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Long-Term Efficacy and Safety of Zanubrutinib in Patients With Relapsed/Refractory Marginal Zone Lymphoma (MZL): Final Analysis of the MAGNOLIA (BGB-3111-214) Trial

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Saturday, December 10, 2022 (2:00 PM - 3:30 PM)
623. Mantle Cell, Follicular, and Other Indolent B Cell Lymphomas: Clinical and Epidemiological

INTRODUCTION

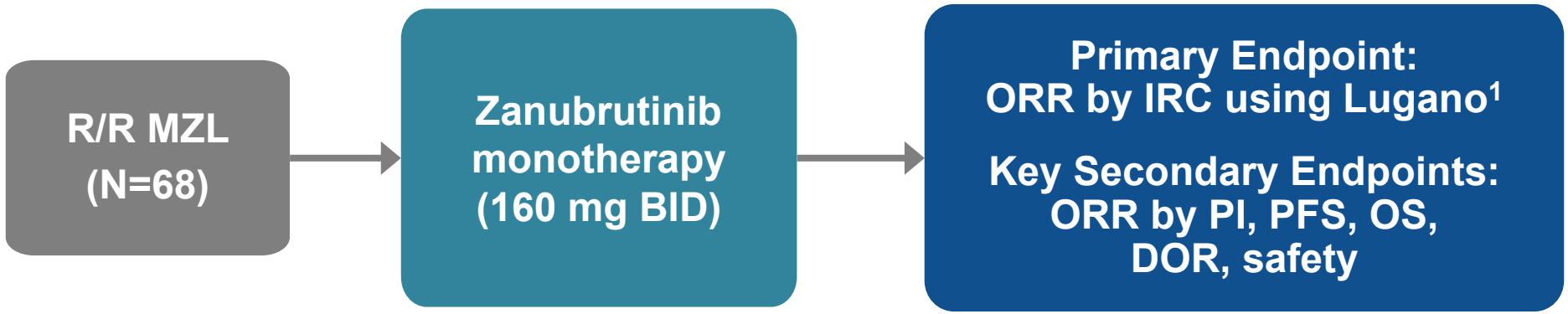
- Advanced-stage MZL is generally incurable[1]
- BCR signaling is a critical pathway in MZL pathogenesis[2]
- BTK plays a key role in BCR signaling[2]
  - BTK inhibition has antitumor activity in various B-cell malignancies[2,3]
- Zanubrutinib (BGB-3111) is a potent and highly specific next-generation BTK inhibitor
  - Designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases[3-5]
  - Can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]
  - 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)[7]
- 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; R/R, relapsed, refractory; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

1. Cheah et al. *Haematologica* 2022;107(1):35-43. 2. Pal Singh et al. *Mol Cancer* 2018;17(1):57. 3. Opat et al. *Clin Cancer Res* 2021;27(23):6323-6332. 4. Guo et al. *J Med Chem* 2019;62(17):7923-7940. 5. Rhodes et al. *Drug Des Devel Ther*. 2021;15:919-926. 6. Ou 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

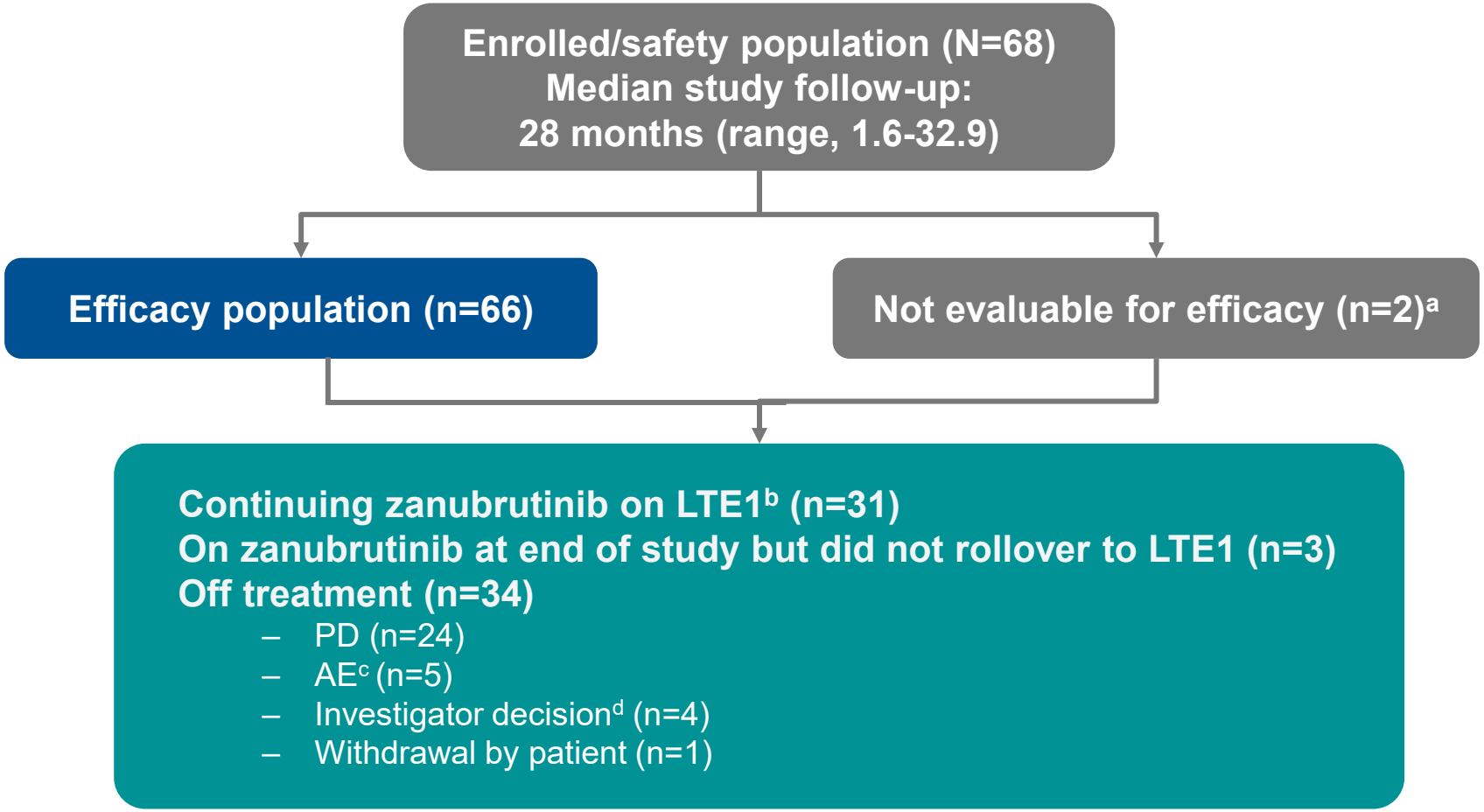


- Patients with R/R MZL who received ≥1 CD20-directed regimen
- Response based on the Lugano classification for NHL[1]
  - PET-based criteria for patients with IRC-confirmed FDG-avid disease
  - CT-based criteria for non-FDG-avid patients
  - Additional sensitivity analysis for all evaluable patients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

CT, computerized tomography; DOR, duration of response; FDG, fluorodeoxyglucose; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PI, principal investigator.

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

Patient Disposition



Data cutoff date: 04 May 2022.

[a]Two patients were excluded owing to lack of central confirmation of MZL. [b]BGB-3111-LTE1 is a BeiGene-sponsored, global, open-label extension study (NCT04170283). [c]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). [d]Four patients discontinued per investigator decision (3 patients required prohibited medications; 1 patient due to lack of clinical benefit).

AE, adverse event; CR, complete remission; LTE, long-term extension; PD, progressive disease.

Baseline Demographics and Disease History

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

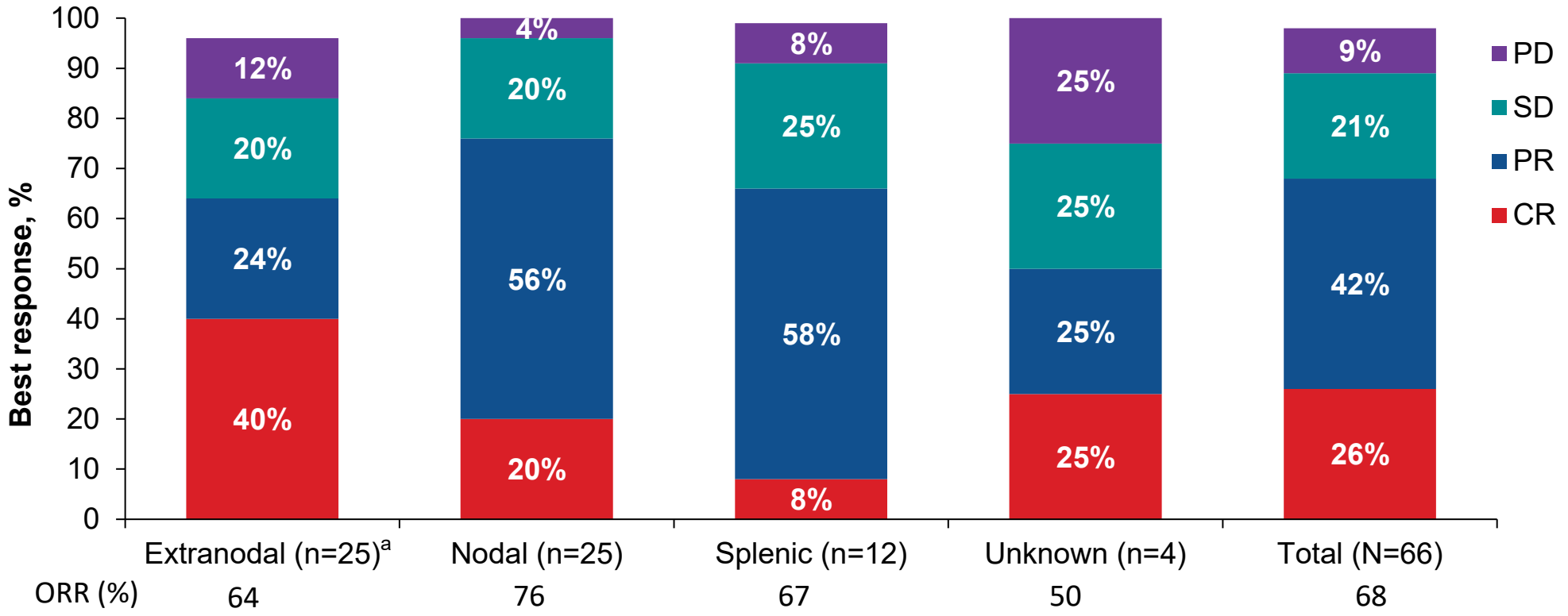
[a]Overall, 43% of patients had ECOG 1/2. [b]Rituximab-based chemotherapy in most patients (n=60; 88%).

Best Overall Response by IRC and Investigator Assessment

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

[a]Two patients were excluded from the efficacy population owing to lack of central confirmation of MZL.
[b]Patients with IRC-confirmed FDG-avid disease were assessed by PET-based criteria; non–FDG-avid patients were assessed by CT-based Lugano criteria.
[c]*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%.
[d]Five (7.6%) patients with stable disease are remaining on study treatment (after 12-18 cycles).
[e]Includes one patient with FDG-avid disease who missed the PET scan at cycle 3 and was assessed as non-PD; CT showed stable disease at cycle 3.
[f]Additional sensitivity analysis using CT-based Lugano criteria for all 66-evaluable patients regardless of PET status at baseline.
INV, investigator; PET, positron emission tomography; PR, partial response; SD, stable disease.

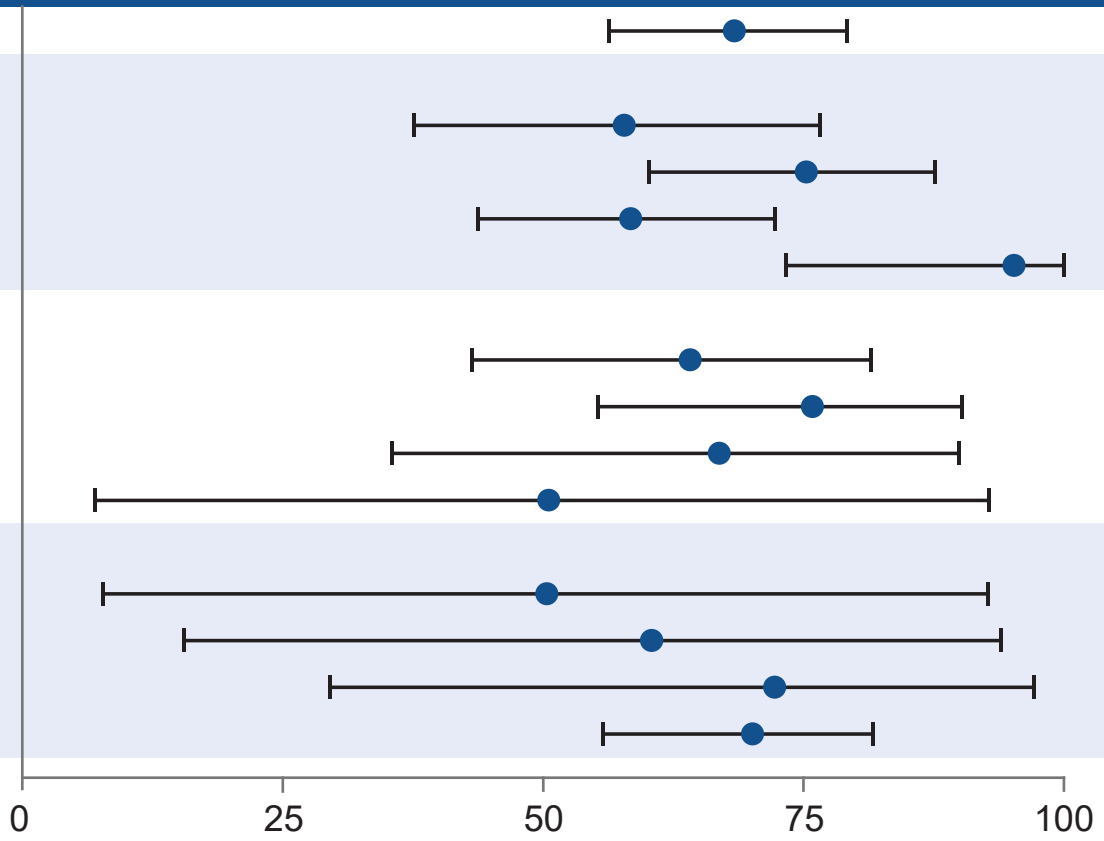
Best Overall Response by IRC and MZL Subtypes



[a]One patient (extranodal MZL) who withdrew consent prior to the first disease assessment was not shown in the graph.

Subgroup Analysis of ORR by IRC

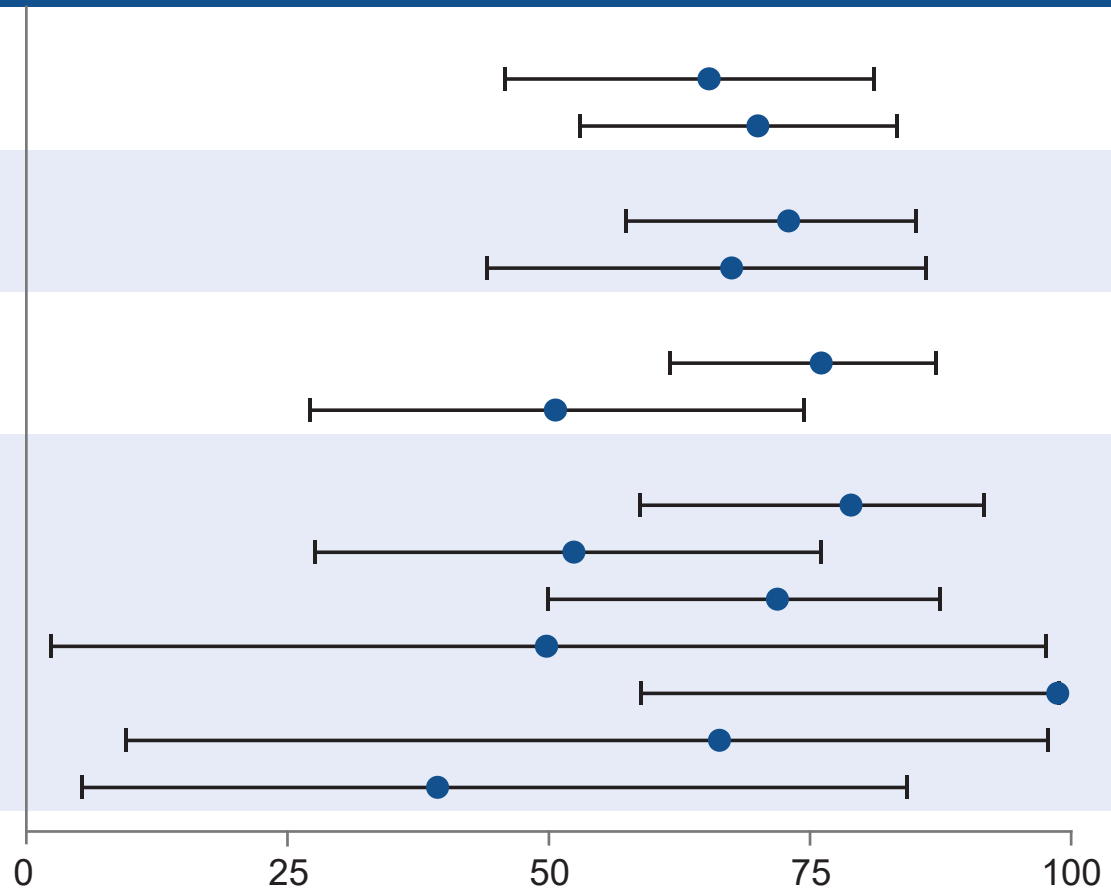
Subgroup	Patients/response	ORR, % (95% CI)[a]
All patients	45/66	68.2 (55.6, 79.1)
Age group		
<65	15/26	57.7 (36.9, 76.7)
≥65	30/40	75.0 (58.8, 87.3)
<75	28/48	58.3 (43.2, 72.4)
≥75	17/18	94.4 (72.7, 99.9)
MZL subtype		
MALT	16/25	64.0 (42.5, 82.0)
NMZL	19/25	76.0 (54.9, 90.6)
SMZL	8/12	66.7 (34.9, 90.1)
Unknown	2/4	50.0 (6.8, 93.2)
Disease stage		
I	2/4	50.0 (6.8, 93.2)
II	3/5	60.0 (14.7, 94.7)
III	5/7	71.4 (29.0, 96.3)
IV	35/50	70.0 (55.4, 82.1)



[a]Two-sided Clopper-Pearson. 95% CIs for ORR.
MALT, mucosa associated lymphoid tissue; NMZL, nodal MZL; SMZL, splenic MZL.

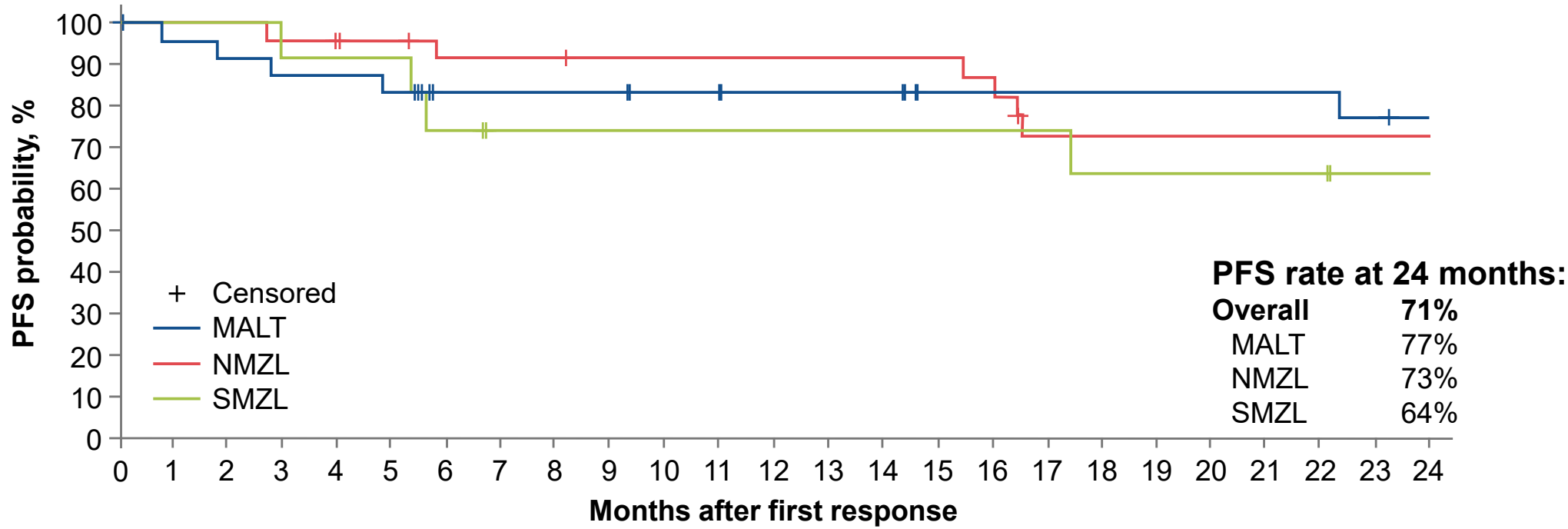
Subgroup Analysis of ORR by IRC (cont.)

Subgroup	Patients/response	ORR, % (95% CI)[a]
Bone marrow involvement		
Yes	19/29	65.5 (45.7, 82.1)
No	26/37	70.3 (53.0, 84.1)
Disease status		
Relapsed	31/43	72.1 (56.3, 84.7)
Refractory	14/21	66.7 (43.0, 85.4)
Prior lines of systemic therapy		
<3	36/48	75.0 (60.4, 86.4)
≥3	9/18	50.0 (26.0, 74.0)
Prior treatment		
RCVP	20/25	80.0 (59.3, 93.2)
RCHOP	9/17	52.9 (27.8, 77.0)
BR	16/22	72.7 (49.8, 89.3)
R-lenalidomide	1/2	50.0 (1.3, 98.7)
Rituximab monotherapy	7/7	100.0 (59.0, 100.0)
CHOP	2/3	66.7 (9.4, 99.2)
R-chlorambucil	2/5	40.0 (5.3, 85.3)



[a]Two-sided Clopper-Pearson. 95% CIs for ORR.

PFS by MZL Subtypes by IRC Assessment



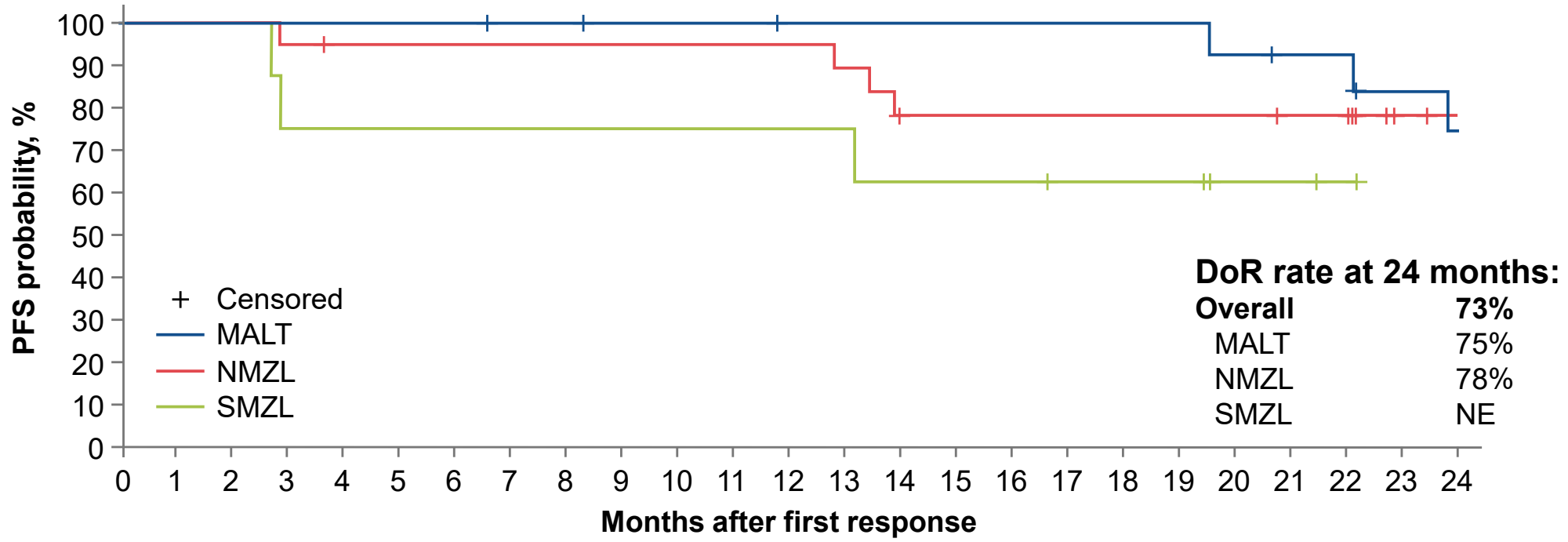
PFS rate at 24 months:

Overall	**71%**
MALT	77%
NMZL	73%
SMZL	64%

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	14	13	12
NMZL	25	25	25	24	24	23	21	21	21	20	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	7	6	6	6	6	6	4	4

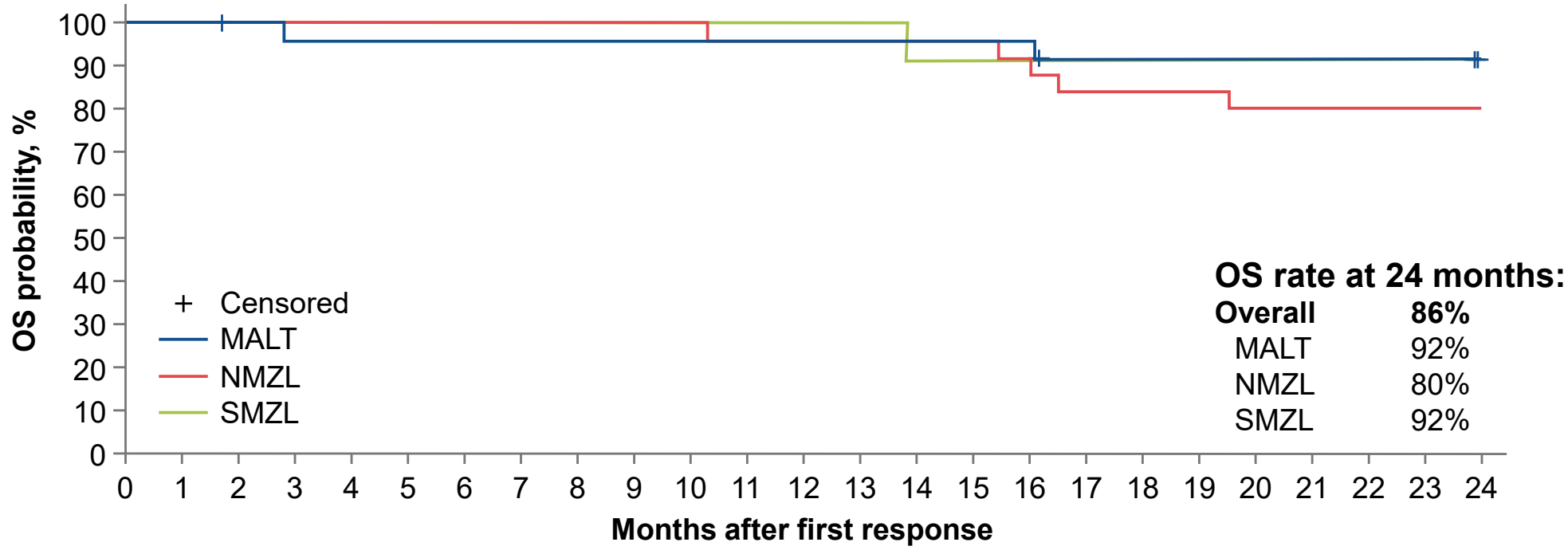
DOR by MZL Subtypes by IRC Assessment



No. at risk

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

Overall Survival by MZL Subtypes



No. at risk

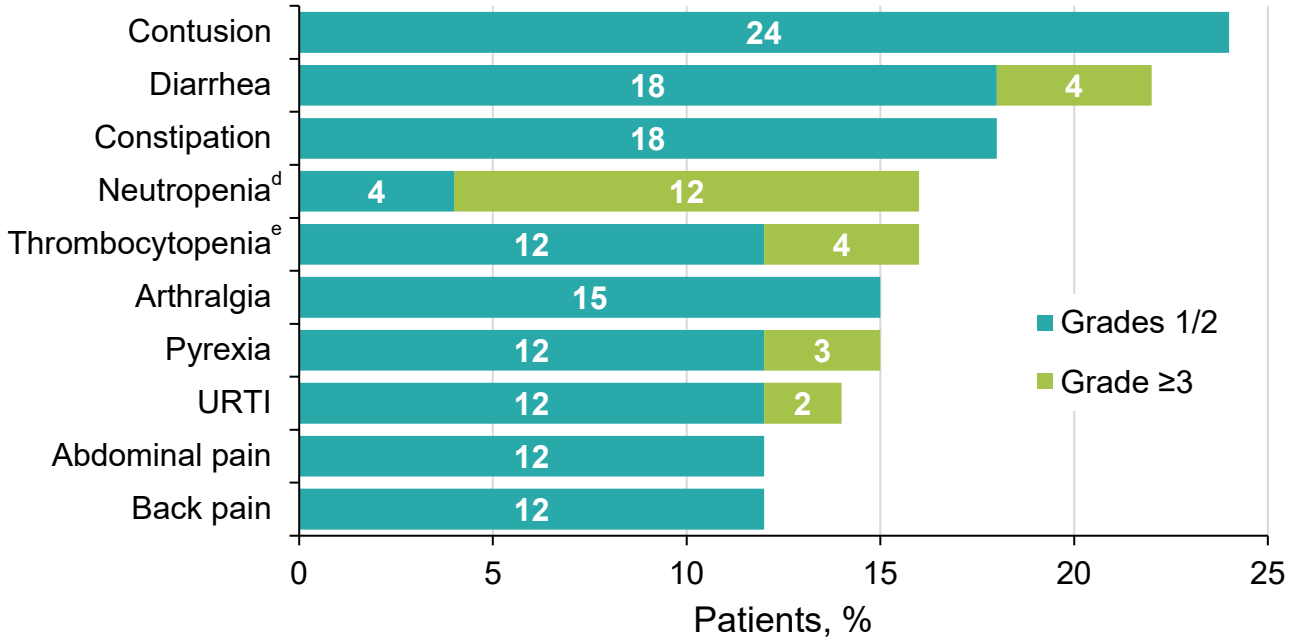
MALT	25	25	24	23	23	23	23	23	23	23	23	23	23	23	23	23	23	21	21	21	21	21	21	21	21
NMZL	25	25	25	25	25	25	25	25	25	25	25	24	24	24	24	24	23	21	21	21	20	20	20	20	20
SMZL	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	10

TEAEs in All Patients

Safety Summary

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

Most Common TEAEs



[a]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]). [b]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). [c]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). [d]Includes neutropenia and neutrophil count decreased. [e]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
Infections	38 (56)	15 (22)[a]
Hemorrhage	28 (41)	1 (1.5)[b]
Cardiac		
Hypertension	3 (4)[c]	2 (3)
Atrial fibrillation/flutter	2 (3)[d]	1 (1.5)
Ventricular extrasystole	1 (1.5)[e]	0
Second primary malignancy	5 (7)[f]	3 (4)

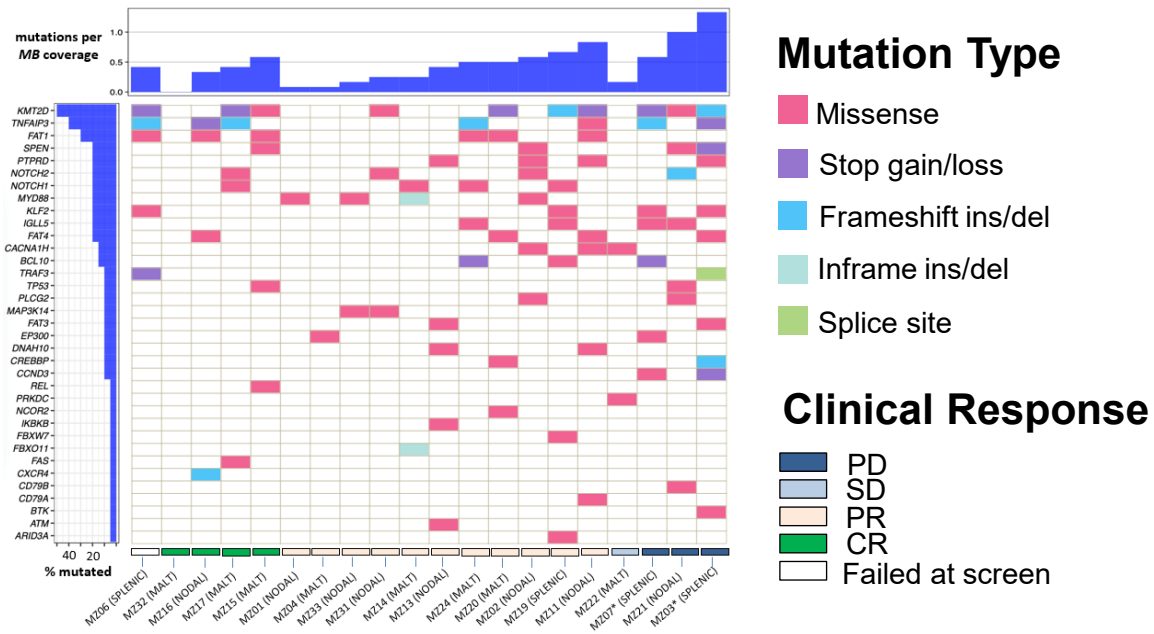
[a]Fatal infection: COVID-19 pneumonia (n=2).
[b]Gastrointestinal hemorrhage (day 862) in a patient who also received anticoagulant for pulmonary embolism; patient continued zanubrutinib with no recurrent bleeding episode.
[c]Two 2 patients had new-onset hypertension; none led to treatment reduction or discontinuation.
[d]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.
[e]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.
[f]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).

Cardiac TEAEs of Clinical Interest

Cardiovascular disorders, n (%)	BGB-3111-214	Pooled analysis B-cell malignancies[c]	
	Zanubrutinib (n=68)	Zanubrutinib (N=1550)	Ibrutinib (N=422)
Median treatment duration, months	24	26.64	19.96
Any cardiovascular medical history			
Atrial fibrillation/flutter	8 (11.7)	101 (6.5)	26 (6.2)
Ventricular arrhythmia[a]	0	14 (0.9)	1 (0.2)
Hypertension[b]	21 (30.9)	669 (43.2)	206 (48.8)
Any cardiovascular AE			
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 ≥2)[a]	1 (1.5)	11 (0.7)	6 (1.4)
Hypertension[b]	3 (4)	225 (14.5)	85 (20.1)

[a]Including ventricular tachyarrhythmia (SMQ narrow), ventricular arrhythmias and cardiac arrest (High Level Term MedDRA v24.0). [b]Including hypertension (SMQ narrow). [c]Pooled analyses of 10 clinical studies of zanubrutinib.[1]
CTCAE, Common Terminology Criteria for Adverse Events; EAIR, exposure-adjusted incident rate; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized MedDRA query.
1. Tam et al. LL&M 2022. Abstract 1324736.

Molecular Correlates Sub-Study[1]
(Australasian Leukaemia and Lymphoma Group)

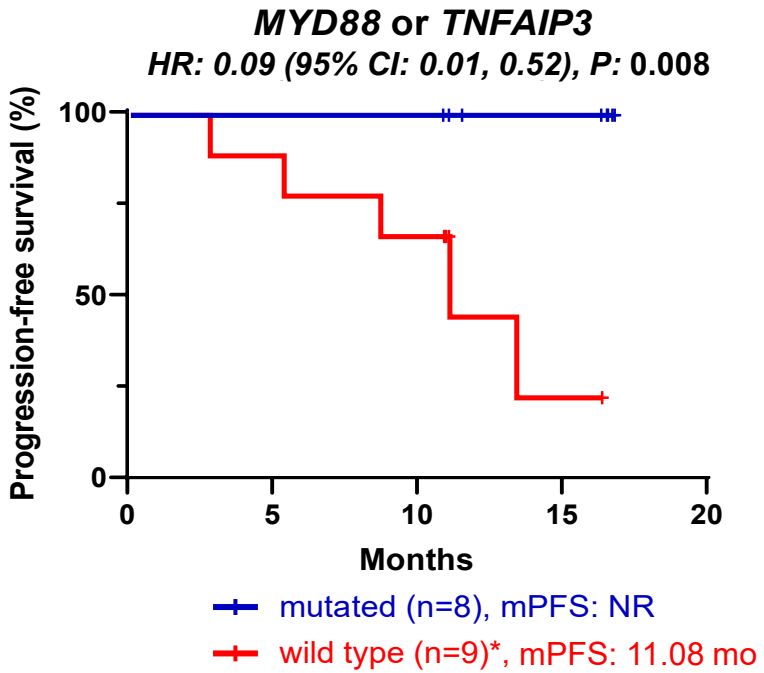


Mutation Type

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

Clinical Response

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



- Baseline WES was performed on 17 patients focusing on 48 genes known to be currently mutated in MZL
- More than 1 mutations were 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[2]

1. Tatarczuch et al. *HemaSphere* 2022;6(3):1146-1147. 2. Noy et al. *Blood Adv* 2020;4(22):5773-5784.
HR, hazard ratio; ins/del, insertion/deletion; mPFS, median PFS; NR, not reached; WES, whole-exome sequencing.

CONCLUSIONS

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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