Poster 442

First Interim Analysis of a Phase 1 Study of Zanubrutinib + Lenalidomide in Patients With Relapsed/Refractory Diffuse Large B-Cell Lymphoma

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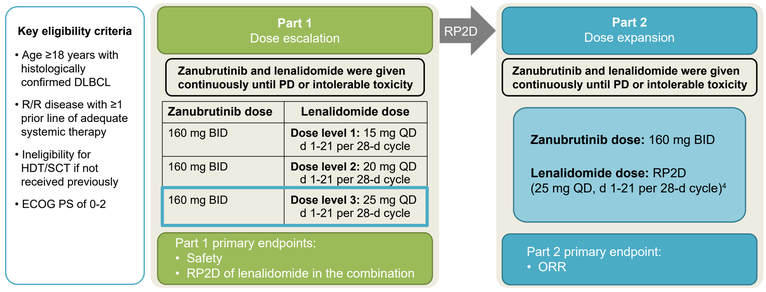
BACKGROUND

- Outcomes in patients with diffuse large B-cell lymphoma (DLBCL) have improved with recent advancements in treatment; however, relapsed/refractory (R/R) disease, which approximately one-third of patients will develop, remains a major cause of mortality[1]
- Effective therapies for R/R DLBCL are limited in China, especially for patients ineligible for high-dose therapy/stem cell transplant (HDT/SCT)[2]
- Preclinical data suggest synergy of lenalidomide with zanubrutinib, a potent and selective Bruton tyrosine kinase inhibitor approved for various B-cell malignancies[3,4]
- Preliminary results for part 1 of this ongoing phase 1, open-label, dose-escalation/expansion study of zanubrutinib plus lenalidomide in Chinese patients with R/R DLBCL (BGB-3111-110; NCT04436107) were previously presented, detailing the recommended dose for expansion[5]
- Here, we present interim analysis results of BGB-3111-110

METHODS

Figure 1. BGB-3111-110 Study Design



BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; HDT/SCT, high-dose therapy/stem cell transplant; QD, once daily; RP2D, recommended part 2 dose.

RESULTS

Patients

- As of November 8, 2022, a total of 46 patients were treated and included in this interim analysis (27 in part 1; 19 in part 2; 30 at the recommended part 2 dose [RP2D])
- Median age was 60 years (range, 29-82 years); 82.6% had stage III-IV disease, 37.0% had refractory disease, and 69.6% had non–germinal center B-cell (non-GCB) disease
- The median number of prior systemic therapies was 1 (range, 1-5)
- Baseline characteristics are summarized in **Table 1**
- Median treatment exposure was 3.9 months (range, 0.4-24.9 months) for zanubrutinib and lenalidomide, and the median follow-up was 6.6 months (range, 0.5-25.5 months)

Table 1. Patient Demographics and Baseline Disease Characteristics

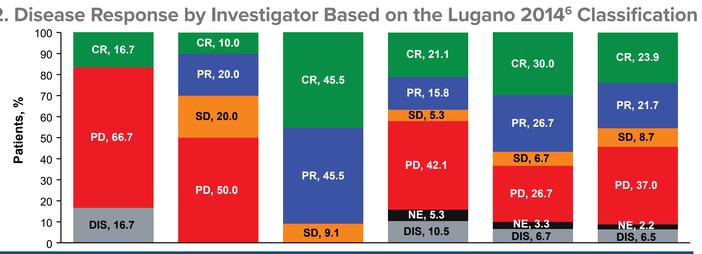
Characteristics, n (%)	Part 1 Zanubrutinib 160 mg BID: Lenalidomide 15 mg QD (dose level 1) (n=6)	Lenalidomide 20 mg QD (dose level 2) (n=10)	Lenalidomide 25 mg QD (dose level 3; RP2D) (n=11)	Part 2 Zanubrutinib 160 mg BID: Lenalidomide 25 mg QD (RP2D) (n=19)	RP2D combined (n=30)	Total (N=46)
Sex						
Male	4 (66.7)	6 (60.0)	5 (45.5)	9 (47.4)	14 (46.7)	24 (52.2)
Female	2 (33.3)	4 (40.0)	6 (54.5)	10 (52.6)	16 (53.3)	22 (47.8)
Age						
Median (range), years	51.5 (29-65)	57.0 (31-77)	60.0 (32-77)	61.0 (42-82)	61.0 (32-82)	60.0 (29-82)
>60 years	1 (16.7)	2 (20.0)	5 (45.5)	12 (63.2)	17 (56.7)	20 (43.5)
ECOG PS						
0	3 (50.0)	4 (40.0)	3 (27.3)	6 (31.6)	9 (30.0)	16 (34.8)
1	3 (50.0)	6 (60.0)	7 (63.6)	12 (63.2)	19 (63.3)	28 (60.9)
2	0	0	1 (9.1)	1 (5.3)	2 (6.7)	2 (4.3)
Disease stage at study entry						
Stage I	1 (16.7)	0	0	0	0	1 (2.2)
Stage II	0	2 (20.0)	4 (36.4)	1 (5.3)	5 (16.7)	7 (15.2)
Stage II bulky	0	0	0	0	0	0
Stage III	0	3 (30.0)	3 (27.3)	7 (36.8)	10 (33.3)	13 (28.3)
Stage IV	5 (83.3)	5 (50.0)	4 (36.4)	11 (57.9)	15 (50.0)	25 (54.3)
Number of prior systemic therapies						
1	3 (50.0)	6 (60.0)	6 (54.5)	12 (63.2)	18 (60.0)	27 (58.7)
2	3 (50.0)	4 (40.0)	2 (18.2)	4 (21.1)	6 (20.0)	13 (28.3)
≥3	0	0	3 (27.3)	3 (15.8)	6 (20.0)	6 (13.0)
Disease status						
Refractory	4 (66.7)	7 (70.0)	3 (27.3)	3 (15.8)	6 (20.0)	17 (37.0)
Relapsed	2 (33.3)	3 (30.0)	8 (72.7)	16 (84.2)	24 (80.0)	29 (63.0)
DLBCL subtype						
GCB	3 (50.0)	3 (30.0)	3 (27.3)	3 (15.8)	6 (20.0)	12 (26.1)
Non-GCB	3 (50.0)	6 (60.0)	8 (72.7)	15 (78.9)	23 (76.7)	32 (69.6)
Unknown	0	1 (10.0)	0	1 (5.3)	1 (3.3)	2 (4.3)
Prior radiotherapy	1 (16.7)	2 (20.0)	3 (27.3)	2 (10.5)	5 (16.7)	8 (17.4)
Prior transplant	0	0	0	0	0	0

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; GCB, germinal center B-cell; non-GCB, non–germinal center B-cell; QD, once daily; RP2D, recommended part 2 dose.

Efficacy

- The overall response rate (ORR) was 45.7% (95% CI, 30.9%-61.0%; complete response [CR] rate, 23.9%) (**Figure 2**)
  - At RP2D, the ORR was 56.7% (95% CI, 37.4%-74.5%; CR, 30.0%) in all patients
  - At RP2D, the ORR was 60.9% (95% CI, 38.5%-80.3%; CR, 34.8%) in patients with non-GCB disease and 50.0% (95% CI, 11.8%-88.2%; CR, 16.7%) in patients with GCB disease (**Figure 3**)
- Overall, the median duration of response (DOR) was not reached, and the 6-month event-free rate was 63.5% (95% CI, 32.8%-83.0%) (**Figures 4-6**)
  - At data cutoff, 16 of the 21 responders were still progression free, with the longest progression-free survival (PFS) of >20.8 months observed in a patient receiving dose level 1 (**Figure 4**)
  - At RP2D, DOR was not reached, and the 6-month event-free rate was 59.4% (95% CI, 23.8%-82.8%)
- Overall, median PFS was 5.5 months (95% CI, 2.8-8.3 months), with a 9-month event-free rate of 31.1% (95% CI, 16.4%-47.0%) (**Figures 7** and **8**)
  - At RP2D, the median PFS was 5.5 months (95% CI, 2.8 months-not evaluable [NE]), with a 9-month event-free rate of 37.4% (95% CI, 17.6%-57.4%)

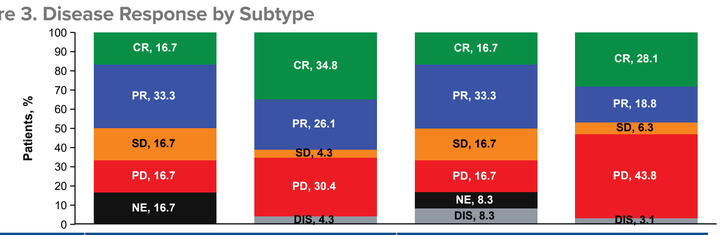
Figure 2. Disease Response by Investigator Based on the Lugano 2014[6] Classification



	Part 1, dose level 1 (n=6)	Part 1, dose level 2 (n=10)	Part 1, dose level 3/RP2D (n=11)	Part 2/RP2D (n=19)	RP2D combined (n=30)	Total (N=46)
ORR (95% CI), %[a]	16.7 (0.4-64.1)	30.0 (6.7-65.2)	90.9 (58.7-99.8)	36.8 (16.3-61.6)	56.7 (37.4-74.5)	45.7 (30.9-61.0)
CR rate (95% CI), %[b]	16.7 (0.4-64.1)	10.0 (0.3-44.5)	45.5 (16.7-76.6)	21.1 (6.1-45.6)	30.0 (14.7-49.4)	23.9 (12.6-38.8)

DIS, discontinued prior to first treatment; NE, not evaluable; RP2D, recommended part 2 dose.
[a] Overall response is defined as achieving at least a best overall response of PR or better. [b] Two-sided Clopper-Pearson 95% CI.

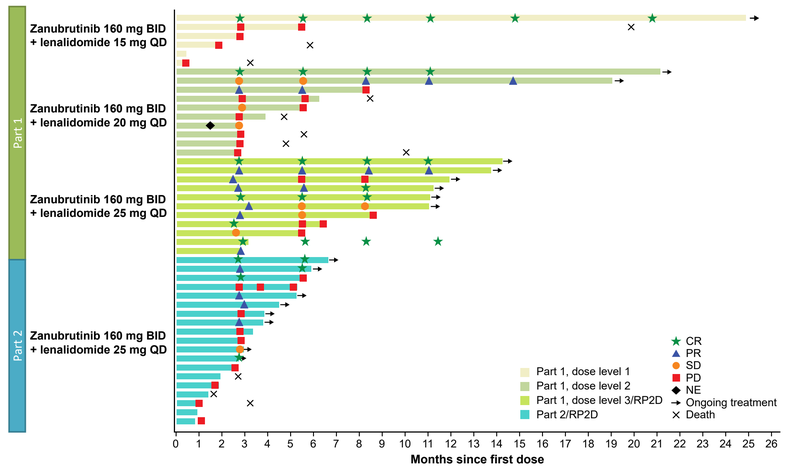
Figure 3. Disease Response by Subtype



	RP2D combined (n=30): GCB (n=6)	RP2D combined (n=30): Non-GCB (n=23)	Total (N=46): GCB (n=12)	Total (N=46): Non-GCB (n=32)
ORR (95% CI), %[a]	50.0 (11.8-88.2)	60.9 (38.5-80.3)	50.0 (21.1-78.9)	46.9 (29.1-65.3)
CR rate (95% CI), %[b]	16.7 (0.4-64.1)	34.8 (16.4-57.3)	16.7 (2.1-48.4)	28.1 (13.7-46.7)

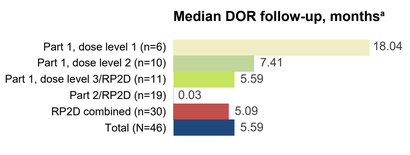
DIS, discontinued prior to first assessment; NE, not evaluable; RP2D, recommended part 2 dose.
[a] Overall response is defined as achieving at least a best overall response of PR or better. [b] Two-sided Clopper-Pearson 95% CI.

Figure 4. Swimlane Plot of Treatment Duration With Response per Overall Assessment by Investigator



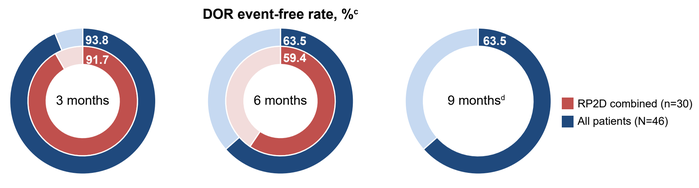
BID, twice daily; NE, not evaluable; QD, once daily; RP2D, recommended part 2 dose.

Figure 5. DOR by Investigator Based on the Lugano 2014[6] Classification



DOR, months[b]

	Median (95% CI)	Range
Part 1, dose level 1 (n=6)	NE (NE-NE)	18.04+ to 18.04+
Part 1, dose level 2 (n=10)	NE (5.55-NE)	5.55 to 8.34+
Part 1, dose level 3/RP2D (n=11)	NE (3.02-NE)	0.03+ to 8.54+
Part 2/RP2D (n=19)	NE (2.76-NE)	0.03+ to 2.92+
RP2D combined (n=30)	NE (3.02-NE)	0.03+ to 8.54+
Total (N=46)	NE (3.02-NE)	0.03+ to 18.04+



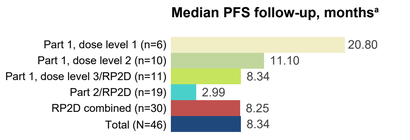
Percentages are based on number of responders (patients with best overall response of at least PR). DOR in responders (CR or PR) is defined as the time from the date of the earliest qualifying response (PR or better) to the date of PD or death of any cause, whichever occurs earlier.
NE, not evaluable; RP2D, recommended part 2 dose.
[a] Median follow-up 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.
[d] The 9-month event-free rate for the RP2D combined group was NE.

Figure 6. Kaplan-Meier Estimate of DOR by Investigator Based on the Lugano 2014[6] Classification

No. of patients at risk												
Part 1, dose level 1	1	1	1	1	1	1	1	1	1	1	1	0
Part 1, dose level 2	3	3	3	2	1	0						
Part 1, dose level 3/RP2D	10	9	7	3	3	0						
Part 2/RP2D	7	3	0									
RP2D combined	17	12	7	3	3	0						

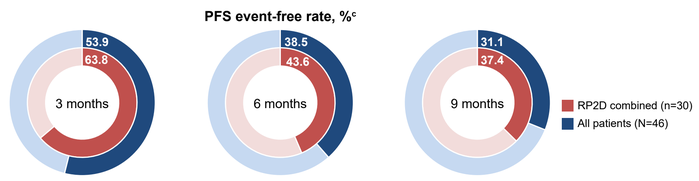
PFS, progression-free survival; RP2D, recommended part 2 dose.

Figure 7. PFS by Investigator Based on the Lugano 2014[6] Classification



PFS, months[b]

	Median (95% CI)	Range
Part 1, dose level 1 (n=6)	2.79 (0.43-NE)	0.03+ to 20.80+
Part 1, dose level 2 (n=10)	2.89 (2.69-NE)	2.69 to 14.72+
Part 1, dose level 3/RP2D (n=11)	NE (5.49-NE)	2.83+ to 11.43+
Part 2/RP2D (n=19)	2.79 (2.53-NE)	0.03+ to 5.62+
RP2D combined (n=30)	5.52 (2.79-NE)	0.03+ to 11.43+
Total (N=46)	5.49 (2.79-8.28)	0.03+ to 20.80+

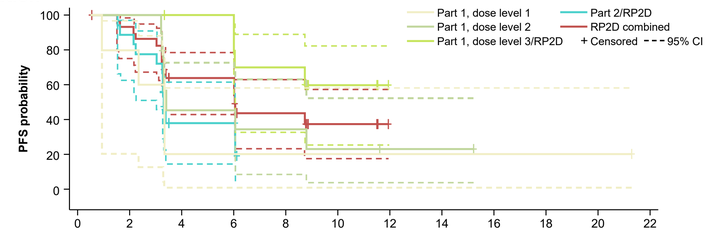


PFS is defined as the time from start of study treatment to PD or death of any cause, whichever occurs first.
NE, not evaluable; RP2D, recommended part 2 dose.
[a] Median follow-up time is estimated by the reverse Kaplan-Meier method.
[b] Medians were estimated by Kaplan-Meier method, with 95% CIs estimated 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

- The zanubrutinib 160 mg twice daily plus lenalidomide 25 mg once daily combination demonstrated an acceptable safety profile and promising efficacy in patients with R/R DLBCL
- Further evaluation of the combination in a larger sample is planned in future analyses

Figure 8. Kaplan-Meier Estimate of PFS by Investigator Based on the Lugano 2014[6] Classification



No. of patients at risk												
Part 1, dose level 1	6	3	1	1	1	1	1	1	1	1	1	0
Part 1, dose level 2	10	10	4	3	3	2	1	1	0			
Part 1, dose level 3/RP2D	11	11	10	7	7	3	0					
Part 2/RP2D	19	14	3	0								
RP2D combined	30	25	13	7	7	3	0					

RP2D, recommended part 2 dose.

Safety

- All 46 patients experienced ≥1 treatment-emergent adverse event (TEAE) (**Table 2**)
- Grade ≥3 TEAEs occurred in 60.9% of patients, were most commonly hematologic toxicities, and were generally manageable across all dose levels (**Table 3**)
  - At RP2D, grade ≥3 TEAEs occurred in 60.0% of patients, most commonly neutrophil count decreased (43.3%), white blood cell count decreased (23.3%), and pneumonia (13.3%); 1 patient (3.3%) had febrile neutropenia (grade 3) but recovered within 2 days
- Four patients (8.7%) experienced TEAEs leading to treatment discontinuation
  - Two patients discontinued both zanubrutinib and lenalidomide (grade 5 cardiopulmonary failure unrelated to study treatment [part 1, dose level 2], grade 3 pulmonary embolism related to lenalidomide [part 1, dose level 3/RP2D])
  - Two patients discontinued lenalidomide (grade 3 platelet count decreased related to both drugs [part 1, dose level 2], grade 1 rash related to both drugs [part 2, RP2D])
- Two TEAEs (cardiopulmonary failure, pneumonia) leading to death were reported; both were unrelated to treatment

Table 2. TEAEs

Preferred term, n (%)	Part 1 Zanubrutinib 160 mg BID: Lenalidomide 15 mg QD (dose level 1) (n=6)	Lenalidomide 20 mg QD (dose level 2) (n=10)	Lenalidomide 25 mg QD (dose level 3; RP2D) (n=11)	Part 2 Zanubrutinib 160 mg BID: Lenalidomide 25 mg QD (RP2D) (n=19)	RP2D combined (n=30)	Total (N=46)
Patients with ≥1 TEAE[a]	6 (100.0)	10 (100.0)	11 (100.0)	19 (100.0)	30 (100.0)	46 (100.0)
Neutrophil count decreased	2 (33.3)	6 (60.0)	10 (90.9)	14 (73.7)	24 (80.0)	32 (69.6)
White blood cell count decreased	3 (50.0)	6 (60.0)	9 (81.8)	13 (68.4)	22 (73.3)	31 (67.4)
Platelet count decreased	1 (16.7)	7 (70.0)	7 (63.6)	8 (42.1)	15 (50.0)	23 (50.0)
Anemia	2 (33.3)	5 (50.0)	7 (63.6)	5 (26.3)	12 (40.0)	19 (41.3)
Lymphocyte count decreased	4 (66.7)	5 (50.0)	5 (45.5)	2 (10.5)	7 (23.3)	16 (34.8)
Hypokalemia	2 (33.3)	3 (30.0)	4 (36.4)	6 (31.6)	10 (33.3)	15 (32.6)
ALT increased	0	2 (20.0)	5 (45.5)	7 (36.8)	12 (40.0)	14 (30.4)
AST increased	0	4 (40.0)	5 (45.5)	5 (26.3)	10 (33.3)	14 (30.4)
Rash	2 (33.3)	4 (40.0)	2 (18.2)	5 (26.3)	7 (23.3)	13 (28.3)
γ-Glutamyltransferase increased	1 (16.7)	1 (10.0)	4 (36.4)	6 (31.6)	10 (33.3)	12 (26.1)
Hypoalbuminemia	1 (16.7)	4 (40.0)	3 (27.3)	2 (10.5)	5 (16.7)	10 (21.7)
Pneumonia	0	2 (20.0)	4 (36.4)	4 (21.1)	8 (26.7)	10 (21.7)
Serious	0	3 (30.0)	3 (27.3)	5 (26.3)	8 (26.7)	11 (23.9)
Leading to death	0	1 (10.0)	0	1 (5.3)	1 (3.3)	2 (4.3)
Leading to treatment discontinuation	0	2 (20.0)	1 (9.1)	1 (5.3)	2 (6.7)	4 (8.7)
Leading to dose modification	3 (50.0)	6 (60.0)	7 (63.6)	10 (52.6)	17 (56.7)	26 (56.5)
Leading to dose interruption	3 (50.0)	6 (60.0)	6 (54.5)	8 (42.1)	14 (46.7)	23 (50.0)
Leading to dose reduction	0	0	3 (27.3)	2 (10.5)	5 (16.7)	5 (10.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; QD, once daily; RP2D, recommended part 2 dose.
[a] TEAEs are defined as adverse events that had an onset date on or after the date of first dose of study drug up to 30 days after the last dose of zanubrutinib or lenalidomide (whichever comes later) or to the start of new anticancer therapy, whichever comes first. Any-grade TEAEs occurring in ≥20% of patients are shown.

Table 3. Grade ≥3 TEAEs

Preferred term, n (%)	Part 1 Zanubrutinib 160 mg BID: Lenalidomide 15 mg QD (dose level 1) (n=6)	Lenalidomide 20 mg QD (dose level 2) (n=10)	Lenalidomide 25 mg QD (dose level 3; RP2D) (n=11)	Part 2 Zanubrutinib 160 mg BID: Lenalidomide 25 mg QD (RP2D) (n=19)	RP2D combined (n=30)	Total (N=46)
Grade ≥3 TEAEs[a]	4 (66.7)	6 (60.0)	8 (72.7)	10 (52.6)	18 (60.0)	28 (60.9)
Neutrophil count decreased	2 (33.3)	6 (60.0)	6 (54.5)	7 (36.8)	13 (43.3)	21 (45.7)
White blood cell count decreased	0	4 (40.0)	4 (36.4)	3 (15.8)	7 (23.3)	11 (23.9)
Lymphocyte count decreased	2 (33.3)	1 (10.0)	1 (9.1)	1 (5.3)	2 (6.7)	5 (10.9)
Pneumonia	0	1 (10.0)	1 (9.1)	3 (15.8)	4 (13.3)	5 (10.9)
Platelet count decreased	0	2 (20.0)	2 (18.2)	0	2 (6.7)	4 (8.7)
Anemia	0	2 (20.0)	0	1 (5.3)	1 (3.3)	3 (6.5)
Hypokalemia	0	0	2 (18.2)	1 (5.3)	3 (10.0)	3 (6.5)
Neutropenia	0	0	2 (18.2)	0	2 (6.7)	2 (4.3)

BID, twice daily; QD, once daily; RP2D, recommended part 2 dose.
[a] TEAEs are defined as adverse events that had an onset date on or after the date of the first dose of study drug up to 30 days after the last dose of zanubrutinib or lenalidomide (whichever comes later) or to the start of new anticancer therapy, whichever comes first. Grade ≥3 TEAEs occurring in >1 patient are shown.

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DISCLOSURES

YG: Honoraria: Merck Serono, Roche, MSD, and BMS; Member of the board of directors or advisory committee: Merck Serono, MSD, Bayer, Roche, and GSK. **SH, ZL, JL, YF, AC:** Employment and stock: BeiGene. **HZ, YC, HY, LZ, LZ, JC, HH, ZW, KZ:** Nothing to disclose.

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