D (zanubrutinib 160 mg twice daily continuously, len 25 mg once daily on days 1-21 of each 28-day cycle), is now recruiting

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ABBREVIATIONS

BID, twice daily; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell–like; HDT/SCT, high-dose therapy/stem cell transplantation; len, lenalidomide; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; PR, partial response; QD, once daily; RP2D, recommended phase 2 dose; R/R, relapsed/refractory; SD, stable disease; TEAE, treatment-emergent adverse event.

DISCLOSURES

YG: honoraria from Merck Serono, Roche, MSD, BMS, and membership on an entity's board of directors or advisory committee for Merck Serono, MSD, Bayer, Roche, and GSK
SH, ZL, HuY, NB, YF, HuZ: employment and stock with BeiGene
HuZ, KZ, YC, LZ, HaY, LZ, JC, HH, ZW: nothing to disclose

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