

# Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of MAGNOLIA (BGB-3111-214)

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Kim M. Linton<sup>1</sup>, Judith Trotman<sup>2</sup>, Pamela McKay<sup>3</sup>, Kirit Ardeschna<sup>4</sup>, Sunil Iyengar<sup>5</sup>, Alessandra Tedeschi<sup>6</sup>, Bei Hu<sup>7</sup>, Sophie Leitch<sup>8</sup>, Jie Jin<sup>9</sup>, Mingyuan Sun<sup>10</sup>, Magdalena Sobieraj-Teague<sup>11</sup>, Pier Luigi Zinzani<sup>12</sup>, Peter Browett<sup>13</sup>, Xiaoyan Ke<sup>14</sup>, Craig A. Portell<sup>15</sup>, Catherine Thieblemont<sup>16</sup>, Fontanet Bijou<sup>17</sup>, Patricia Walker<sup>18</sup>, Eliza A. Hawkes<sup>19</sup>, Shir-Jing Ho<sup>20</sup>, Keshu Zhou<sup>21</sup>, Zhiyu Liang<sup>22</sup>, Jianfeng Xu<sup>22</sup>, Chris Tankersley<sup>22</sup>, Richard Delarue<sup>22</sup>, Melannie Co<sup>22</sup>, and Stephen Opat<sup>23</sup>

<sup>1</sup>Manchester Cancer Research Centre, Division of Cancer Sciences, Manchester, UK; <sup>2</sup>Concord Repatriation General Hospital, University of Sydney, Concord, New South Wales, Australia; <sup>3</sup>Beatson West of Scotland Cancer Centre, Glasgow, UK; <sup>4</sup>University College London Hospitals, London, UK; <sup>5</sup>Royal Marsden Hospital, London, UK; <sup>6</sup>ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; <sup>7</sup>Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; <sup>8</sup>North Shore Hospital, Auckland, New Zealand; <sup>9</sup>The First Affiliated Hospital, Zhejiang University, Hangzhou, Zhejiang, China; <sup>10</sup>Institute of Hematology & Blood Disease Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; <sup>11</sup>Flinders Medical Centre, Bedford Park, South Australia, Australia; <sup>12</sup>Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; <sup>13</sup>Auckland City Hospital, Grafton, New Zealand; <sup>14</sup>Peking University Third Hospital, Beijing, China; <sup>15</sup>University of Virginia, Comprehensive Cancer Center, Charlottesville, VA, USA; <sup>16</sup>APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; <sup>17</sup>Institut Bergonié, Bordeaux, France; <sup>18</sup>Peninsula Private Hospital, Frankston, Victoria, Australia; <sup>19</sup>Box Hill Hospital, Box Hill, Victoria, Australia; <sup>20</sup>St. George Hospital, Kogarah, New South Wales, Australia; <sup>21</sup>Henan Cancer Hospital, Zhengzhou, Henan, China; <sup>22</sup>BeiGene (Beijing) Co., Ltd., Beijing, China, BeiGene Switzerland GmbH and BeiGene USA, Inc., San Mateo, CA, USA; and <sup>23</sup>Monash Health and Monash University, Clayton, Victoria, Australia

## Disclosures for Dr. Kim M. Linton

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# INTRODUCTION

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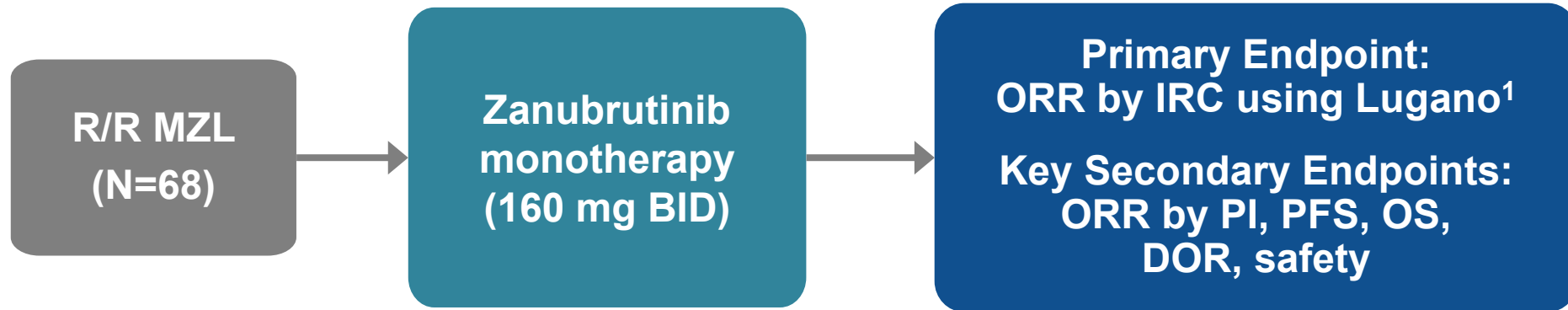
- Advanced-stage MZL is generally incurable<sup>1</sup>
- BCR signaling is a critical pathway in MZL pathogenesis<sup>2</sup>
- BTK plays a key role in BCR signaling<sup>2</sup>
  - BTK inhibition has antitumor activity in various B-cell malignancies<sup>2,3</sup>
- Zanubrutinib (BGB-3111) is a potent and highly specific next-generation BTK inhibitor
  - Designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases<sup>3-5</sup>
  - Can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents<sup>6,7</sup>
  - Recently approved for the treatment of patients with R/R MZL based on the primary analysis results of the MAGNOLIA study (BGB-3111-214; NCT03846427)<sup>7</sup>
- Here we present the final analysis of MAGNOLIA at a median follow-up of 28 months

BCR, B-cell receptor; BTK, Bruton tyrosine kinase; CYP3A, cytochrome P450, subtype 3A; EGFR, epidermal growth factor receptor; MZL, marginal zone lymphoma; R/R, relapsed/refractory; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

1. Cheah CY, et al. *Haematologica*. 2022;107(1):35-43. 2. Pal Singh S, et al. *Mol Cancer*. 2018;17(1):57. 3. Opat S, et al. *Clin Cancer Res*. 2021;27(23):6323-6332. 4. Guo Y, et al. *J Med Chem*. 2019;62(17):7923-7940. 5. Rhodes JM and Mato A. *Drug Des Devel Ther*. 2021;15:919-926. 6. Ou YC, et al. *Br J Clin Pharmacol*. 2021;87(7):2926-2936. 7. BRUKINSA® (zanubrutinib) [package insert]. BeiGene USA, Inc. September 2021.

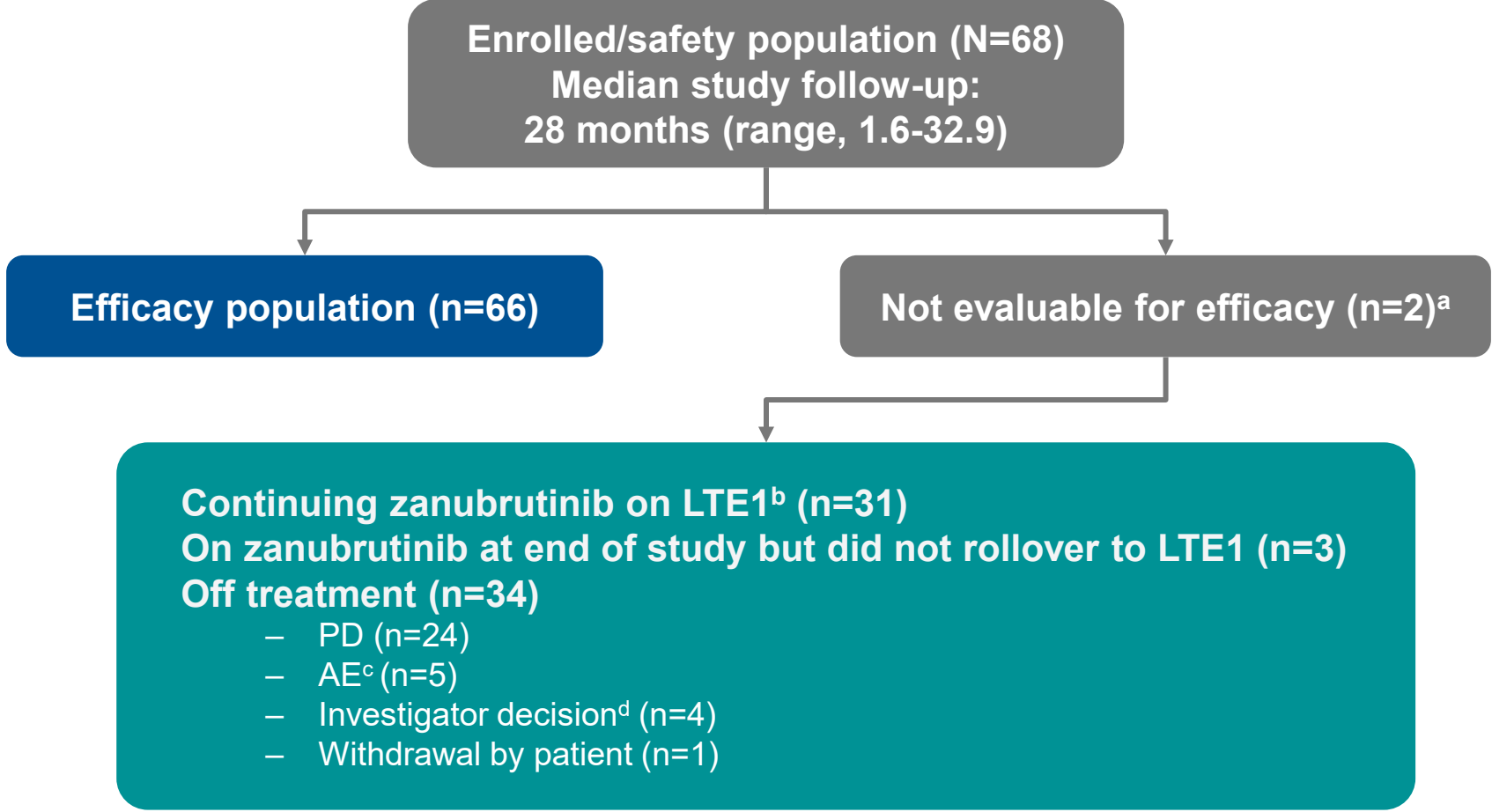
# MAGNOLIA (BGB-3111-214) Study Design

## A Phase 2, Multicenter, Open-label, Single-Arm Study



- Patients with R/R MZL who received  $\geq 1$  CD20-directed regimen
- Response based on the Lugano classification for NHL<sup>1</sup>
  - PET-based criteria for patients with IRC-confirmed FDG-avid disease
  - CT-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients using CT-based criteria
- Biomarker correlative sub-study by the Australasian Leukaemia and Lymphoma Group

# Patient Disposition



Data cutoff date: 04 May 2022.

<sup>a</sup>Two patients were excluded owing to lack of central confirmation of MZL. <sup>b</sup>BGB-3111-LTE1 is a BeiGene-sponsored, global, open-label extension study (NCT04170283). <sup>c</sup>Five patients discontinued treatment owing to AEs (2 patients with fatal COVID-19 pneumonia; 1 patient with pyrexia later attributed to disease progression; 1 patient with fatal myocardial infarction in a patient with preexisting cardiovascular disease; 1 patient who died from septic encephalopathy after bladder surgery (in CR at the time of death)). <sup>d</sup>Four patients discontinued per investigator decision (3 patients required prohibited medications; 1 patient due to lack of clinical benefit). AE, adverse event; LTE, long-term extension; PD, progressive disease.

# Baseline Demographics and Disease History

Characteristics, n (%)	Total (N=68)
<b>Median age</b> (range), years	70 (37-95)
≥65	41 (60)
≥75	19 (28)
<b>Male</b>	36 (53)
<b>ECOG PS 0/1<sup>a</sup></b>	63 (93)
<b>MZL subtypes</b>	
Extranodal	26 (38)
Nodal	26 (38)
Splenic	12 (18)
Unknown	4 (6)
<b>Disease status</b>	
Relapsed	44 (65)
Refractory	22 (32)
<b>Stage III/IV</b>	59 (87)
<b>FDG-avid (by IRC)</b>	61 (90)
<b>Extranodal site involvement</b>	53 (78)
<b>Bone marrow infiltration</b>	29 (43)
<b>Median prior lines of systemic therapy (range)</b>	2 (1-6)
Immunochemotherapy	61 (90) <sup>b</sup>
Rituximab monotherapy	7 (10)

<sup>a</sup>Overall, 43% of patients had ECOG PS 1/2. <sup>b</sup>Rituximab-based chemotherapy in most patients (n=60; 88%).  
 ECOG PS, Eastern Cooperative Oncology Group Performance Status; IRC, independent review committee; FDG, fluorodeoxyglucose; MZL, marginal zone lymphoma.

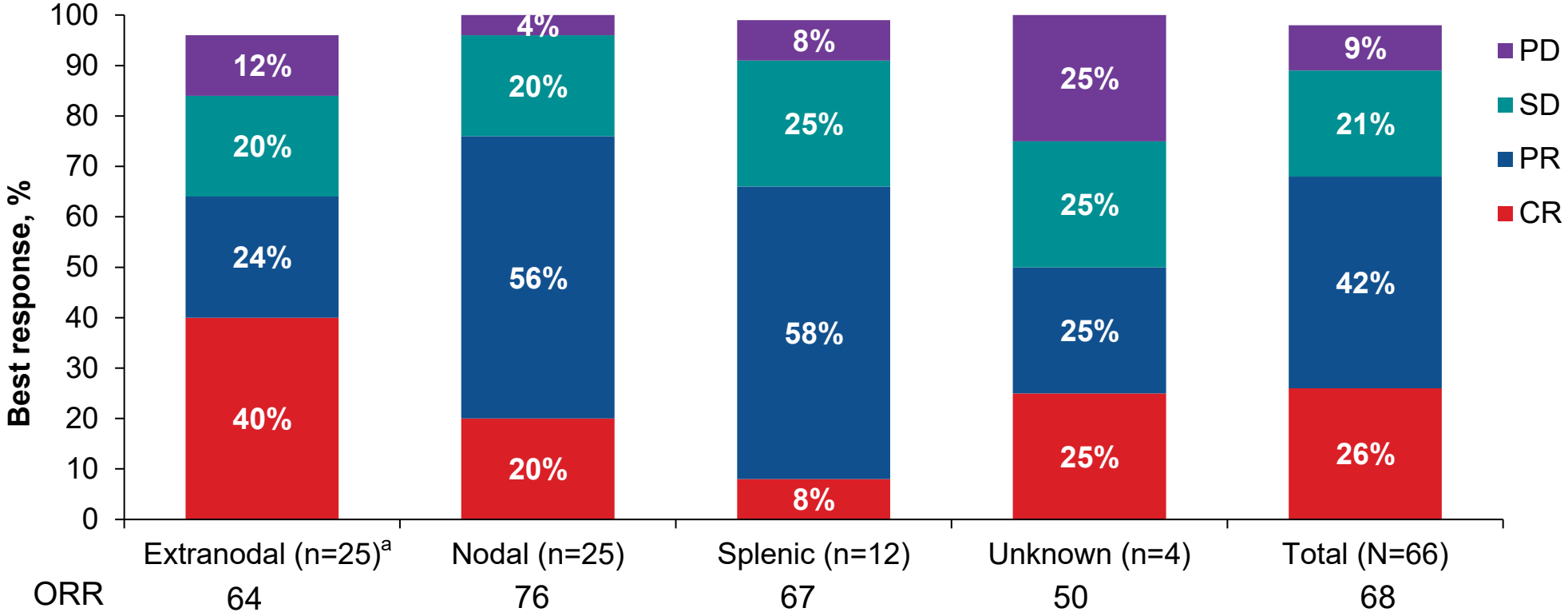
# Best Overall Response by IRC and Investigator Assessment

Efficacy	(N=66) <sup>a</sup>		
	IRC		INV
	PET and/or CT (primary endpoint) <sup>b</sup>	CT only (sensitivity analysis) <sup>f</sup>	PET and/or CT
<b>ORR, n (%)</b>	45 (68)	44 (67)	50 (76)
[95% CI]	[55.6, 79.1]	[54.0, 77.8]	[63.6 85.5]
<i>P</i> -value	<0.0001 <sup>c</sup>		
<b>Best response, n (%)</b>			
CR	17 (26)	16 (24)	19 (29)
PR	28 (42)	28 (42)	31 (47)
SD	14 (21) <sup>d,e</sup>	16 (24)	10 (15)
PD	6 (9)	5 (8)	5 (8)
<b>Discontinued study prior to 1st assessment, n (%)</b>	1 (1)	1 (1)	1 (1)
<b>Median time to response (range), months</b>	2.8 (1.7-11.1)	3.0 (1.8-22.2)	2.8 (1.7-16.6)

<sup>a</sup>Two patients were excluded from the efficacy population owing to lack of central confirmation of MZL. <sup>b</sup>Patients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non-FDG-avid patients were assessed by CT-based Lugano criteria. <sup>c</sup>*P*-value for the primary endpoint was computed with the binomial exact test against the null hypothesis of ORR = 30% with alternative of ORR > 30%. <sup>d</sup>Five (7.6%) patients with SD are remaining on study treatment (after 12-18 cycles). <sup>e</sup>Includes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed SD at cycle 3. <sup>f</sup>Additional sensitivity analysis using CT-based Lugano criteria for all 66-evaluable patients regardless of PET status at baseline.

CI, confidence interval; CR, complete response; CT, computerized tomography; INV, investigator; IRC, independent review committee; ORR, overall response rate; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease.

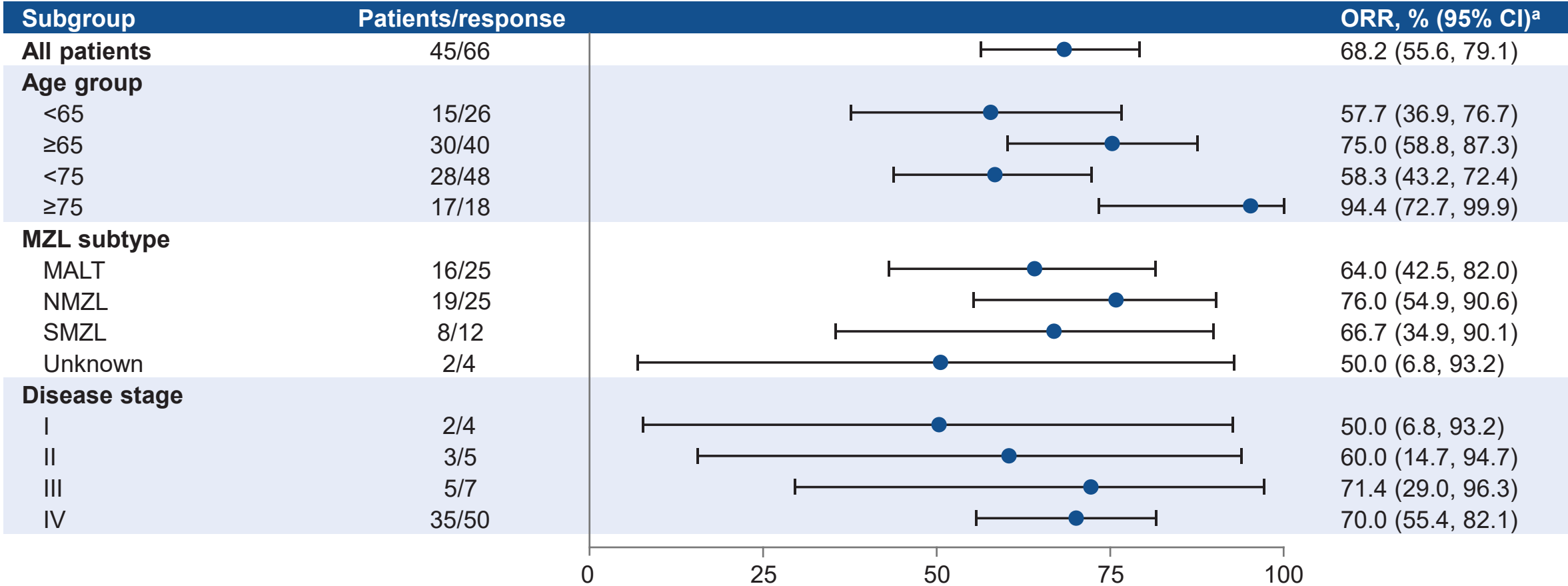
# Best Overall Response by IRC and MZL Subtypes



<sup>a</sup>One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.  
 CR, complete response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.



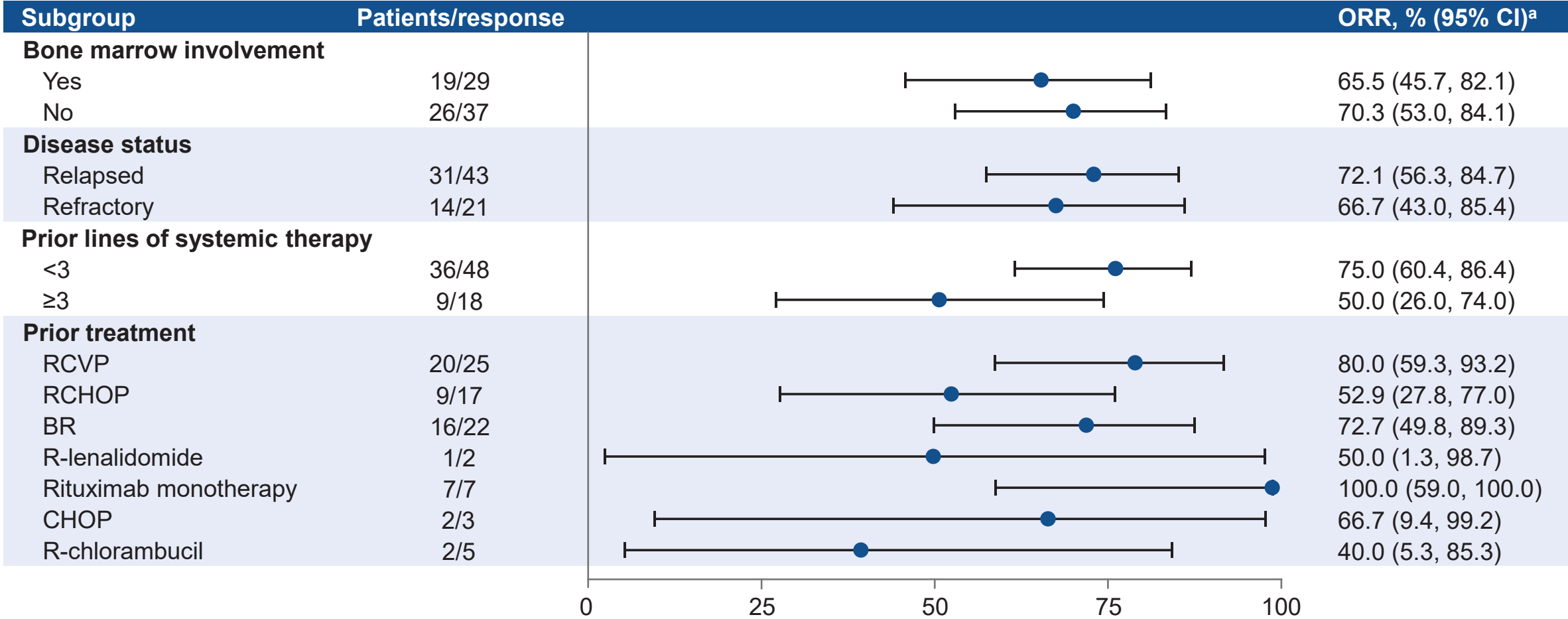
# Subgroup Analysis of ORR by IRC



<sup>a</sup>Two-sided Clopper-Pearson. 95% CIs for ORR.

CI, confidence interval; IRC, independent review committee; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; NMZL, nodal MZL; ORR, overall response rate; SMZL, splenic MZL.

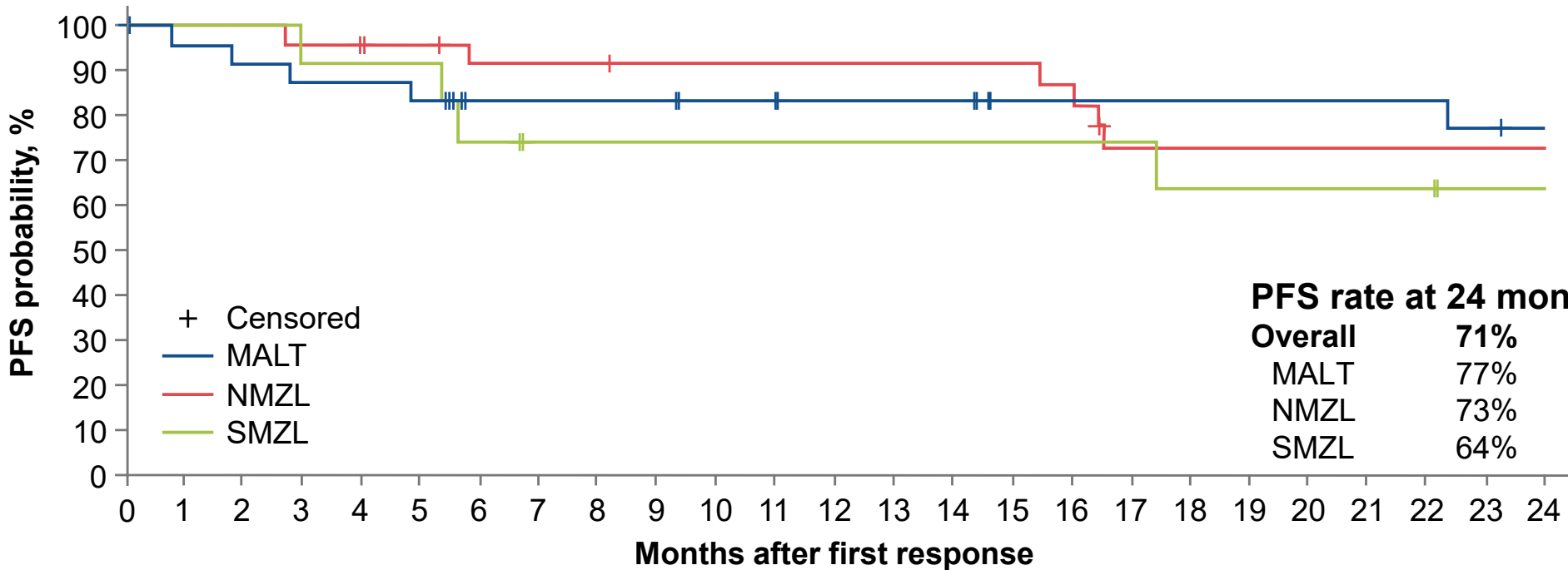
# Subgroup Analysis of ORR by IRC (cont.)



<sup>a</sup>Two-sided Clopper-Pearson. 95% CIs for ORR.

BR, bendamustine/rituximab; CHOP, cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; CI, confidence interval; IRC, independent review committee; ORR, overall response rate; R-chlorambucil, rituximab-chlorambucil; RCHOP, rituximab cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; RCVP, rituximab cyclophosphamide-vincristine-prednisone; R-lenalidomide, rituximab-lenalidomide

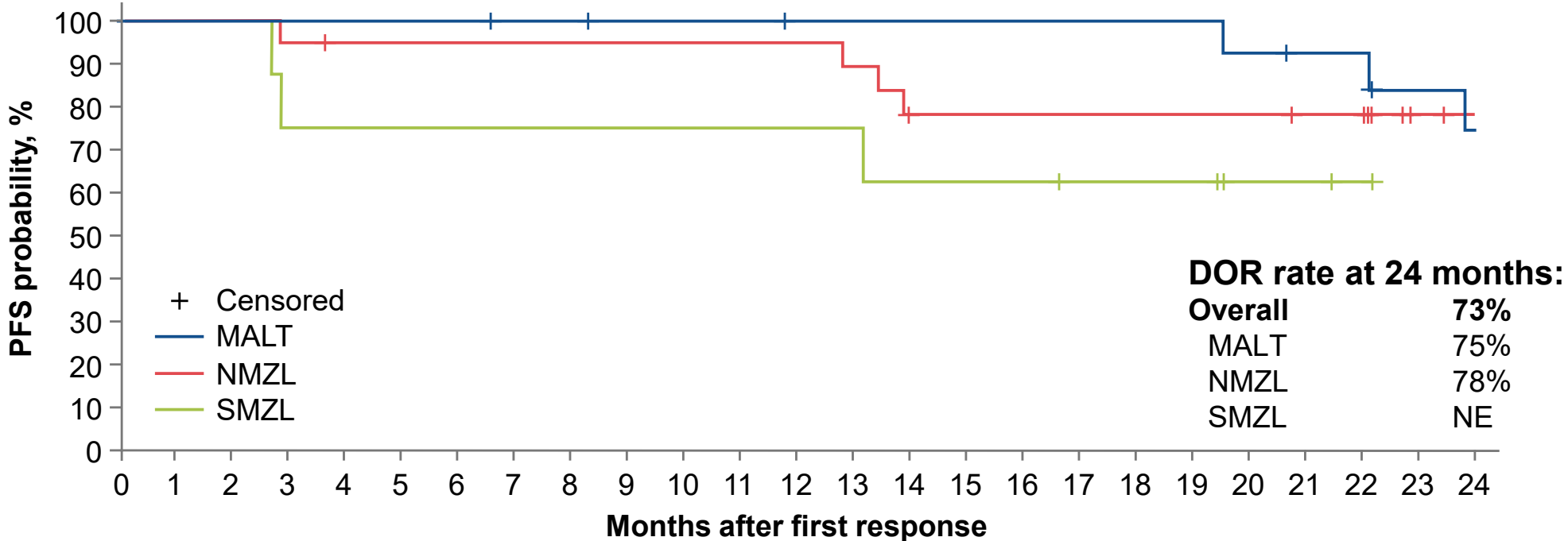
# PFS by MZL Subtypes by IRC Assessment



**No. at risk**

MALT	25	23	22	21	21	20	18	18	18	18	17	17	16	16	16	14	14	14	14	14	14	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	20	20	20	20	20	19	15	15	15	15	15	15	15	15
SMZL	12	12	12	11	11	11	8	7	7	7	7	7	7	7	7	7	7	6	6	6	6	6	4	4

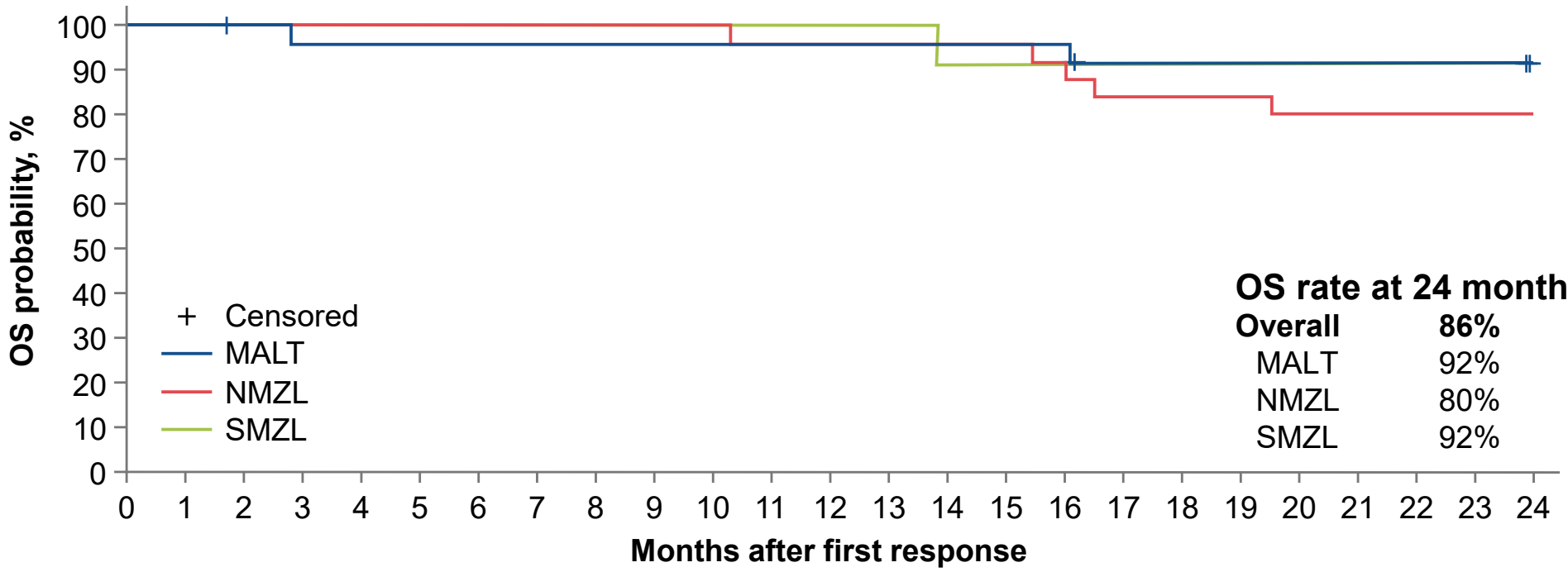
# DOR by MZL Subtypes by IRC Assessment



**No. at risk**

MALT	16	16	16	16	16	16	16	15	15	14	14	14	13	13	13	13	13	13	13	12	11	11	9	8
NMZL	19	19	19	18	17	17	17	17	17	17	17	17	17	17	16	13	13	13	13	13	12	11	7	6
SMZL	8	8	8	6	6	6	6	6	6	6	6	6	6	5	5	5	4	4	4	2	2	1	0	

# Overall Survival by MZL Subtypes



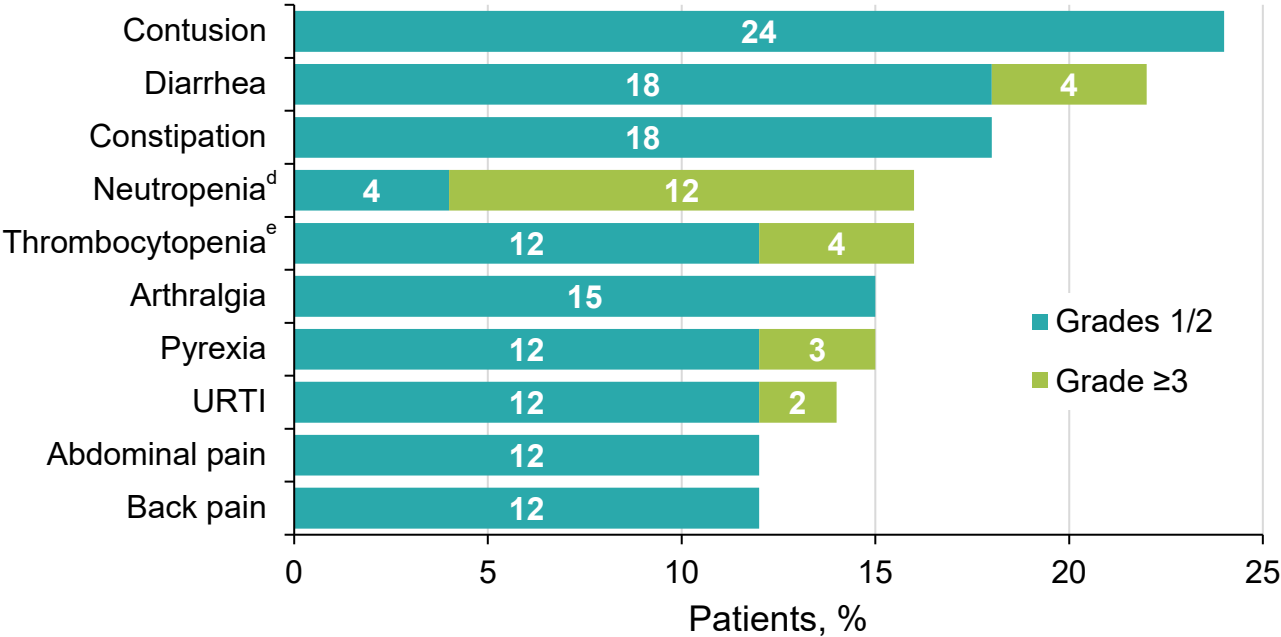
No. at risk		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
MALT	25	25	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	23	21	21	21	21	21	21	21	21
NMZL	25	25	25	25	25	25	25	25	25	25	25	24	24	24	24	24	23	21	21	21	21	20	20	20	20	20
SMZL	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	10

# TEAEs in All Patients

## Safety Summary

TEAEs, n (%)	N=68
<b>Patients with ≥1 TEAE</b>	68 (100)
Grade ≥3 TEAE	33 (48)
Serious TEAE	30 (44)
Leading to death	5 (7) <sup>a</sup>
Leading to dose interruption	25 (37) <sup>b</sup>
Leading to study drug discontinuation	5 (7) <sup>c</sup>
Leading to dose reduction	0

## Most Common TEAEs



<sup>a</sup>Five patients died owing to AEs: COVID-19 pneumonia (n=2); myocardial infarction in a patient with preexisting cardiovascular disease (n=1); acute myeloid leukemia in a patient with prior exposure to an alkylating agent (n=1); septic encephalopathy following radical cystectomy and ileal conduit in a patient with recurrent bladder cancer (in CR at the time of death; [n=1]). <sup>b</sup>Most common AEs leading to dose interruption: COVID-19 pneumonia (n=4), neutropenia (n=3), diarrhea (n=2), lower respiratory tract infection (n=2), pneumonia (n=2), pyrexia (n=2), syncope (n=2), and tonsillitis (n=2). <sup>c</sup>Five patients discontinued owing to AEs: COVID-19 pneumonia (n=2); pyrexia later attributed to disease progression (n=1); myocardial infarction (n=1); septic encephalopathy (n=1). <sup>d</sup>Includes neutropenia and neutrophil count decreased. <sup>e</sup>Includes thrombocytopenia and platelet count decreased. TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

# TEAEs of Clinical Interest

TEAEs of interest, n (%)	N=68	
	All grade	Grade ≥3
<b>Infections</b>	38 (56)	15 (22) <sup>a</sup>
<b>Hemorrhage</b>	28 (41)	1 (1.5) <sup>b</sup>
<b>Cardiac</b>		
Hypertension	3 (4) <sup>c</sup>	2 (3)
Atrial fibrillation/flutter	2 (3) <sup>d</sup>	1 (1.5)
Ventricular extrasystole	1 (1.5) <sup>e</sup>	0
<b>Second primary malignancy</b>	5 (7) <sup>f</sup>	3 (4)

<sup>a</sup>Fatal infection: COVID-19 pneumonia (n=2). <sup>b</sup>Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode. <sup>c</sup>Two patients had new-onset hypertension; none led to treatment reduction or discontinuation. <sup>d</sup>Atrial fibrillation in a patient with preexisting atrial fibrillation (21 days after end of treatment owing to disease progression). Patient with atrial flutter recovered spontaneously and continued zanubrutinib. <sup>e</sup>Ventricular extrasystole in an 83-year-old patient with no known cardiac history, was non-serious, transient, resolved on the same day, and did not lead to treatment modification or discontinuation. <sup>f</sup>Includes basal cell and squamous cell carcinoma and basal cell carcinoma (with history of skin cancer); papillary thyroid carcinoma (with preexisting thyroid nodule); recurrent bladder cancer and prostate cancer (with history of bladder cancer); and acute myeloid leukemia (with prior chemotherapy with alkylating agent).  
TEAE, treatment-emergent adverse event.

# Cardiac TEAEs of Clinical Interest

Cardiovascular disorders, n (%)	BGB-3111-214	Pooled analysis B-cell malignancies <sup>c</sup>	
	Zanubrutinib (N=68)	Zanubrutinib (N=1550)	Ibrutinib (N=422)
<b>Median treatment duration, months</b>	24	26.64	19.96
<b>Any cardiovascular medical history</b>			
Atrial fibrillation/flutter	8 (11.7)	101 (6.5)	26 (6.2)
Ventricular arrhythmia <sup>a</sup>	0	14 (0.9)	1 (0.2)
Hypertension <sup>b</sup>	21 (30.9)	669 (43.2)	206 (48.8)
<b>Any cardiovascular AE</b>			
Atrial fibrillation/flutter	2 (3)	60 (3.9)	60 (14.2)
		EAIR: 0.13 vs 0.82 person-month ( $P < 0.0001$ )	
Ventricular arrhythmia (Grade $\geq 2$ ) <sup>a</sup>	1 (1.5)	11 (0.7)	6 (1.4)
Hypertension <sup>b</sup>	3 (4)	225 (14.5)	85 (20.1)

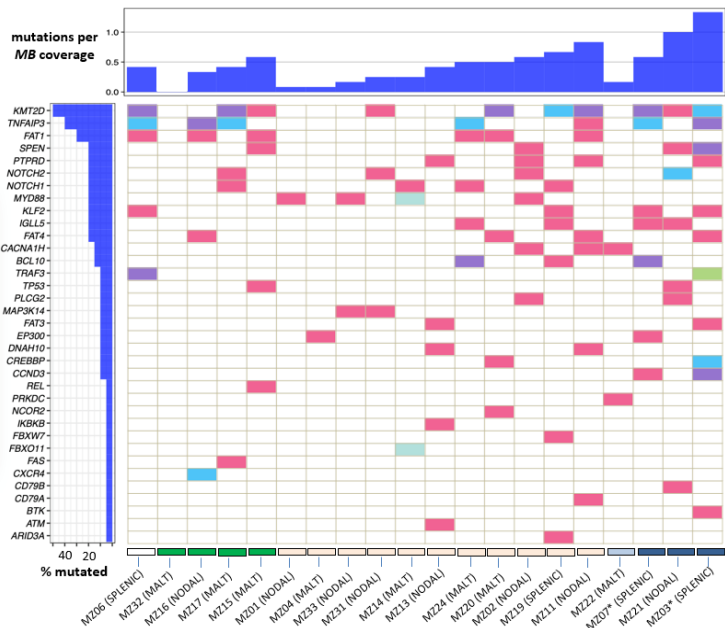
<sup>a</sup>Including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). <sup>b</sup>Including hypertension (SMQ narrow). <sup>c</sup>Pooled analyses of 10 clinical studies of zanubrutinib.<sup>1</sup>  
 AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incident rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query;  
 TEAE, treatment-emergent adverse event.

1. Tam CS, et al. LL&M 2022. Abstract 1324736.



# Molecular Correlates Sub-Study<sup>1</sup>

## (Australasian Leukaemia and Lymphoma Group)

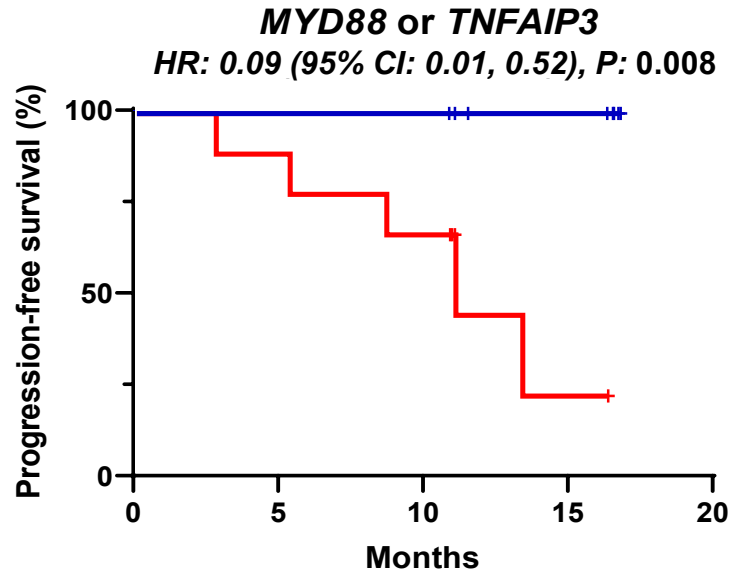


### Mutation Type

- Missense
- Stop gain/loss
- Frameshift ins/del
- Inframe ins/del
- Splice site

### Clinical Response

- PD
- SD
- PR
- CR
- Failed at screen



- + mutated (n=8), mPFS: NR
- + wild type (n=9), mPFS: 11.08 months

- Baseline WES was performed on 17 patients focusing on 48 genes known to be currently mutated in MZL
- More than 1 mutation was found in 16/17 (94%) patients
- *MYD88* or *TNFAIP3* mutations were associated with improved PFS
- Similar observation was reported by Noy et al. with ibrutinib<sup>2</sup>

CI, confidence interval; CR, complete response; HR, hazard ratio; ins/del, insertion/deletion; mPFS, median PFS; MYD88, myeloid differentiation primary response 88; MZL, marginal zone lymphoma; NR, not reached; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TNFAIP3, tumor necrosis factor alpha-induced protein 3; WES, whole-exome sequencing.  
 1. Tatarczuch M, et al. *HemaSphere*. 2022;6(3):1146-1147. 2. Noy A, et al. *Blood Adv*. 2020;4(22):5773-5784.

# Conclusions

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At a median study follow-up of 28 months:

- Zanubrutinib showed high response rates and durable disease control in R/R MZL
  - ORR of 68% (by PET and/or CT) and 67% (by CT only) with a CR of ~25% by IRC
  - Responses in all MZL subtypes and in difficult-to-treat subgroups
  - At 24 months: PFS rate, 71%; DOR rate, 73%; OS rate, 86%
- Zanubrutinib was generally well tolerated
  - Hypertension and atrial fibrillation/flutter were uncommon; comparable rate to zanubrutinib pooled safety analyses and lower than reported for ibrutinib
  - One (1.5%) patient had major gastrointestinal hemorrhage while receiving concomitant anticoagulant
  - No new safety signals observed

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## **Corresponding Author:**

Kim M. Linton; email: [Kim.M.Linton@manchester.ac.uk](mailto:Kim.M.Linton@manchester.ac.uk)