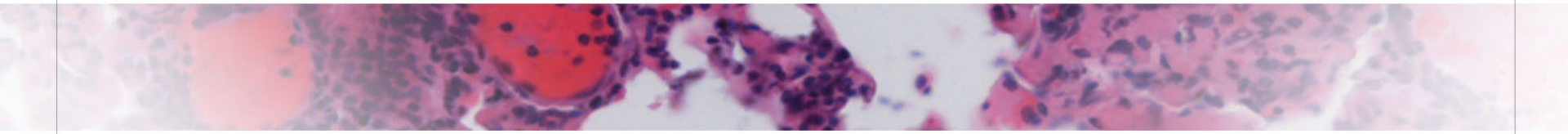
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



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

Zheng Song,[1] Ying Cheng,[2] Haiyan Yang,[3] Liling Zhang,[4] Liqun Zou,[5] Ye Guo,[6] Junning Cao,[7] Huiqiang Huang,[8] Zhao Wang,[9] Sha Huang,[10] Yiqian Fang,[10] Jiaoyan Lyu,[11] Keshu Zhou,[12] Huilai Zhang[1]

[1]Tianjin Medical University Cancer Institute & Hospital, Tianjin, China; [2]Jilin Cancer Hospital, Changchun, China; [3]The Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China; [4]Union Hospital of Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [5]West China Hospital, Sichuan University, Chengdu, China; [6]Shanghai East Hospital, School of Medicine, Tongji University, Shanghai, China; [7]Fudan University Shanghai Cancer Center, Shanghai, China; [8]Sun Yat-sen University Cancer Center, Guangzhou, China; [9]Beijing Friendship Hospital, Capital Medical University, Beijing, China; [10]BeiGene (Shanghai) Co, Ltd, Shanghai, China; [11]BeiGene (Beijing) Co, Ltd, Beijing, China; [12]Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China

Presentation #986

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 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 dose-escalation part detailing the recommended dose for expansion,[3] and results for interim analysis of the study[4] have been previously presented
- Presented here is the final analysis of BGB-3111-110

AE, adverse event; BTK, Bruton tyrosine kinase; DLBCL, diffuse large B-cell lymphoma; R/R, relapsed/refractory.

1. Ip A, et al. *Adv Ther.* 2024;41:1226-1244. 2. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 3. Zhang H, et al. ASCO 2023. Abstract 7557. 4. Zhang H, et al. ASH 2022. Abstract 1627.

BGB-3111-110 Study Design (NCT04436107)

Key eligibility criteria

- Adults with histologically confirmed DLBCL
- R/R disease with ≥1 prior line of adequate systemic therapy for DLBCL
- Ineligible for HDT/SCT if not received previously
- ECOG PS 0-2
- No prior exposure to BTK inhibitor, lenalidomide, or thalidomide

Part 1
Dose escalation (3+3 design)

Dose Level	Zanubrutinib	Lenalidomide
1	160 mg BID	15 mg QD (d1-21 per 28-d cycle)
2	160 mg BID	20 mg QD (d1-21 per 28-d cycle)
3	160 mg BID	25 mg QD (d1-21 per 28-d cycle)

Primary endpoints
Safety per CTCAE v5.0
RP2D of lenalidomide

RP2D[a] →

Part 2
Dose expansion

Zanubrutinib	Lenalidomide
160 mg BID	RP2D: 25 mg QD (d1-21 per 28-d cycle)

Primary endpoint
ORR per Lugano 2014 criteria

Patients received zanubrutinib + lenalidomide continuously until disease progression or unacceptable toxicity

[a] Preliminary results for part 1 of this study detailing the recommended dose for expansion were previously presented at ASH 2022 (Zhang H, et al. ASH 2022. Abstract 1627)
BTK, Bruton tyrosine kinase; CTCAE, Common Terminology Criteria for Adverse Events; d, day; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; HDT, high-dose therapy; ORR, overall response rate; R/R, relapsed/refractory; RP2D, recommended phase 2 dose; SCT, stem cell transplant.

Baseline Characteristics

- As of March 28, 2024, 66 patients were enrolled and received zanubrutinib + lenalidomide
- Median follow-up, all patients: 16.5 months (range, 0.5-41.6 months)
- Patients had a median of 2 prior lines of therapy
- 83% had stage III/IV disease, 42% had refractory disease, and 55% had extranodal lesions
- 65% had non-GCB disease per IHC; 67% had ABC disease per GEP

	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)	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)
Prior lines of therapy, median (range)	2 (1-2)	2 (1-4)	1 (1-5)	1 (1-5)	1 (1-5)	**2 (1-5)**
ECOG performance status, n (%)						
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**)
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)

ABC, activated B-cell like; GCB, germinal center B-cell like; GEP, gene expression profiling; IHC, immunohistochemistry; len, lenalidomide; zanu, zanubrutinib.

Overall Safety Summary

- Median exposure to zanubrutinib + lenalidomide was 4.9 months
- No DLTs occurred; 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

	Part 1			Part 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.
DLT, dose-limiting toxicity; len, lenalidomide; RP2D, recommended phase 2 dose; TEAE, treatment-emergent adverse event; zanu, zanubrutinib.

TEAEs Were Consistent With the Known Safety Profiles of Zanubrutinib and Lenalidomide

- Grade ≥3 TEAEs were mostly **hematologic events** and were generally manageable with concomitant medications and/or dose modification
  - Febrile neutropenia only occurred in 1 patient (grade 3), but event resolved within 2 days
  - No grade ≥3 hemorrhage occurred
- 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)

TEAEs in >20% of All Patients

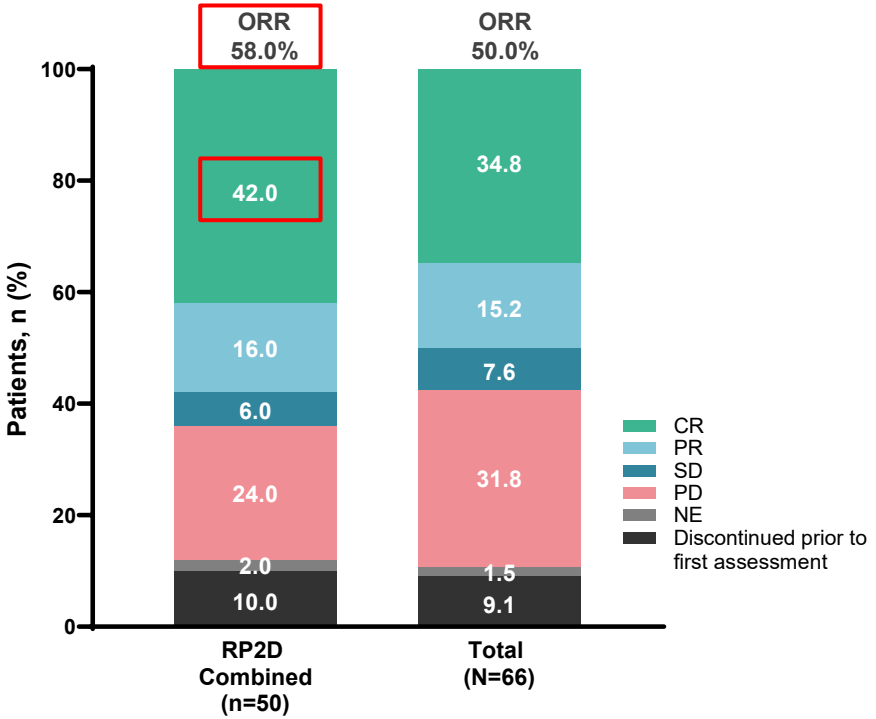
	All (N=66)	
Patients, n (%)	**All Grade**	**Grade ≥3**
Neutrophil count decreased	51 (77.3)	38 (**57.6**)
White blood cell count decreased	48 (72.7)	19 (28.8)
Platelet count decreased	40 (60.6)	10 (**15.2**)
Anemia	36 (54.5)	11 (**16.7**)
Lymphocyte count decreased	29 (43.9)	13 (19.7)
Hypokalemia	27 (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**)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; TEAE, treatment-emergent adverse event.

Response Rates Increased by Dose Level, Reaching an ORR of 58% With a CR Rate of 42% at RP2D

- ORR and CR rates increased with the increasing dose level of lenalidomide
- In the 50 patients who received lenalidomide at RP2D, an ORR of 58% with a CR of 42% was reached

Patients, n (%)	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)

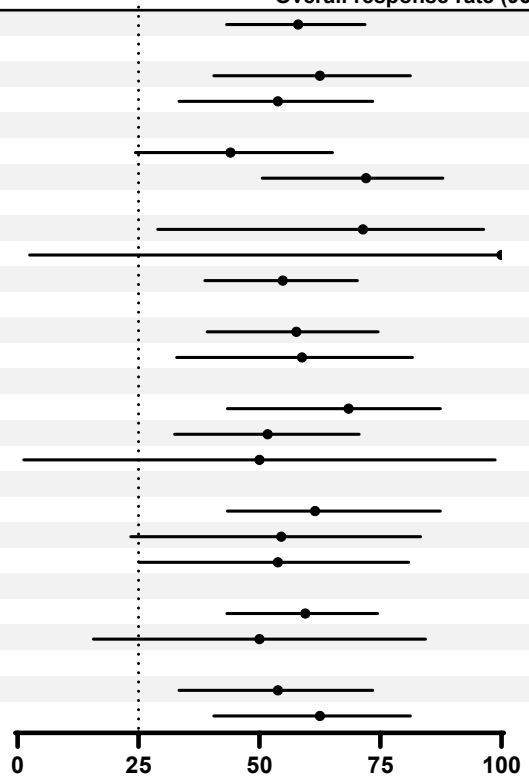


[a] ORR is defined as best overall response of PR or CR.

CR, complete response; len, lenalidomide; NE, not estimable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; zanu, zanubrutinib.

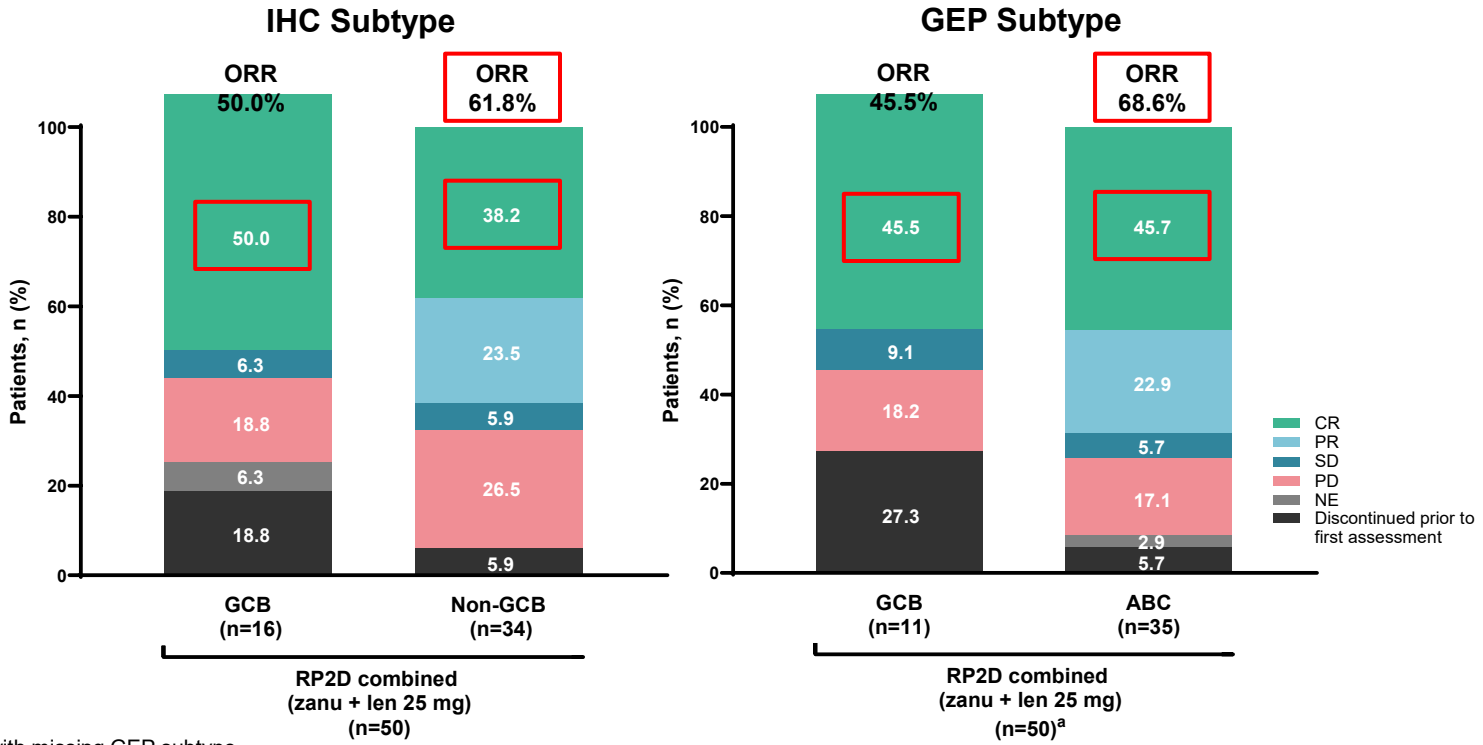
At RP2D, ORR Benefit was Observed Across All Subgroups

Subgroup	Responders/patients	Overall response rate (95% CI)
All patients at RP2D	29/50	58.0 (43.2-71.8)
Age		
<60 years	15/24	62.5 (40.6-81.2)
≥60 years	14/26	53.8 (33.4-73.4)
Sex		
Male	11/25	44.0 (24.4-65.1)
Female	18/25	72.0 (50.6-87.9)
Disease stage at study entry		
I/II	5/7	71.4 (29.0-96.3)
II bulky	1/1	100 (2.5-100)
III/IV	23/42	54.8 (38.7-70.2)
Disease status		
Relapsed	19/33	57.6 (39.2-74.5)
Refractory	10/17	58.8 (32.9-81.6)
ECOG PS		
0	13/19	68.4 (43.4-87.4)
1	15/29	51.7 (32.5-70.6)
2	1/2	50.0 (1.3-98.7)
No. of prior lines		
1	16/26	61.5 (40.6-79.8)
2	6/11	54.5 (23.4-83.3)
≥3	7/13	53.8 (25.1-80.8)
Bulky disease		
≤7.5 cm	25/42	59.5 (43.3-74.4)
>7.5 cm	4/8	50.0 (15.7-84.3)
Extranodal site		
Yes	14/26	53.8 (33.4-73.4)
No	15/24	62.5 (40.6-81.2)



ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; RP2D, recommended phase 2 dose.

At RP2D, Non-GCB Subtype by IHC and ABC Subtype by GEP had Numerically Higher ORR, but CR Rates Were Similar Between Subtypes

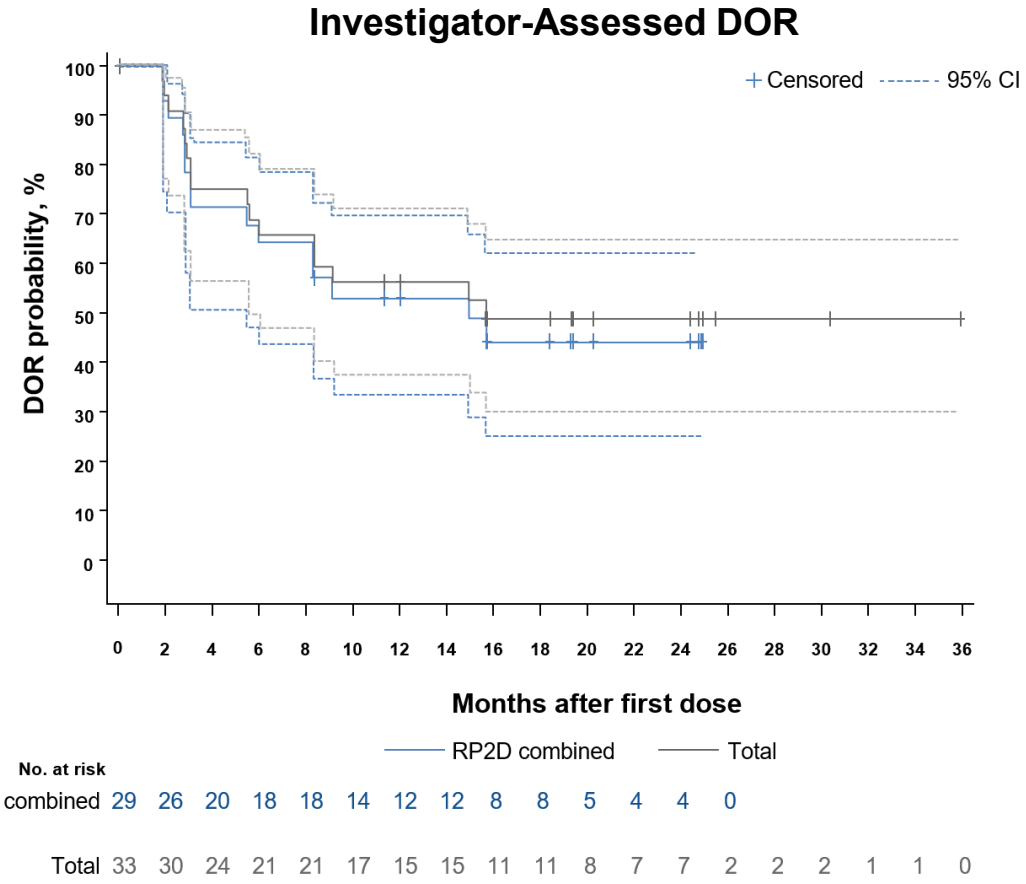


[a] Includes 4 patients with missing GEP subtype.

ABC, activated B-cell like; GCB, germinal center B-cell like; GEP, gene expression profiling; IHC, immunohistochemistry; len, lenalidomide; NE, not estimable; zanu, zanubrutinib.

Duration of Response

Patients, n (%)	RP2D combined (n=50)	All (N=66)
DOR follow-up time, median (range), months	19.3 (0.03-24.9)	20.3 (0.03-35.9)
DOR, median (95% CI), months	14.9 (5.5-NE)	15.7 (5.6-NE)
12-month DOR rate (95% CI), %	53.3 (33.5-69.7)	56.1 (37.4-71.2)

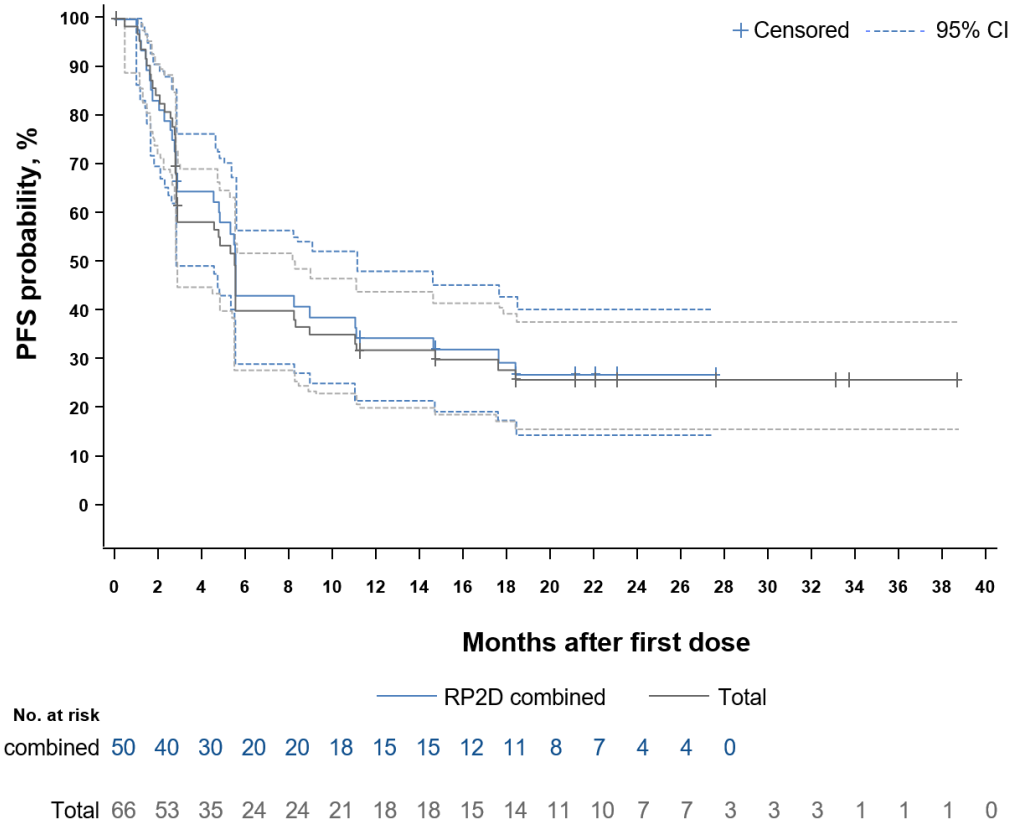


DOR, duration of response; NE, not estimable; RP2D, recommended phase 2 dose.

Progression-Free Survival

Patients, n (%)	RP2D combined (n=50)	All (N=66)
PFS follow-up time, median (range), months	22.1 (0.03-27.6)	22.1 (0.03-38.7)
PFS, median (95% CI), months	5.5 (2.9-11.1)	5.5 (2.8-8.3)
12-month PFS rate (95% CI), %	34.4 (21.3-47.9)	31.7 (20.5-43.5)

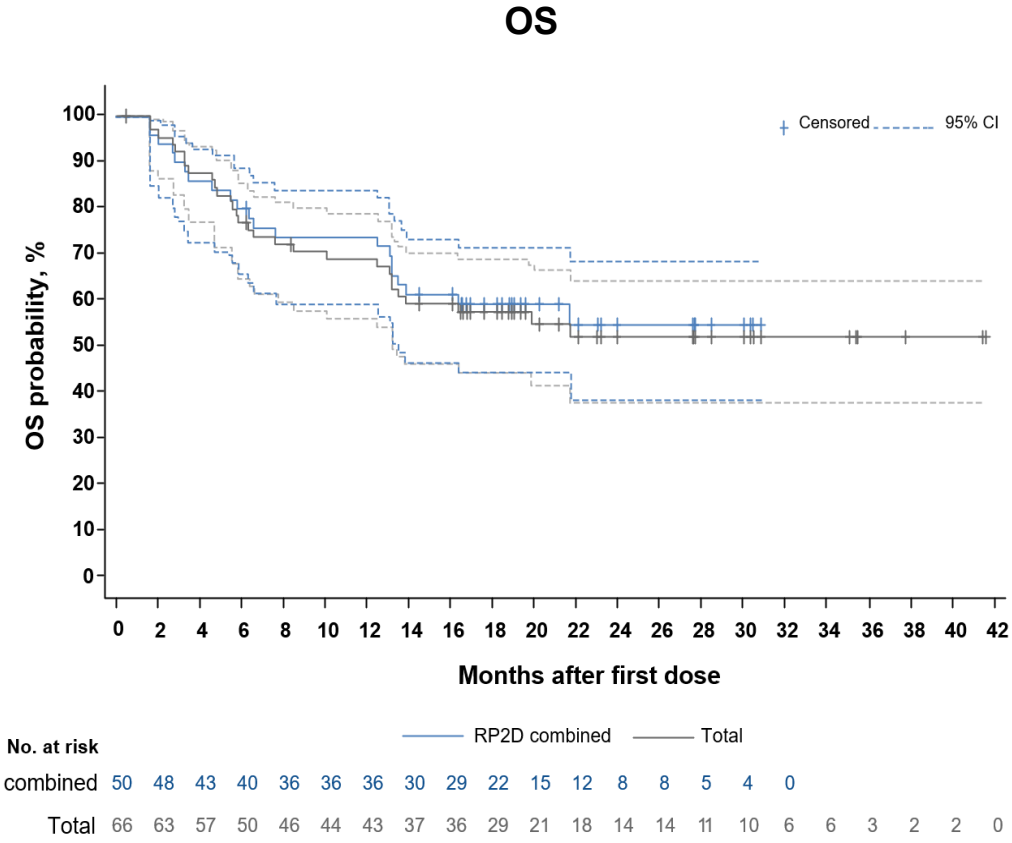
Investigator-Assessed PFS



NE, not estimable; PFS, progression-free survival; RP2D, recommended phase 2 dose.

Overall Survival

Patients, n (%)	RP2D combined (n=50)	All (N=66)
OS follow-up time, median (range), months	20.2 (1.6-30.9)	22.1 (0.5-41.6)
OS, median (95% CI), months	NE (13.5-NE)	NE (13.2-NE)
12-month OS rate (95% CI), %	73.8 (59.2-83.9)	69.0 (56.2-78.8)



NE, not estimable; OS, overall survival; RP2D, recommended phase 2 dose.

Conclusions

- In the BGB-3111-110 study, the RP2D of zanubrutinib 160 mg twice daily plus lenalidomide 25 mg once daily had an acceptable safety profile in patients with R/R DLBCL, with hematologic events being the most common grade ≥3 TEAEs, but rarely leading to discontinuation
- The combination demonstrated encouraging antitumor activity at the RP2D
  - ORR reached 58% with a CR rate of 42%
  - Responses were durable, with a median DOR of 14.9 months
  - Median PFS was 5.5 months
  - Median 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

Acknowledgments

- The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers
- This study was sponsored by BeiGene, Ltd
- Medical writing support was provided by Shanen Perumal, PhD, of Nucleus Global, an Inizio company, and supported by BeiGene

Corresponding Authors:

Huilai Zhang (main), zhlwgq@126.com;

Keshu Zhou (second), drzhouks77@163.com