Results of Zanubrutinib Monotherapy in Chinese Patients with Relapsed or Refractory Mantle Cell Lymphoma: A Single Arm, Multicenter, Pivotal Phase 2 Study

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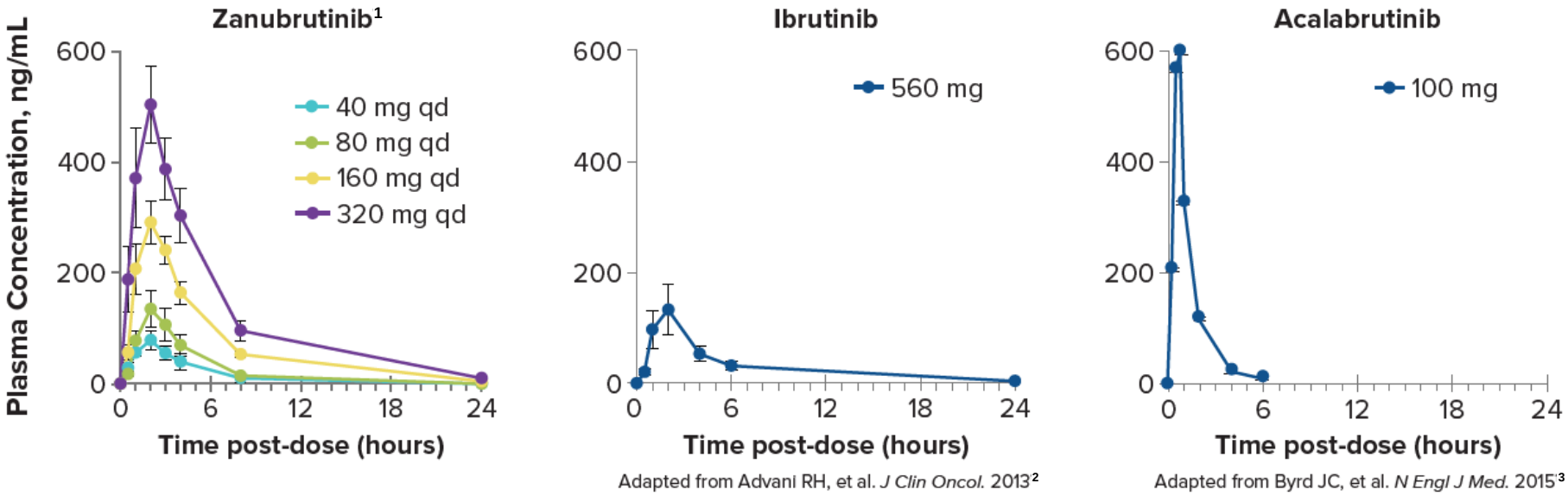
Introduction

- Bruton's tyrosine kinase (BTK) plays a critical role in B-cell receptor signaling, which mediates B-cell proliferation, migration, and adhesion[1-3]
  - BTK is constitutively activated in mantle cell lymphoma (MCL) and is a key mediator in cell survival
- First- and second-generation BTK inhibitors ibrutinib and acalabrutinib have shown activity in MCL[4,5]
- Zanubrutinib (BGB-3111) is a 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[6]

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, NEJM, 2013. 5. Wang M, et al. ASH 2017. 6. Tam CS, et al. ASH 2016.

Pharmacokinetics of zanubrutinib, ibrutinib, and acalabrutinib

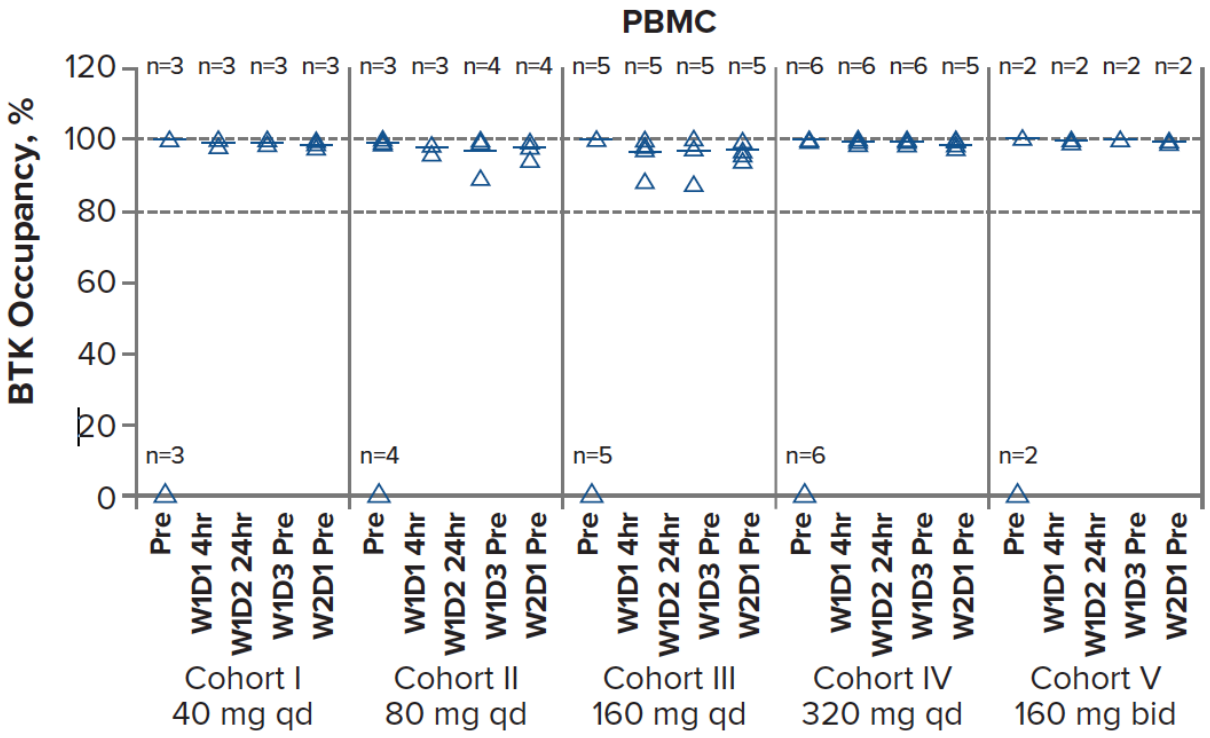


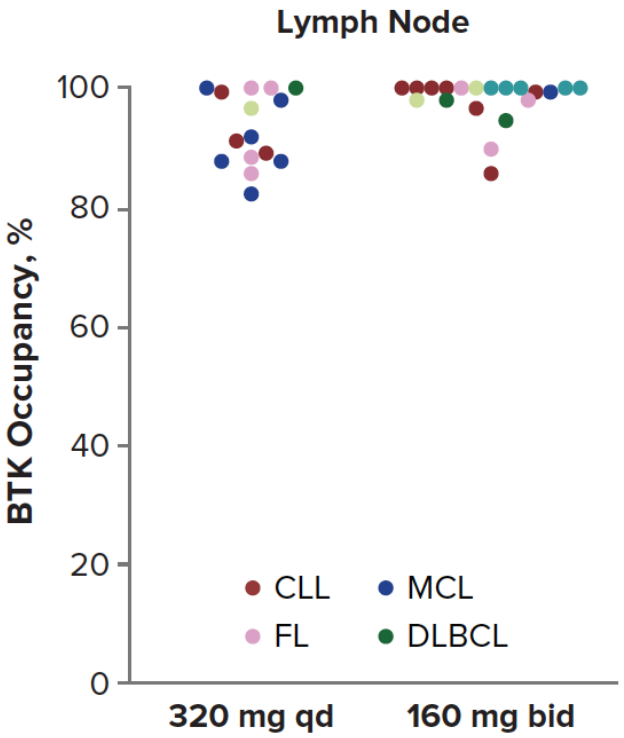
- With the high specificity of zanubrutinib, zanubrutinib was able to be dosed at much high exposure compared to that of ibrutinib and acalabrutinib.
- Zanubrutinib has similar half-life as that of ibrutinib, much longer than that of acalabrutinib.

Note: these data are from 3 separate analyses and differences in studies should be considered.

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. *N Engl J Med*. 2016;374:323-332.

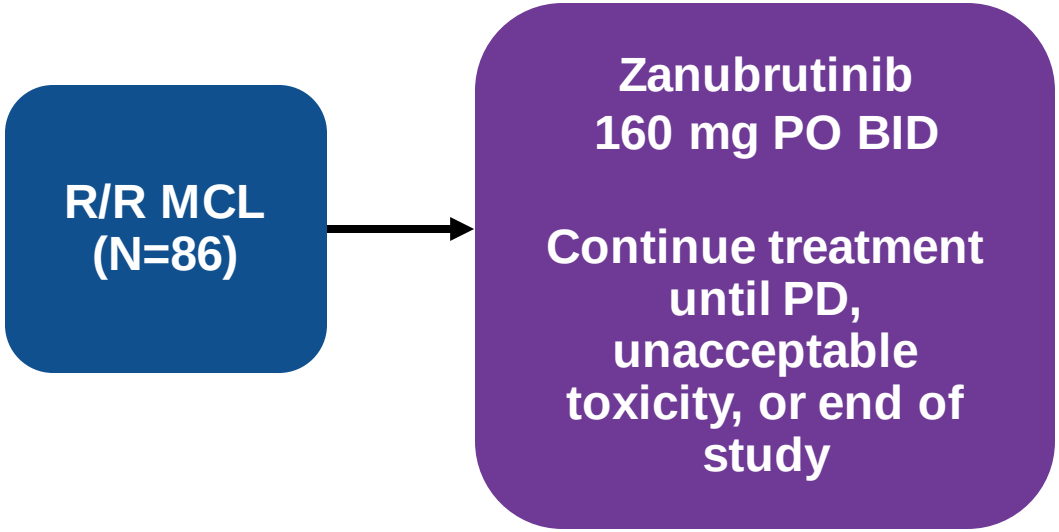
Sustained BTK inhibition in peripheral blood and lymph nodes





- Complete and sustained BTK occupancy is seen in paired PBMC following doses as low as 40 mg (left figure) and lymph node biopsy samples (right figure) collected pre-dose on day 3
- 100% median occupancy at trough plasma concentrations (pre-dose, day 3) at a dose of 160 mg bid; 94% of patients had >90% occupancy in lymph nodes as measured in patients with various B-cell malignancies

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



Primary endpoint:

- ORR assessed by IRC per the Lugano criteria

Key Secondary endpoints:

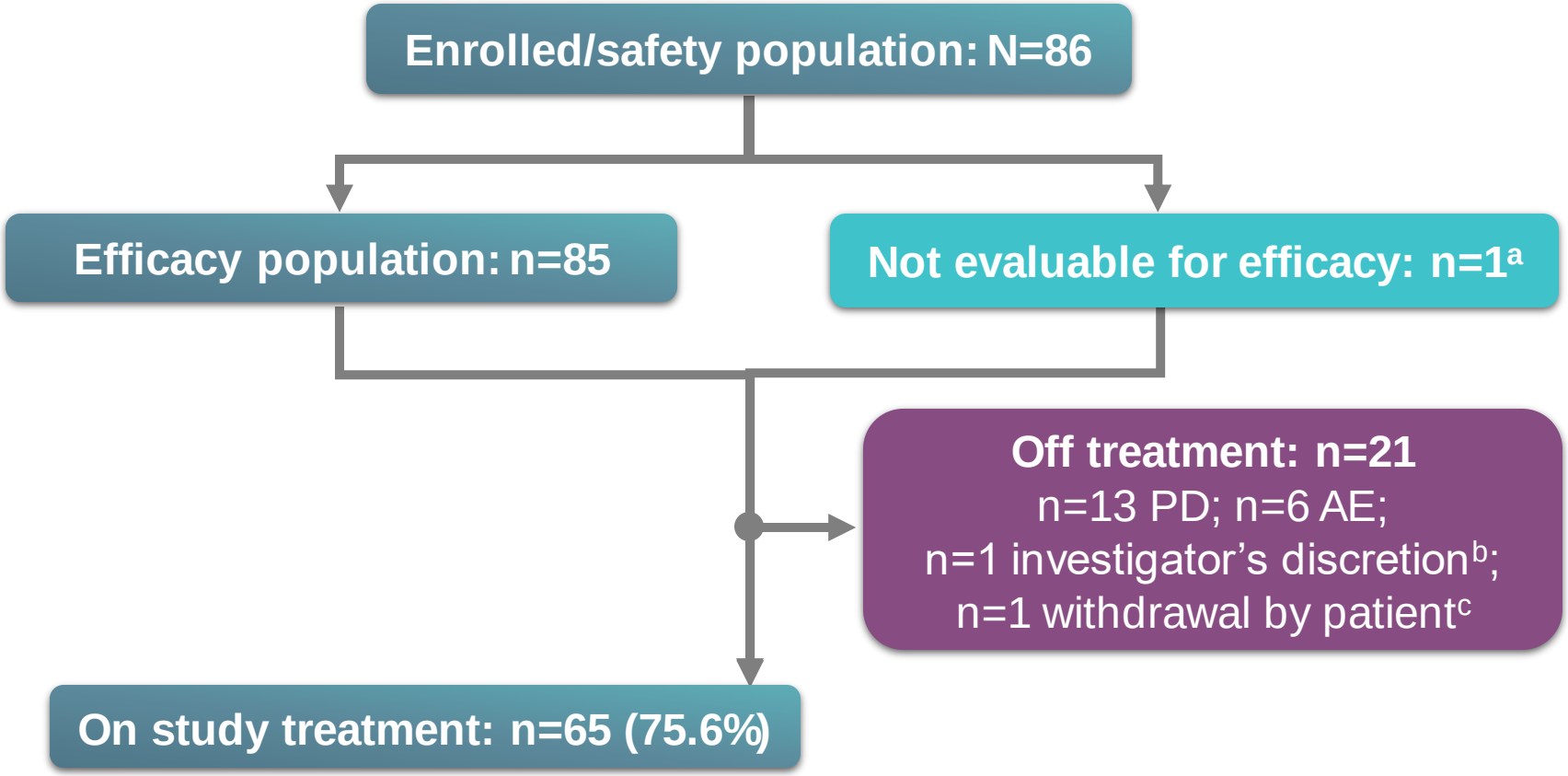
- PFS, DOR, TTR

Response assessments:

- Response assessments were assessed by IRC using PET-based imaging according to the Lugano Classification (Cheson 2014)

BID, twice daily; DOR, duration of response; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PK, pharmacokinetics; PO, oral; TTR, time to response.

Patient Disposition



- Median follow up: 35.9 weeks (range, 1.1-55.9)

[a]One subject was excluded due to lack of central pathology confirmation. [b]The subject was discontinued per the investigator's discretion 1 month after starting study drug. [c]The subject achieved CR and withdrew consent.

Patient and Disease Characteristics

Characteristic	Total (N=86)
Age, years, median (range)	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 (%)	
Relapse	41 (47.7)
Refractory	45 (52.3)
Prior lines of systemic therapy, No., 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 (%)	
> 10cm	7 (8.1)
> 5cm	37 (43)
Blastoid variant of MCL, n (%)	12 (14.0)

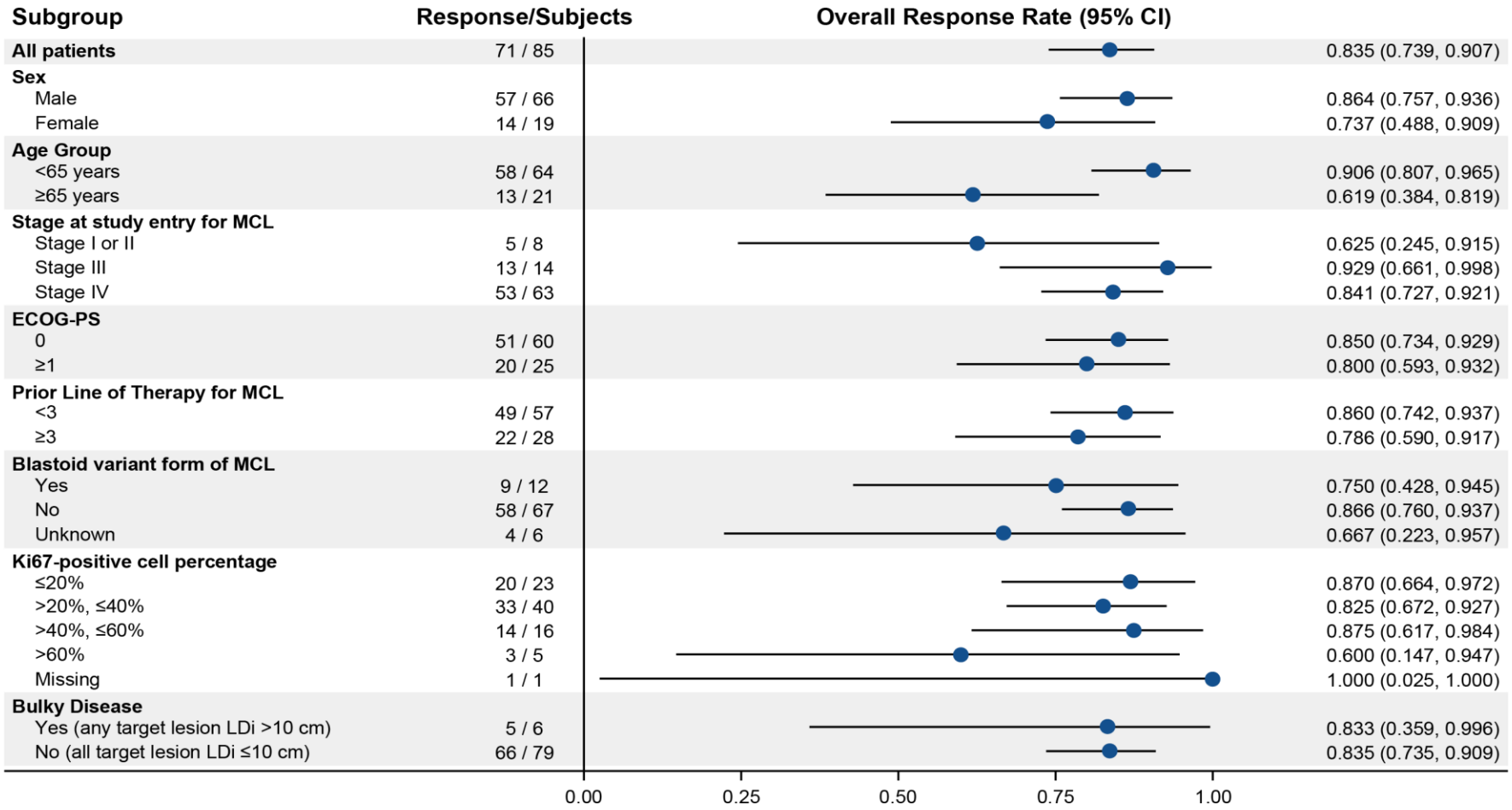
MIPI-b, Mantle Cell Lymphoma International Prognostic index Combined Biologic Index.

Efficacy: Best Overall Response by IRC

Best response‡, n (%)	N=85
ORR (CR or PR), n (%)	71 (83.5)
Complete response	50 (58.8)
Partial response	21 (24.7)
Stable disease	2 (2.4)
Progressive disease	6 (7.1)
Discontinued prior to first assessment[a]	5 (5.9)
No evidence of disease[b]	1 (1.2)

[a] Patients discontinued prior to first disease assessment.
[b] One subject was assessed at Screening by investigator as having one measurable lesion; however, the IRC was unable to identify any measurable disease at baseline.
‡ Response Criteria: Lugano 2014

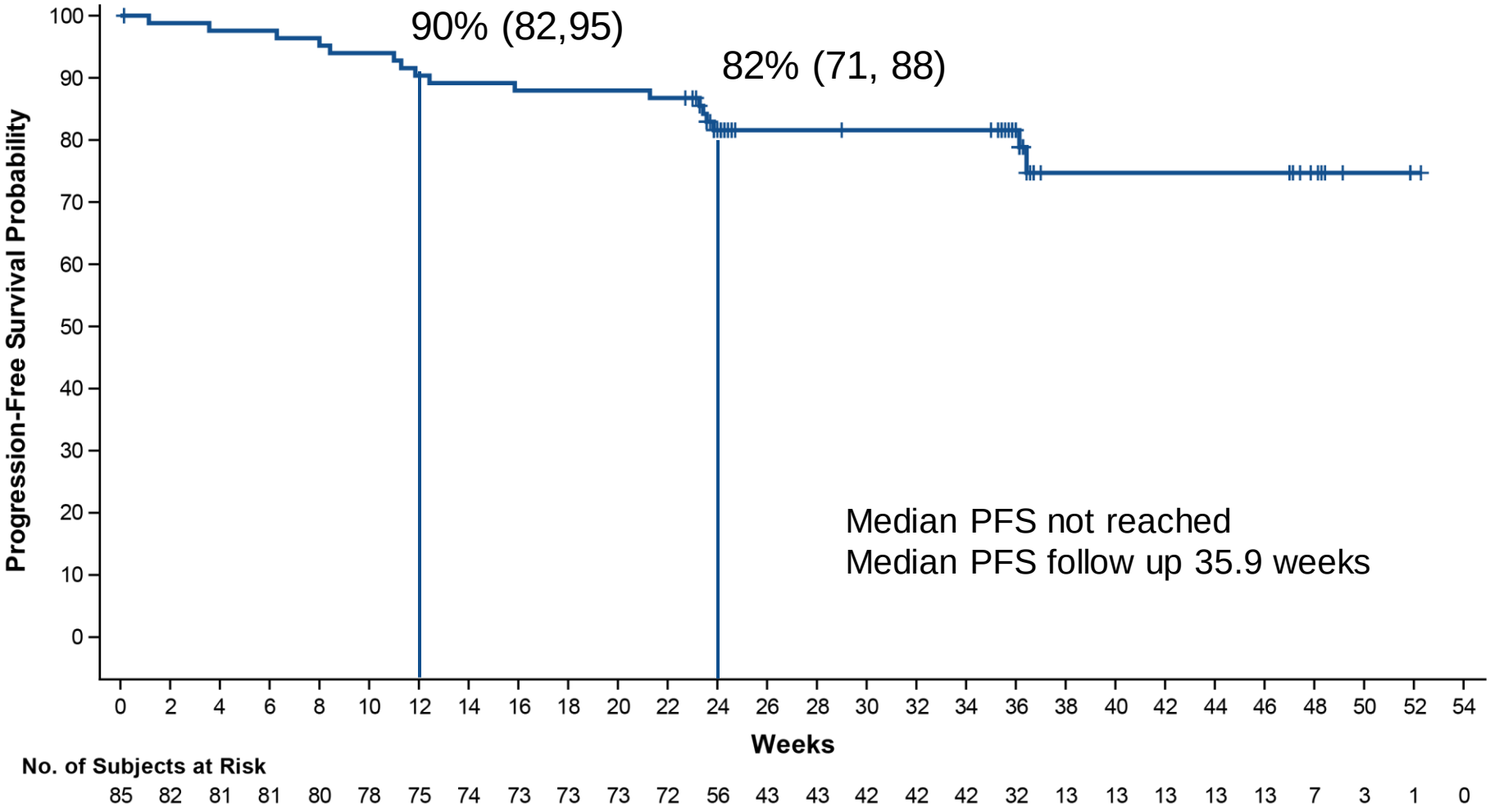
Forest Plot of ORR Based on IRC by Subgroup



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

LDi, longest diameter; MCL, mantle cell lymphoma.

Progression-free Survival

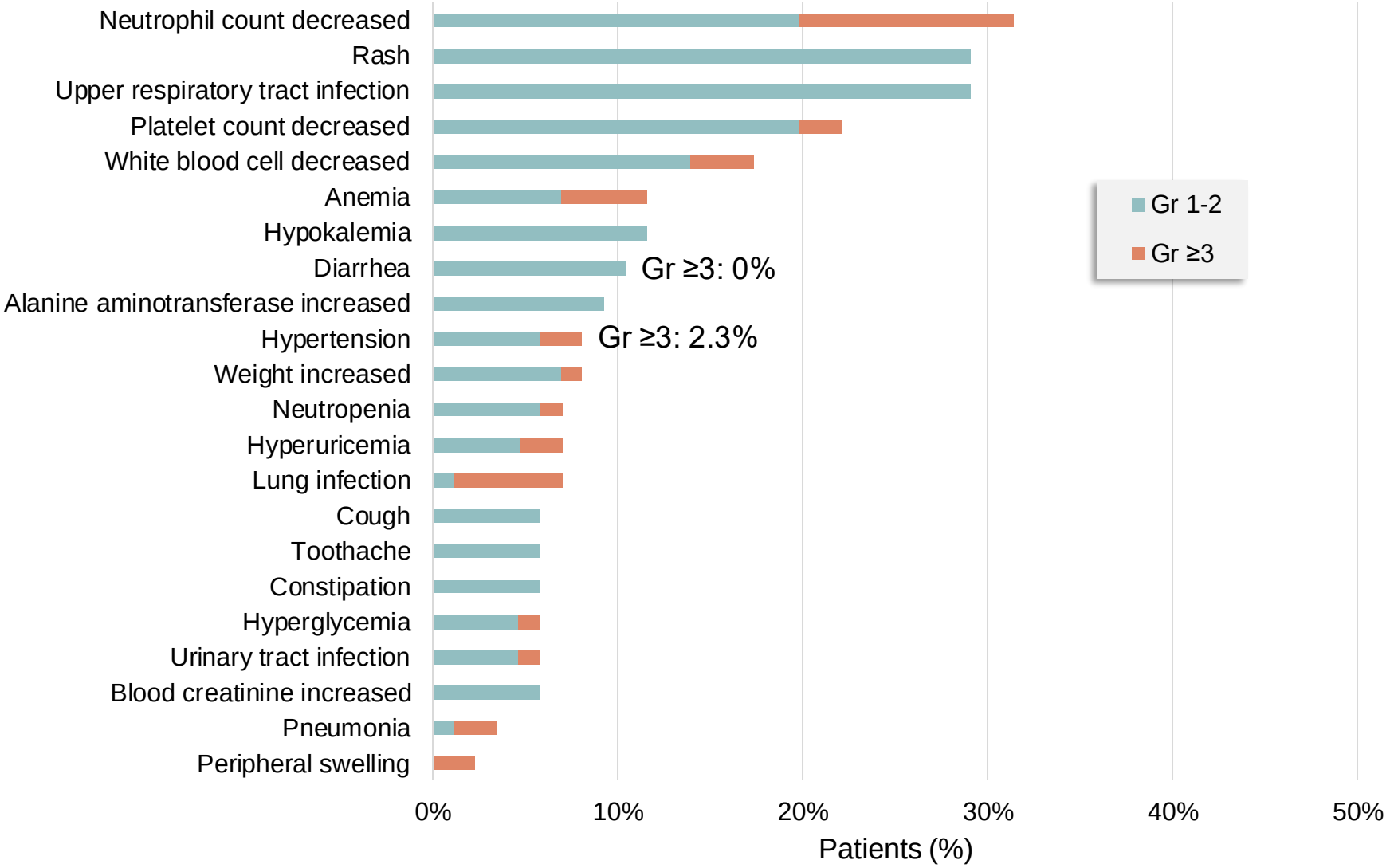


Summary of Treatment-Emergent Adverse Events (TEAE) Regardless of Causality

Event, n (%)	N = 86
Grade ≥3 TEAE	28 (32.6)
Serious TEAE	14 (16.3)
TEAE leading to study drug discontinuation	6 (7.0)
TEAE leading to death*	4 (4.7)
TEAE of special interest	
Diarrhea	9 (10.5)
Hypertension	7 (8.1)
Petechiae/purpura/contusion	4 (4.7)
Major hemorrhage†	1 (1.2)
Atrial fibrillation/flutter	0

*Pneumonia, cerebral hemorrhage, traffic accident, death in the setting of infection.
†Cerebral hemorrhage.

TEAEs in ≥5% of Patients or Grade ≥3 TEAEs in ≥2 Patients Regardless of Causality



Summary

- Zanubrutinib was shown to be highly active in patients with R/R MCL, as demonstrated by:
  - High ORR and CR rate documented by PET-based imaging, (ORR: 84%; CR: 59%)
  - The responses achieved by zanubrutinib treatment appear durable although longer follow-up is needed (median DOR and PFS were not reached)

- Zanubrutinib tolerability was generally consistent with previous reports of zanubrutinib treatment in patients with various B-cell malignancies

- Data from this phase 2 study was included in the NDA submission to Chinese NMPA for zanubrutinib in patients with R/R MCL

- Updated results from a separate ongoing phase 1 study of zanubrutinib in patients with R/R MCL presented as a poster today (Tam et al, #1592)

Acknowledgements

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Thank you