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

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CONCLUSIONS

- In the BGB-3111-110 study, the recommended phase 2 dose (RP2D) of zanubrutinib 160 mg twice daily plus lenalidomide 25 mg once daily had an acceptable safety profile in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL), with hematologic events being the most common grade ≥3 treatment-emergent adverse events (TEAEs), but rarely leading to discontinuation
- The combination demonstrated encouraging antitumor activity at the RP2D
  - Overall response rate (ORR) reached 58% with a complete response (CR) rate of 42%
  - Responses were durable, with a median duration of response (DOR) of 14.9 months
  - Median progression-free survival (PFS) was 5.5 months
  - Median overall survival (OS) was not reached
- ORR benefits were observed across subgroups and across cell of origin subtypes
- The study results highlight the great potential of this orally administered combination as a convenient therapeutic option for patients with R/R DLBCL in the future.
- Further analyses of resistance biomarkers and mechanisms of disease are ongoing

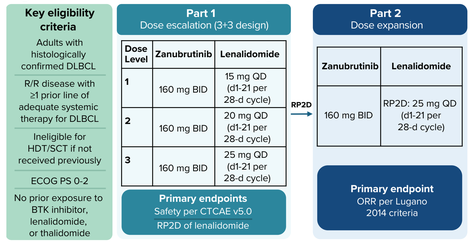
INTRODUCTION

- Up to 50% of patients with DLBCL experience R/R disease, which is associated with a poor prognosis[1]
- The pursuit of effective chemotherapy-free treatment options for R/R DLBCL is longstanding
  - Despite recent treatment advances, a need remains for novel, easily-administered treatment options
- Zanubrutinib is a potent, selective, orally-administered next-generation Bruton tyrosine kinase (BTK) inhibitor designed to provide complete and sustained BTK occupancy for efficacy across multiple B-cell malignancies with fewer off-target AEs compared with other BTK inhibitors[2]
- BGB-3111-110 is a phase 1, open-label, dose-escalation/expansion study (NCT04436107) of zanubrutinib plus lenalidomide in Chinese patients with R/R DLBCL
  - Preliminary study results for the dose-escalation part detailing the recommended dose for expansion,[3] and results from an interim analysis of the study[4] have been previously presented
- Here we present the final safety and efficacy data of BGB-3111-110

METHODS

- BGB-3111-110 (NCT04436107) is a phase 1, open-label, dose-escalation (part 1) and -expansion (part 2) study of zanubrutinib + lenalidomide in patients in Chinese patients with R/R DLBCL (**Figure 1**)
- Primary endpoints were safety per Common Terminology Criteria for Adverse Events v5.0 and RP2D of lenalidomide (part 1), and ORR per Lugano 2014 criteria[5] (part 2)
- Patients received zanubrutinib + lenalidomide continuously until disease progression or unacceptable toxicity

Figure 1. BGB-3111-110 Study Design



Abbreviations: BID, twice daily; CTCAE, Common Terminology Criteria for Adverse Events; d, day; ECOG PS, Eastern Cooperative Oncology Group performance status; HDT, high-dose therapy; QD, once daily; RP2D, recommended phase 2 dose; SCT, stem cell transplant.

RESULTS

Baseline Characteristics

- As of March 28, 2024, 66 patients were enrolled and received zanubrutinib + lenalidomide
- Median follow-up was 16.5 months (range, 0.5-41.6 months)
- Overall, patients had received median of 2 prior lines of therapy, 83% had stage III/IV disease, 42% had refractory disease, 55% had extranodal lesions, 65% had non-germinal center B-cell like (GCB) disease per immunohistochemistry (IHC), and 67% had activated B-cell like (ABC) disease per gene expression profiling (GEP) (**Table 1**)

Table 1. Demographic and Baseline Characteristics

	Part 1			Part 2	Part 1 and 2	
	Zanu + len 15 mg (n=6)	Zanu + len 20 mg (n=10)	Zanu + len 25 mg (n=11)	Zanu + len 25 mg (n=39)	RP2D combined (n=50)	All (N=66)
Male sex, n (%)	4 (66.7)	6 (60.0)	5 (45.5)	20 (51.3)	25 (50.0)	35 (53.0)
Age, median (range), years	51.5 (29-65)	57.0 (31-77)	60.0 (32-77)	59.0 (23-85)	60.0 (23-85)	59.0 (23-85)
ECOG PS						
1	3 (50.0)	6 (60.0)	7 (63.6)	22 (56.4)	29 (58.0)	38 (57.6)
2	0	0	1 (9.1)	1 (2.6)	2 (4.0)	2 (3.0)
No. of prior lines of therapy, median (range)	2 (1-2)	2 (1-4)	1 (1-5)	1 (1-5)	1 (1-5)	2 (1-5)
Refractory disease at study entry n (%)	4 (66.7)	7 (70.0)	3 (27.3)	14 (35.9)	17 (35.9)	28 (42.4)
≥1 extranodal site, n (%)	5 (83.3)	5 (50.0)	6 (54.5)	20 (51.3)	26 (52.0)	36 (54.5)
Disease stage at study entry, n (%)						
I/II	1 (16.7)	2 (20.0)	4 (36.4)	3 (7.7)	7 (14.0)	10 (15.1)
II bulky	0	0	0	1 (2.6)	1 (2.0)	1 (1.5)
III/IV	5 (83.3)	8 (80.0)	7 (63.6)	35 (89.7)	42 (84.0)	55 (83.3)
IHC subtype, n (%)						
GCB	3 (50.0)	4 (40.0)	3 (27.3)	13 (33.3)	16 (32.0)	23 (34.8)
Non-GCB	3 (50.0)	6 (60.0)	8 (72.7)	26 (66.7)	34 (68.0)	43 (65.2)
GEP subtype, n (%)						
GCB	1 (16.7)	2 (20.0)	2 (18.2)	9 (23.1)	11 (22.0)	14 (21.2)
ABC	1 (16.7)	8 (80.0)	9 (81.8)	26 (66.7)	35 (70.0)	44 (66.7)
Unclassified	1 (16.7)	0	0	0	0	1 (1.5)
Missing	3 (50.0)	0	0	4 (10.3)	4 (8.0)	7 (10.6)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; len, lenalidomide; RP2D, recommended phase 2 dose; zanu, zanubrutinib.

Safety

- The overall median exposure to zanubrutinib + lenalidomide was 4.9 months
- No dose-limiting toxicities occurred and the RP2D of lenalidomide was determined to be 25 mg
- Safety in patients receiving the RP2D was similar to that in the lenalidomide 20 mg dose group
- A summary of TEAEs is shown in **Table 2**
- Five patients (7.6%) discontinued study drug(s) due to treatment-related TEAEs (platelet count decreased, n=2; pulmonary embolism, n=1; incomplete intestinal obstruction, n=1; rash, n=1)
- The most common all grade TEAEs across all cohorts were neutrophil count decreased (77.3%), white blood cell count decreased (72.7%), and platelet count decreased (60.6%) (**Table 3**)
- Most grade ≥3 TEAEs were hematologic events and were generally manageable with concomitant medications and/or dose modification
  - Grade 3 febrile neutropenia occurred in 1 patient, but the event resolved within 2 days
  - No grade ≥3 hemorrhage occurred

Table 2. TEAE Summary

	Part 1			Part 2	Part 1 and 2	
Patients, n (%)	Zanu + len 15 mg (n=6)	Zanu + len 20 mg (n=10)	Zanu + len 25 mg (n=11)	Zanu + len 25 mg (n=39)	RP2D combined (n=50)	All (N=66)
Any TEAE	6 (100)	10 (100)	11 (100)	39 (100)	50 (100)	66 (100)
Grade ≥3	4 (66.7)	7 (70.0)	8 (72.7)	30 (76.9)	38 (76.0)	49 (74.2)
Grade 5	0	1 (10.0)	0	1 (2.6)	1 (2.0)	2 (3.0)[a]
Serious	0	3 (30.0)	4 (36.4)	14 (35.9)	18 (36.0)	21 (31.8)
Leading to discontinuation	0	2 (20.0)	2 (18.2)	3 (7.7)	5 (10.0)	7 (10.6)
Leading to dose interruption	3 (50.0)	6 (60.0)	7 (63.6)	27 (69.2)	34 (68.0)	43 (65.2)
Leading to dose reduction[b]	0	0	3 (27.3)	4 (10.3)	7 (14.0)	7 (10.6)

[a]Cardiopulmonary failure, n=1; pneumonia; n=1 (neither related to treatment). [b]All events led to lenalidomide dose reduction only; no events led to zanubrutinib dose reduction.
Abbreviations: len, lenalidomide; RP2D, recommended phase 2 dose; zanu, zanubrutinib.

Table 3. TEAEs in >20% of All Patients

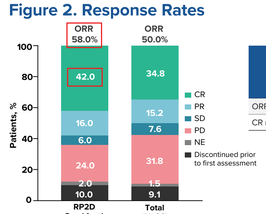
	All (N=66)	
Patients, n (%)	All Grade	Grade ≥3
Neutrophil count decreased	51 (77.3)	38 (57.6)
White blood cell count decreased	48 (72.7)	19 (28.8)
Platelet count decreased	40 (60.6)	10 (15.2)
Anemia	36 (54.5)	11 (16.7)
Lymphocyte count decreased	29 (43.9)	13 (19.7)
Hypokalemia	27 (40.9)	7 (10.6)
Blood lactate dehydrogenase increased	22 (33.3)	0
Hypoalbuminemia	20 (30.3)	0
Rash	20 (30.3)	1 (1.5)
ALT increased	18 (27.3)	1 (1.5)
AST increased	18 (27.3)	1 (1.5)
GGT increased	17 (25.8)	1 (1.5)
Blood alkaline phosphatase increased	14 (21.2)	0
Blood creatinine increased	14 (21.2)	2 (3.0)
Pneumonia	14 (21.2)	7 (10.6)

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase.

Antitumor Activity

- The ORR increased by lenalidomide dose level, reaching an ORR of 58% with a CR rate of 42% at the RP2D (**Figure 2**)
- At the RP2D, the ORR benefit was observed across all subgroups (**Figure 3**)
- At the RP2D, patients with a non-GCB subtype by IHC and an ABC subtype by GEP had a numerically higher ORR, but CR rates were similar between subtypes (**Figure 4**)

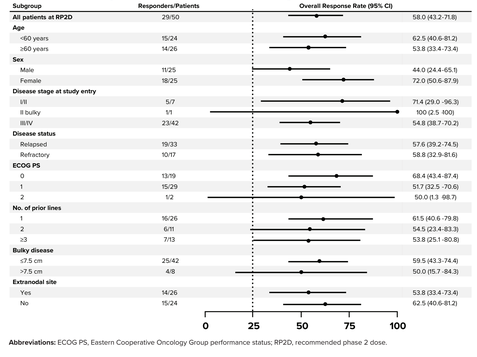
Figure 2. Response Rates



	Part 1			Part 2
	Zanu + len 15 mg (n=6)	Zanu + len 20 mg (n=10)	Zanu + len 25 mg (n=11)	Zanu + len 25 mg (n=39)
ORR, n (%)	1 (16.7)	3 (30.0)	10 (90.9)	19 (48.7)
CR rate, n (%)	1 (16.7)	1 (10.0)	8 (72.7)	13 (33.3)

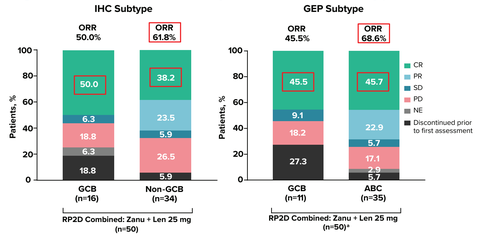
[a]ORR is defined as best overall response of PR or CR.
Abbreviations: CR, complete response; len, lenalidomide; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; zanu, zanubrutinib.

Figure 3. Response Rates at RP2D by Subgroup



Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; RP2D, recommended phase 2 dose.

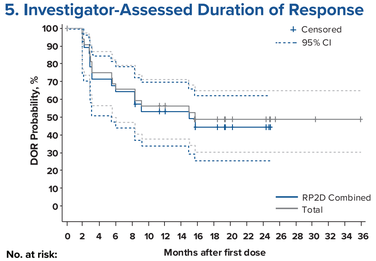
Figure 4. Response Rates by IHC and GEP Subtype



*Includes 4 patients with missing GEP subtype.
Abbreviations: CR, complete response, len, lenalidomide; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SD, stable disease; zanu, zanubrutinib.

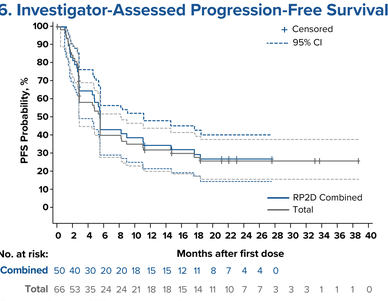
- Median DOR was 15.7 months (range, 5.6-NE months; median follow-up, 20.3 months) in all patients and 14.9 months (range, 5.5-NE months; median follow-up, 19.3 months) at the RP2D (**Figure 5**)
  - DOR rate at 12 months was 56.1% (95% CI, 37.4-71.2) in all patients and 53.3% (95% CI, 33.5-69.7) at the RP2D
- Median PFS was 5.5 months (range, 2.8-8.3 months; median follow-up, 22.1 months) in all patients and 5.5 months (range, 2.9-11.1 months; median follow-up, 22.1 months) at the RP2D (**Figure 6**)
  - PFS rate at 12 months was 31.7% (95% CI, 20.5-43.5) in all patients and 34.4% (95% CI, 21.3-47.9) at the RP2D
- Median OS was not reached in all patients (median follow-up, 22.1 months) and at the RP2D (median follow-up, 20.2 months) (**Figure 7**)
  - OS rate at 12 months was 69.0% (95% CI, 56.2-78.8) in all patients and 73.8% (95% CI, 59.2-83.9) at the RP2D

Figure 5. Investigator-Assessed Duration of Response



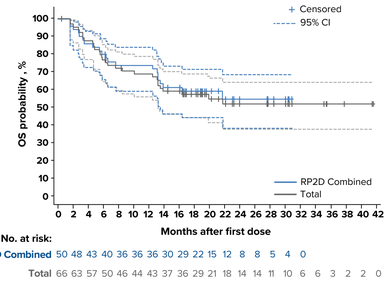
Abbreviations: DOR, duration of response; RP2D, recommended phase 2 dose.

Figure 6. Investigator-Assessed Progression-Free Survival



Abbreviations: PFS, progression-free survival; RP2D, recommended phase 2 dose.

Figure 7. Overall Survival



Abbreviations: OS, overall survival; RP2D, recommended phase 2 dose.

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DISCLOSURES

YG: Honoraria: Merck Serono, Roche, MSD, BMS; Consultant or advisory role: Merck Serono, MSD, Bayer, Roche, GSK. **SH, YF, JL:** Employment and may own stock: BeOne Medicines Ltd. **ZS, YC, HY, L. Zhang, L. Zou, JC, HH, ZW, KZ, HZ:** No disclosures.

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