Zanubrutinib in Patients With Relapsed or Refractory Mantle Cell Lymphoma: A Single-Arm, Multicenter, Pivotal Phase 2 Study

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Background

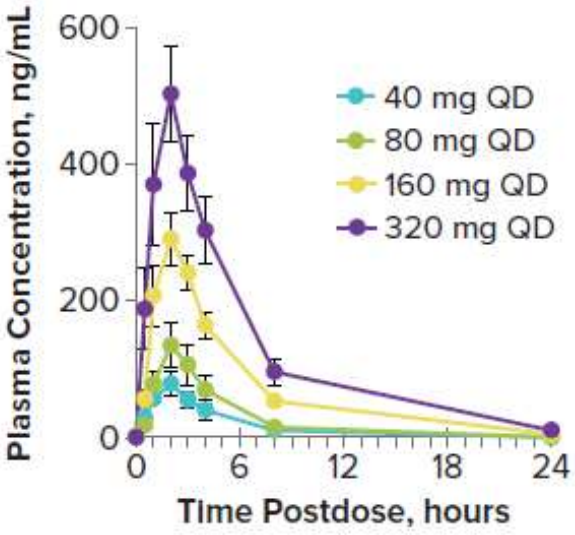
- BTK is a critical component of the B-cell receptor signaling pathway mediating B-cell proliferation, migration, and adhesion.[1-3]
  - Inhibition of BTK is an established therapeutic strategy in B-cell malignancies, including MCL.[4]
- Zanubrutinib (BGB-3111) is an investigational next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases.
  - Has been shown to be a highly potent, selective, bioavailable, and irreversible BTK inhibitor with potentially advantageous PK/PD properties.[5]
  - Complete and sustained BTK occupancy observed in both peripheral blood mononuclear cells and in lymph nodes.[5]

BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; MCL, mantle cell lymphoma; PK/PD, pharmacokinetic/pharmacodynamic.

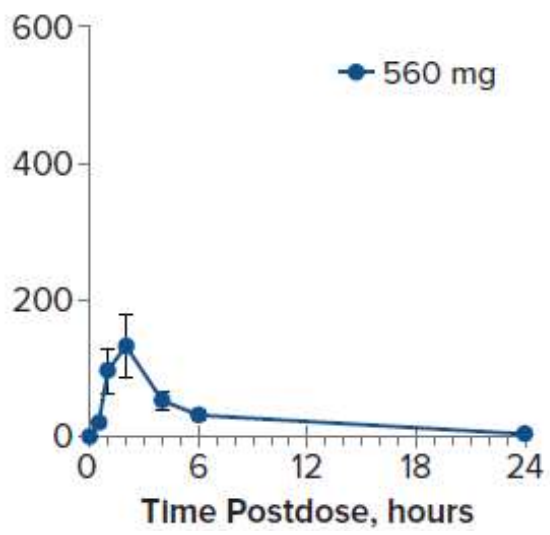
1. Rickert RC. *Nat Rev Immunol.* 2013;13:578-591. 2. Choe H, Ruan J. *Oncology (Williston Park)*. 2016;30:847-858. 3. Aalipour A, Advani RH. *Br J Haematol.* 2013;163:436-443.
4. Wang ML et al, *New Engl J Med.* 2013. 5. Tam CS, et al. *Blood.* 2016;128:642 [oral presentation].

Pharmacokinetics of Zanubrutinib, Ibrutinib, and Acalabrutinib

Zanubrutinib[1]

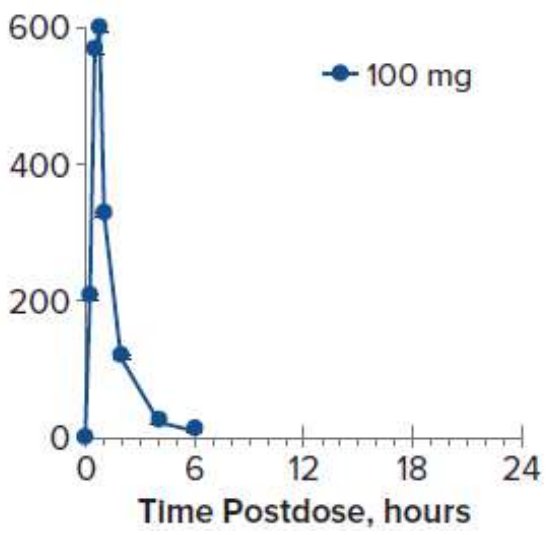


Ibrutinib[2]



Adapted from Advani, et al. *J Clin Oncol*. 2013[2]

Acalabrutinib[3]

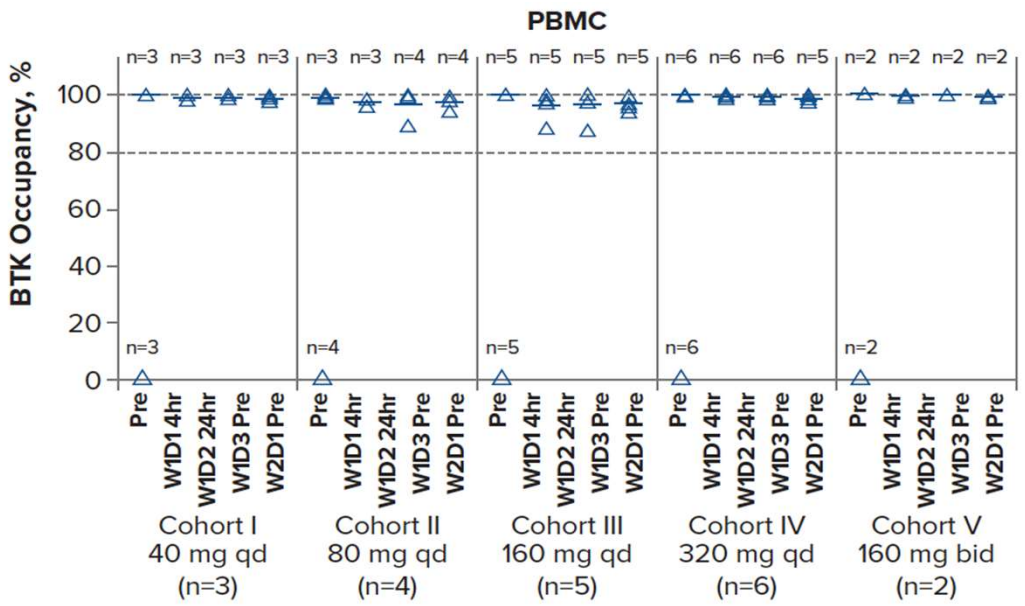


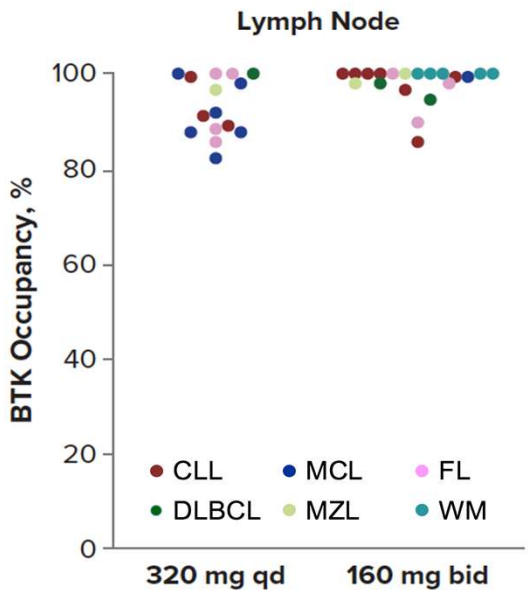
Adapted from Byrd, et al. *New Engl J Med*. 2016[3]

QD, once daily.

1. Tam CS, et al. *Blood*. 2015;126:832 [oral presentation]. 2. Advani RH, et al. *J Clin Oncol*. 2013;31:88-94. 3. Byrd JC, et al. *New Engl J Med*. 2016;374:323-332.

Sustained BTK Inhibition in Peripheral Blood and Lymph Nodes

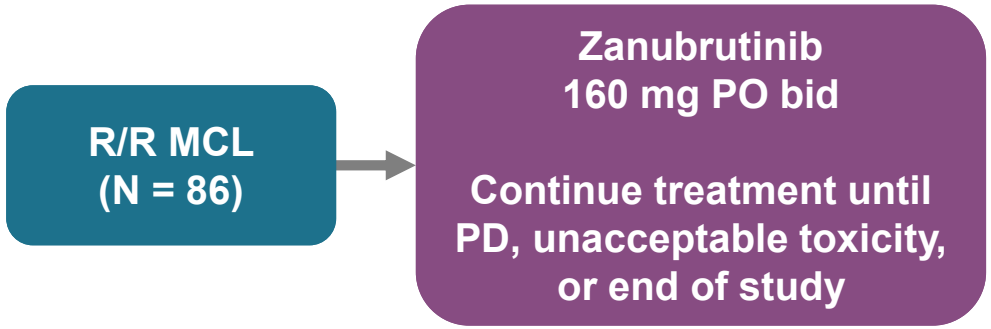




- Complete and sustained BTK occupancy is seen in paired PBMC (left figure) and lymph node biopsy samples (right figure) collected pre-dose on Day 3. In blood samples, complete BTK occupancy was seen at the lowest dose (40 mg).
- Note, 100% median trough occupancy at a dose of 160 mg twice daily with 94% of subjects having >90% occupancy in lymph nodes across malignancies.

bid, twice daily; BTK, Bruton's tyrosine kinase; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PBMC, peripheral blood mononuclear cells; qd, once daily; WM, Waldenstrom macroglobulinemia.

BGB-3111-206: Multicenter, Open-Label, Single-Arm Trial



Primary endpoint:

- ORR assessed by IRC per the Lugano criteria

Key secondary endpoints:

- PFS, DOR, TTR

Response assessments:

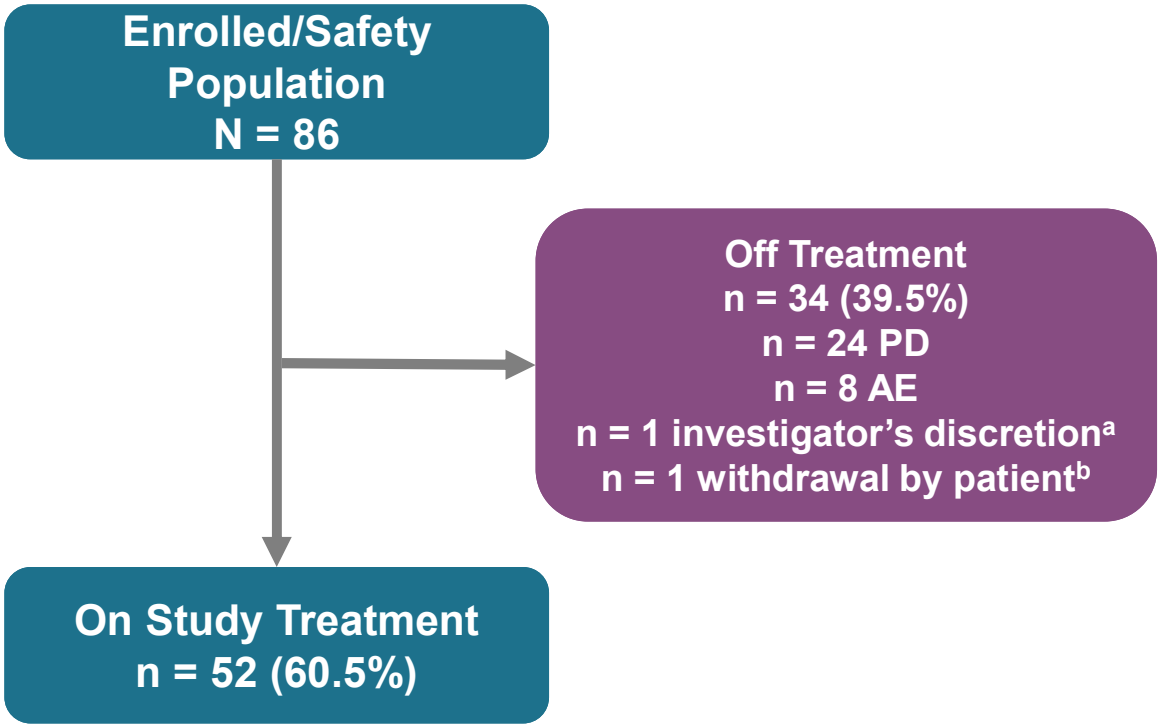
- Responses were assessed using PET-based imaging according to the Lugano Classification.[1]

bid, twice daily; DOR, duration of response; IRC, independent review committee; MCL, mantle cell lymphoma; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PFS, progression-free survival; PO, oral; R/R, relapsed/refractory; TTR, time to response.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32(27):3059-3067.

Data cut: Feb 15, 2019

Patient Disposition



- Median follow-up: 18.4 months (range, 0.3-23.5)

[a]The patient was discontinued per the investigator's discretion 1 month after starting study drug. [b]The patient achieved CR and withdrew consent.
AE, adverse event; CR, complete remission; PD, progressive disease.

Data cut: *Feb 15, 2019*

Patient and Disease Characteristics

Characteristic	Total (N = 86)
Age, median (range), years	60.5 (34-75)
Sex, n (%)	
Male	67 (77.9)
Female	19 (22.1)
ECOG performance status, n (%)	
0/1	82 (95.3)
2	4 (4.7)
Disease status, n (%)	
Relapsed	41 (47.7)
Refractory	45 (52.3)
Prior lines of systemic therapy, median (range)	2 (1-4)
Stage III/IV disease, n (%)	78 (90.7)
MIPI-b intermediate/high risk, n (%)	72 (83.7)
Bulky disease, n (%)	
LDi >10 cm	7 (8.1)
LDi >5 cm	37 (43.0)
Blastoid variant of MCL, n (%)	12 (14.0)

ECOG, Eastern Cooperative Oncology Group; LDi, longest diameter; MCL, mantle cell lymphoma; MIPI-b, Mantle Cell Lymphoma International Prognostic Index Combined Biologic Index.

Investigator and IRC Best Overall Response: 8.2 Months Median Follow-Up

Data cut: March 2018

Best response n (%)	Data cutoff Mar 2018 N = 85[a]	
	INV	IRC
ORR	72/85 (84.7)	71/85 (83.5)
Complete Response	62 (72.9)	50 (58.8)
Partial Response	10 (11.8)	21 (24.7)
Stable Disease	1 (1.2)	2 (2.4)
Progressive Disease	8 (9.4)	6 (7.1)
Discontinued prior to first assessment	4 (4.7)	5 (5.9)
No evidence of disease	-	1 (1.2)

[a]The efficacy report was based on modified safety population which excluded patient 20612006 who had local pathological diagnosis of MCL only but did not have confirmation of MCL by central review.

CR, complete remission; INV, investigator; IRC, independent review committee; ORR, overall response rate.

Investigator-Assessed Best Overall Response: 18.4 Months Median Follow-Up

Data cut: *Feb 15, 2019*

Best response, n (%)	N = 86
ORR (CR or PR)	72 (83.7)
Complete response	67 (77.9)
Partial response	5 (5.8)
Stable disease	1 (1.2)
Progressive disease	8 (9.3)
Discontinued prior to first assessment	5 (5.8)

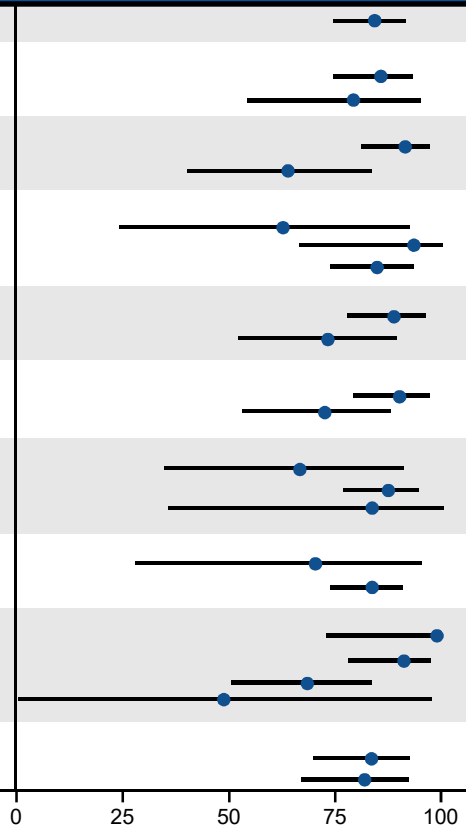
CR, complete remission; ORR, overall response rate; PR, partial response.

Investigator-Assessed ORR by Subgroup

Data cut: Feb 15, 2019

- Subgroup analysis revealed that the treatment benefit of zanubrutinib was generally consistent across all subgroups.

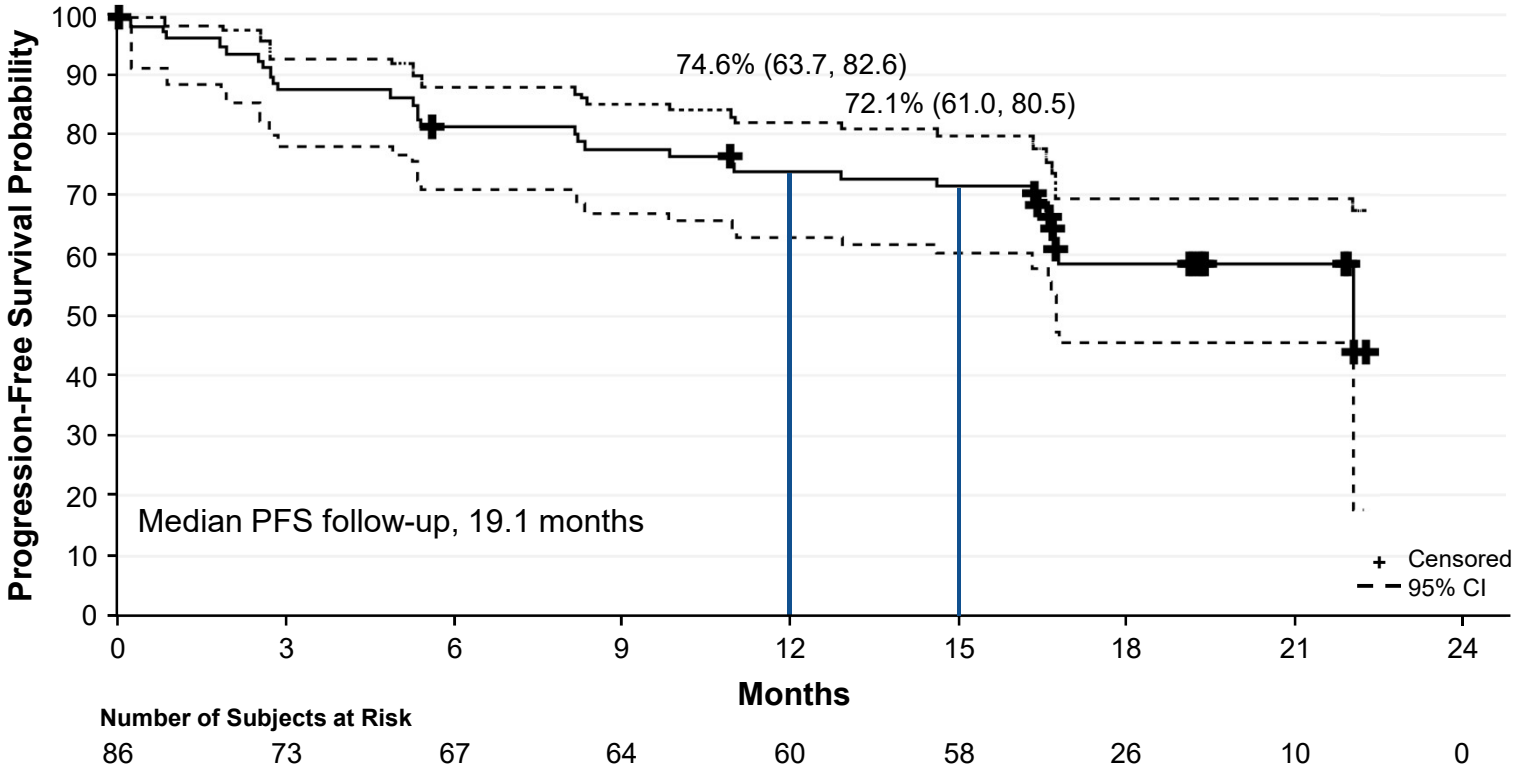
Subgroup	Response/Subjects	ORR (95% CI)
All patients	72/86	83.7 (74.2, 90.8)
Sex		
Male	57/67	85.1 (74.3, 92.6)
Female	15/19	78.9 (54.4, 93.9)
Age group		
<65 years	58/64	90.6 (80.7, 96.5)
≥65 years	14/22	63.6 (40.7, 82.8)
Stage at study entry for MCL		
Stage I or II	5/8	62.5 (24.5, 91.5)
Stage III	13/14	92.9 (66.1, 99.8)
Stage IV	54/64	84.4 (73.1, 92.2)
ECOG-PS		
0	53/60	88.3 (77.4, 95.2)
≥1	19/26	73.1 (52.2, 88.4)
Prior line of therapy for MCL		
<3	51/57	89.5 (78.5, 96.0)
≥3	21/29	72.4 (52.8, 87.3)
Blastoid histology		
Yes	8/12	66.7 (34.9, 90.1)
No	59/68	86.8 (76.4, 93.8)
Unknown	5/6	83.3 (35.9, 99.6)
Bulky disease		
Yes (any target lesion LDi >10 cm)	5/7	71.4 (29.0, 96.3)
No (all target lesion LDi ≤10 cm)	67/79	84.8 (75.0, 91.9)
MIPI-b		
Low	12/12	100.0 (73.5, 100.0)
Intermediate	36/39	92.3 (79.1, 98.4)
High	23/33	69.7 (51.3, 84.4)
Missing	1/2	50.0 (1.3, 98.7)
Refractory disease		
Yes	38/45	84.4 (70.5, 93.5)
No	34/41	82.9 (67.9, 92.8)



CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; LDi, longest diameter; MCL, mantle cell lymphoma; MIPI-b, Mantle Cell Lymphoma International Prognostic Index Combined Biologic Index; ORR, overall response rate.

Data cut: *Feb 15, 2019*

Progression-Free Survival by Investigator

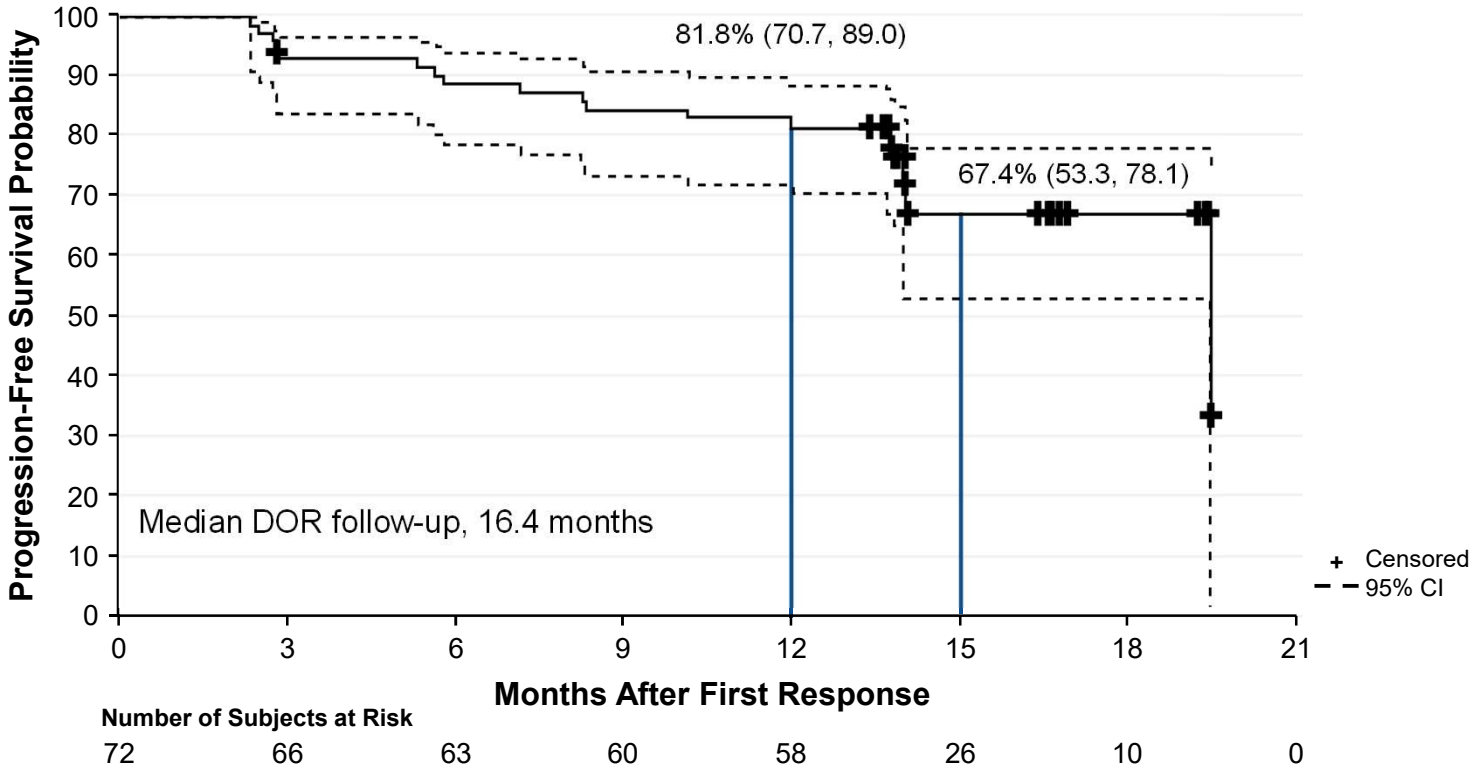


Note: Only 4 patients were at risk at the last event time.

CI, confidence interval; PFS, progression-free survival.

Data cut: *Feb 15, 2019*

Duration of Response by Investigator



Note: Only 2 patients were at risk at the last event time.

CI, confidence interval; DOR, duration of response.

Data cut: Feb 15, 2019

Summary of TEAEs Regardless of Causality

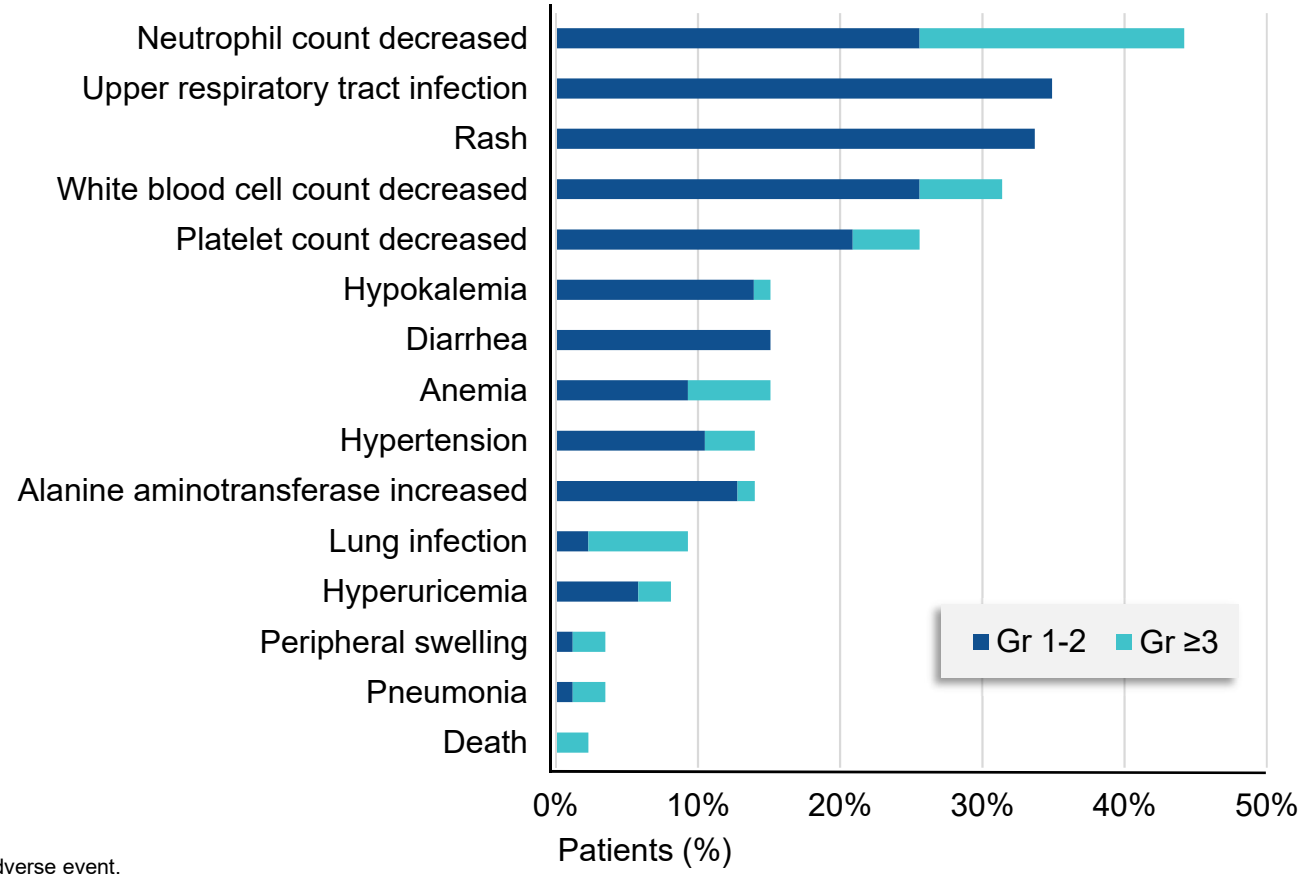
Event, n (%)	N = 86
Grade ≥3 TEAEs	36 (41.9)
Serious TEAEs	21 (24.4)
TEAEs leading to study drug discontinuation	8 (9.3)
TEAEs leading to death[a]	5 (5.8)[b]
Death	2 (2.3)[c]
Pneumonia	1 (1.2)
Cerebral hemorrhage	1 (1.2)
Traffic accident	1 (1.2)
TEAEs of special interest	
Hypertension	13 (15.1)
Petechiae/purpura/contusion	4 (4.7)
Major hemorrhage[d]	3 (3.5)
Atrial fibrillation/flutter	0
Secondary primary malignancy	0
Tumor lysis syndrome	0

[a]Death within 30 days of last dose of zanubrutinib. [b]Four events related, 1 event unrelated (traffic accident). [c]One subject discontinued treatment due to disease progression prior to death. [d]Cerebral hemorrhage (1 subject), gastrointestinal hemorrhage (2 subjects).

TEAE, treatment-emergent adverse event.

TEAEs in ≥10% of Patients or Grade ≥3 TEAEs in ≥2 Patients Regardless of Causality

Data cut: *Feb 15, 2019*



TEAE, treatment-emergent adverse event.

Summary

- Zanubrutinib demonstrated high activity in patients with R/R MCL.
  - High ORR and CR rates documented by PET-based imaging (ORR, 84%; CR, 78%)
  - The responses achieved by zanubrutinib treatment appear durable (15-month DOR, 67.4%; 15-month PFS, 72.1%).
- Zanubrutinib tolerability was generally consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies.
- Data from this phase 2 study were included in the NDA submission to the Chinese NMPA for zanubrutinib in patients with R/R MCL.

CR, complete remission; DOR, duration of response; FDA, Food and Drug Administration; MCL, mantle cell lymphoma; NDA, new drug application; NMPA, National Medical Products Administration; ORR, overall response rate; PET, positron emission tomography; PFS, progression-free survival; R/R, relapsed/refractory.

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Thank you!