# 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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# Disclosures for Zheng Song

- Nothing to disclose

# 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 the 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; ECOG, Eastern Cooperative Oncology Group; 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**

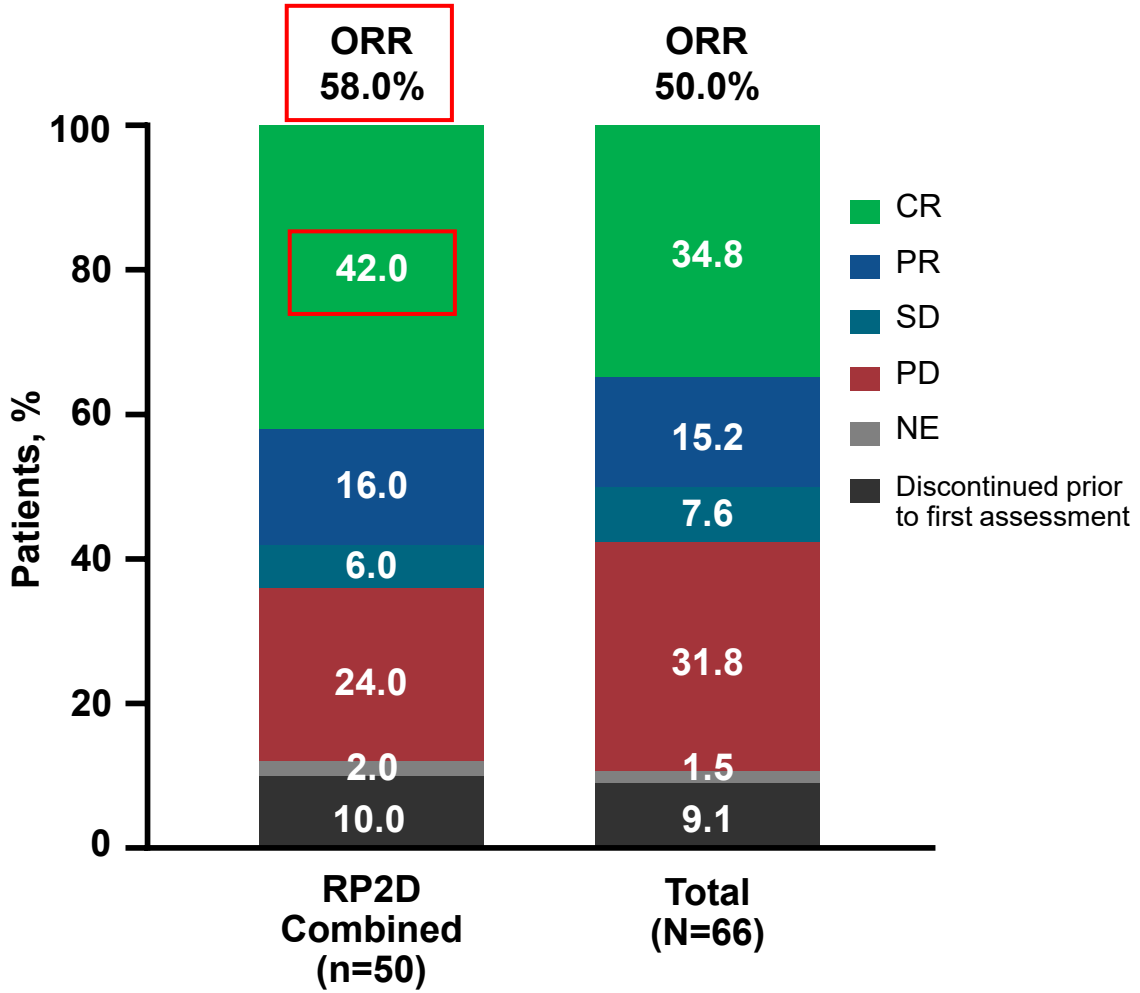
| | All (N=66) | |
|---|---|---|
| **Patients, n (%)** | **All Grade** | **Grade ≥3** |
| **Neutrophil count decreased** | 51 (77.3) | 38 (**57.6**) |
| White blood cell count decreased | 48 (72.7) | 19 (28.8) |
| **Platelet count decreased** | 40 (60.6) | 10 (**15.2**) |
| **Anemia** | 36 (54.5) | 11 (**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

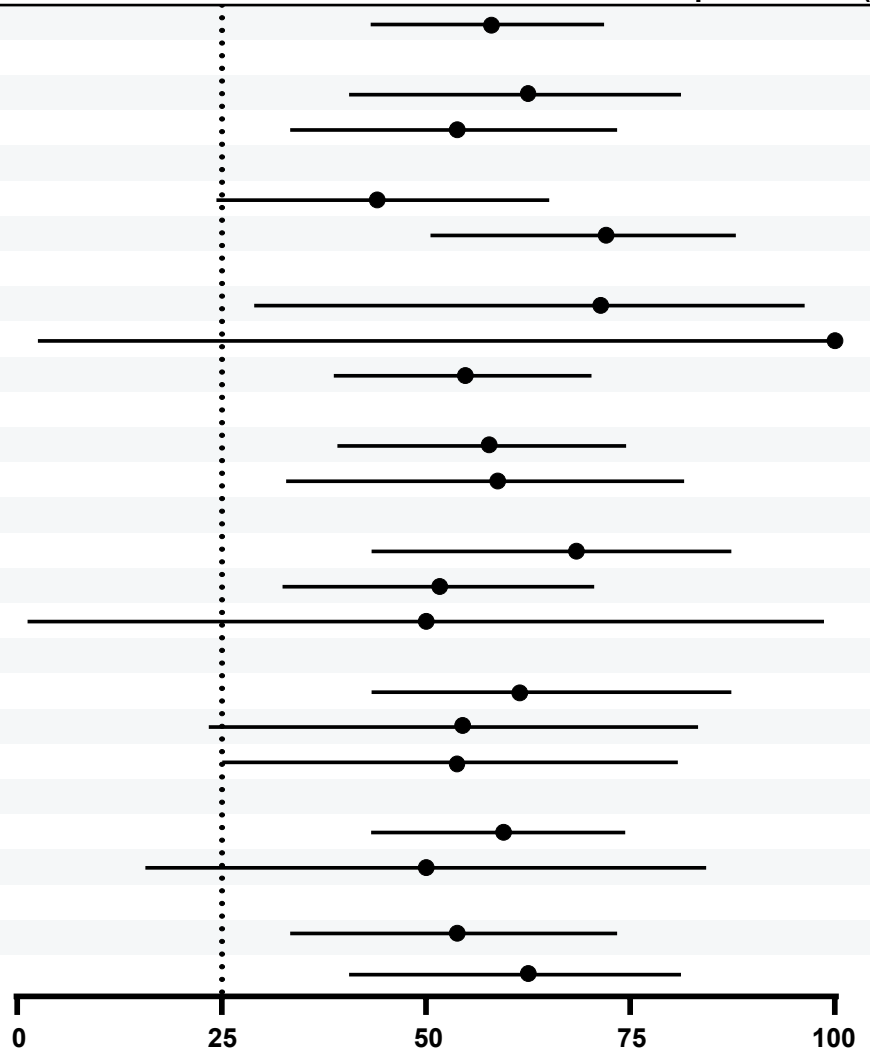
| | Part 1 | | | Part 2 |
|---|---|---|---|---|
| Patients, n (%) | Zanu + Len 15 mg (n=6) | Zanu + Len 20 mg (n=10) | Zanu + Len 25 mg (n=11) | Zanu + Len 25 mg (n=39) |
| ORR, n (%) | 1 (16.7) | 3 (30.0) | 10 (90.9) | 19 (48.7) |
| CR rate, n (%) | 1 (16.7) | 1 (10.0) | 8 (72.7) | 13 (33.3) |




[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.

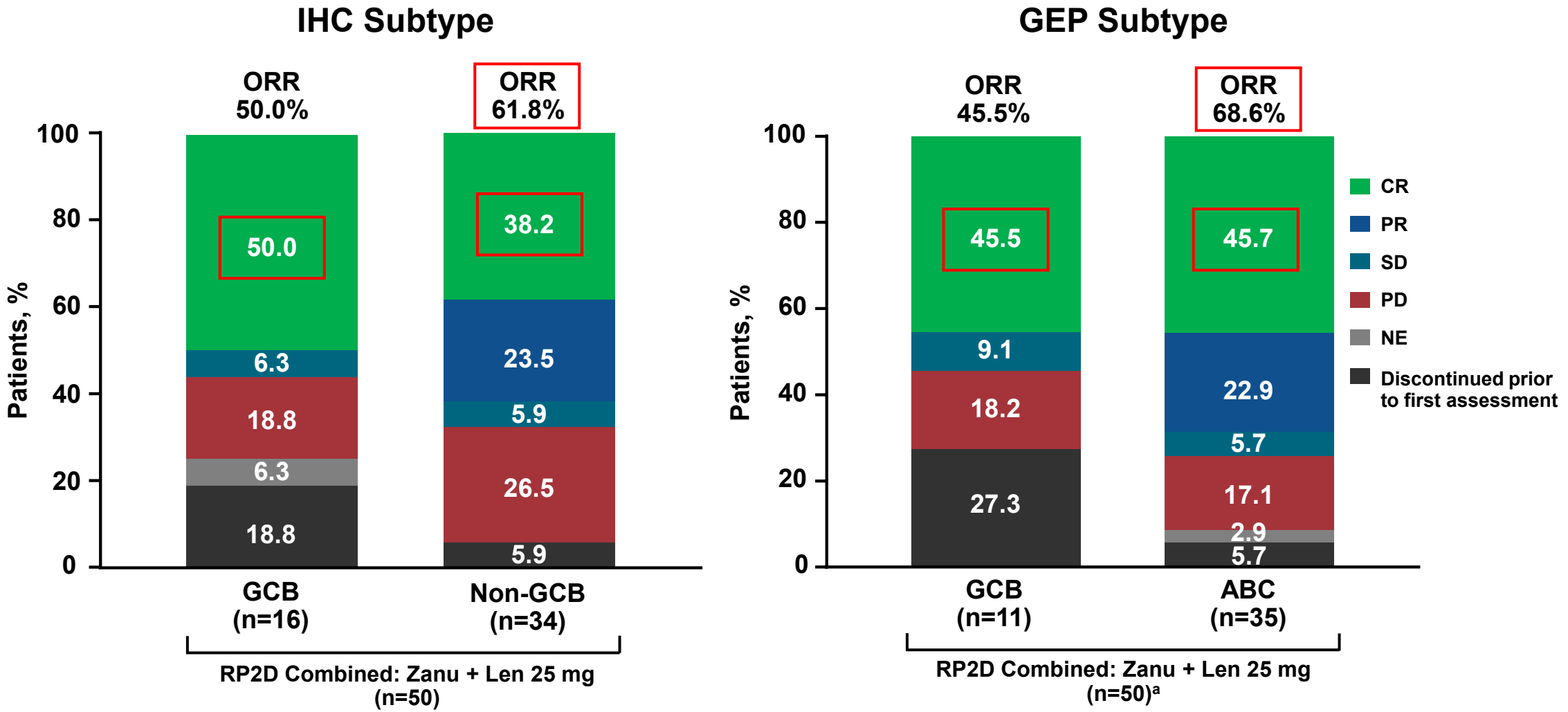
# At RP2D, ORR Benefit was Observed Across All Subgroups

| 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.

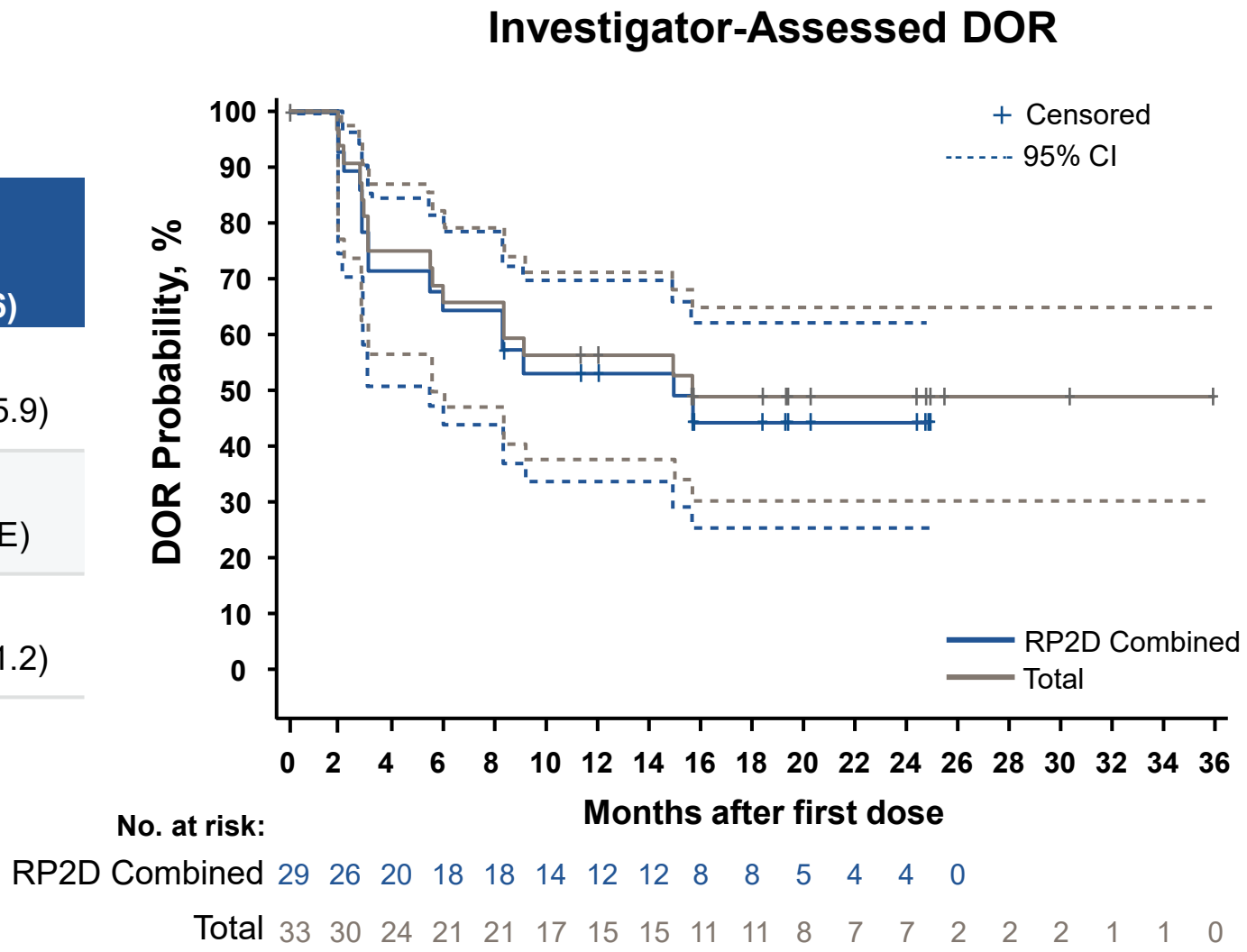
# At RP2D, Non-GCB Subtype by IHC and ABC Subtype by GEP Had Numerically Higher ORR, but CR Rates Were Similar Between Subtypes




[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

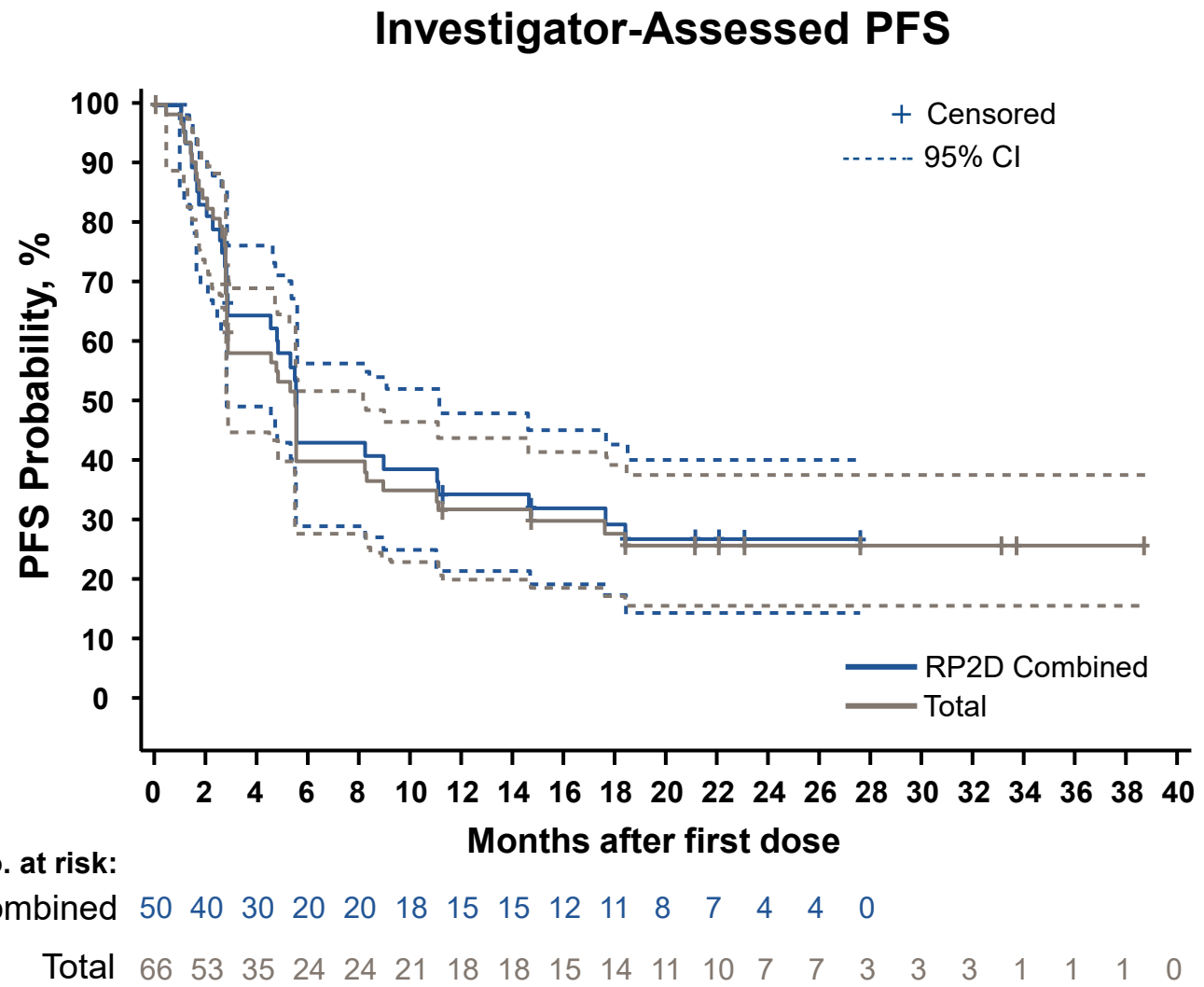
| Patients, n (%) | RP2D Combined (n=50) | All (N=66) |
|---|---|---|
| DOR follow-up time, median (range), months | 19.3 (0.03-24.9) | 20.3 (0.03-35.9) |
| DOR, median (95% CI), months | 14.9 (5.5-NE) | 15.7 (5.6-NE) |
| 12-month DOR rate (95% CI), % | 53.3 (33.5-69.7) | 56.1 (37.4-71.2) |




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

# Progression-Free Survival

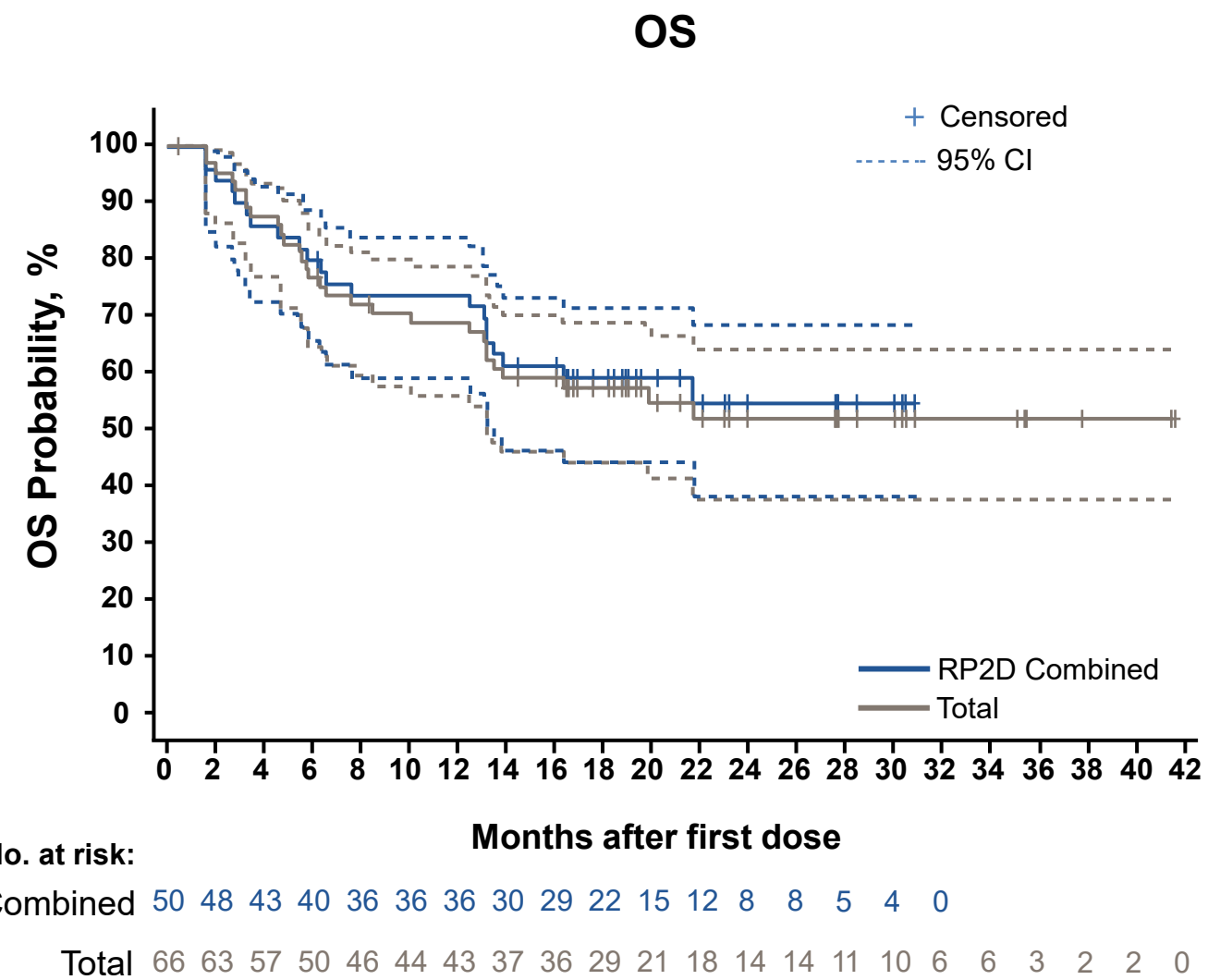
| Patients, n (%) | RP2D Combined (n=50) | All (N=66) |
|---|---|---|
| PFS follow-up time, median (range), months | 22.1 (0.03-27.6) | 22.1 (0.03-38.7) |
| PFS, median (95% CI), months | 5.5 (2.9-11.1) | 5.5 (2.8-8.3) |
| 12-month PFS rate (95% CI), % | 34.4 (21.3-47.9) | 31.7 (20.5-43.5) |




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

CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival RP2D, recommended phase 2 dose; R/R, relapsed/refractory; TEAE, treatment-emergent adverse event.

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