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Zanubrutinib in Older Patients with R/R Marginal Zone Lymphoma: Subgroup Analysis of the MAGNOLIA Study

Alessandra Tedeschi[1], Judith Trotman[2], Pier Luigi Zinzani[3], Federica Cavallo[4], Roberto Marasca[5], Anna Marina Liberati[6], Bei Hu[7], Kim M. Linton[8], Pamela McKay[9], Henry Chan[10], Jie Jin[11], Mingyuan Sun[12], Magdalena Sobieraj-Teague[13], Morton Coleman[14], Peter Browett[15], Xiaoyan Ke[16], Craig A. Portell[17], Catherine Thieblemont[18], Kirit Ardeshna[19], Fontanet Bijou[20], Patricia Walker[21], Eliza A. Hawkes[22], Shir-Jing Ho[23], Ke-Shu Zhou[24], Melannie Co[25], Jianfeng Xu[25], Stephen Opat[26]

[1]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy;[2]Concord Repatriation General Hospital, University of Sydney, Concord, NSW, Australia; [3]Institute of Hematology "Seràgnoli" University of Bologna, Bologna, Italy; [4]University of Turin, Medical School, Turin, Italy; [5]Hematology Unit, Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Modena, Italy; [6]Azienda Ospedaliera "Santa Maria", Terni, Italy; [7]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA; [8]The Christie Hospital NHS Foundation Trust, Manchester, UK; [9]Beatson West of Scotland Cancer Centre, Glasgow, UK; [10]North Shore Hospital, Auckland, New Zealand; [11]The First Affiliated Hospital, Zhejiang University College of Medicine, Hangzhou, Zhejiang, China; [12]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China; [13]Flinders Medical Centre, Bedford Park, SA, Australia; [14]Clinical Research Alliance/Weill Cornell Medicine, Lake Success, NY, USA; [15]Auckland City Hospital, Grafton, New Zealand; [16]Peking University Third Hospital, Beijing, China; [17]University of Virginia Health System, Charlottesville, VA, USA; [18]APHP, Hôpital Saint-Louis, Hemato-oncology, Paris University Diderot, Paris, France; [19]University College London Hospitals, London, UK; [20]Institut Bergonié, Bordeaux, France; [21]Peninsula Private Hospital, Frankston, VIC, Australia; [22]Box Hill Hospital, Box Hill, VIC, Australia; [23]St. George Hospital, Kogarah, NSW, Australia; [24]Henan Cancer Hospital, Zhengzhou, Henan, China; [25]BeiGene (Beijing) Co., Ltd., Beijing, China and BeiGene USA, Inc., San Mateo, CA, USA; [26]Monash Health and Monash University, Clayton, VIC, Australia

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Disclosures for Alessandra Tedeschi

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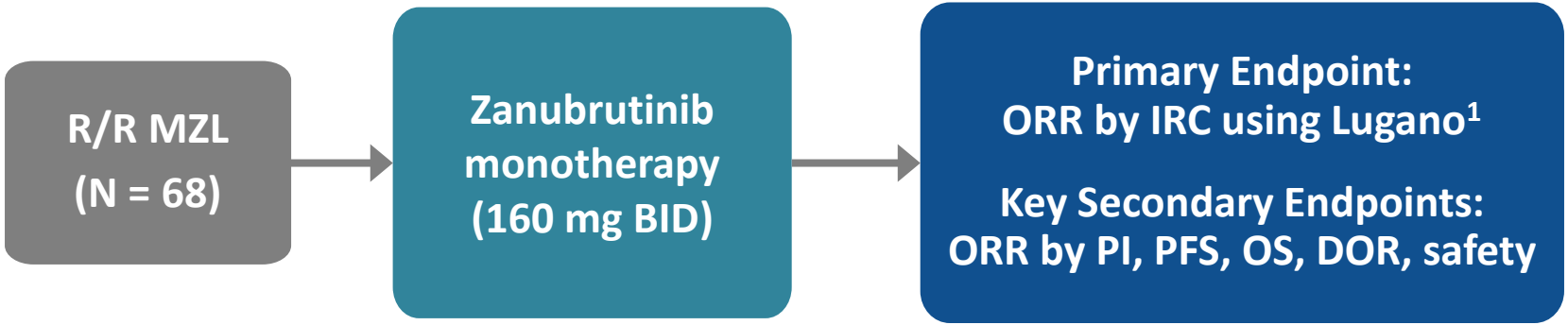
Introduction

- MZL is the second most common lymphoma in older patients
  - Choosing an optimal treatment can be challenging because of patient- or disease-related risk factors and treatment-related toxicities[1]
- 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
- Zanubrutinib received accelerated approval from the United States Food and Drug Administration for the treatment of patients with R/R MZL based on the results of the MAGNOLIA (BGB-3111-214) study[2,3]
  - Enrollment in this study is complete; a total of 68 patients received at least 1 dose of zanubrutinib[3]
- Here, we present efficacy and safety of zanubrutinib in a subgroup of patients with R/R MZL aged ≥ 65 years

BTK, Bruton tyrosine kinase; EGFR, epidermal growth factor receptor; MZL, marginal zone lymphoma; R/R, relapsed/refractory.

1. Bron et al. *Curr Opin Oncol* 2019;31(5):386-393; 2. Cheah et al. *Haematologica* 2022;107(1):35-43; 3. Opat et al. *Clin Cancer Res* 2021;27(23):6323-6332.

Study Schema



- The MAGNOLIA study is a phase 2, single-arm, multicenter study of zanubrutinib in patients with R/R MZL who had received ≥ 1 CD20-based regimen
- The primary endpoint was ORR as determined by an IRC based on the Lugano 2014 classification

BID, twice daily; DOR, duration of response; IRC, independent review committee; MZL, marginal zone lymphoma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PI, principal investigator; R/R, relapsed/refractory.

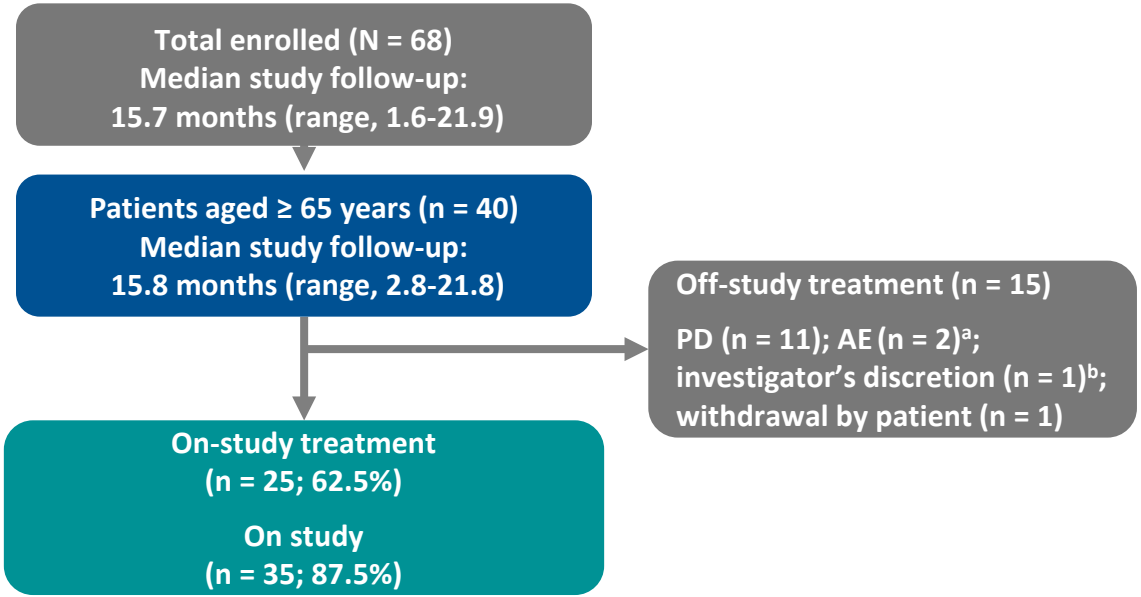
1. Cheson et al. *J Clin Oncol* 2014;32(27):3059-3067.

Key Eligibility Criteria

- Age ≥ 18 years
- Histologically confirmed MZL including splenic, nodal, and extranodal subtypes
- Previously received ≥ 1 CD20-directed regimen, with documented failure to achieve at least partial response or documented progressive disease after the most recent systemic treatment
- Measurable disease by computerized tomography or magnetic resonance imaging
- Adequate organ function
- No prior BTK inhibitor exposure

BTK, Bruton tyrosine kinase; MZL, marginal zone lymphoma.

Patient Disposition



- Of 68 patients enrolled in the study, 25 remained on treatment as of the data cutoff date of January 18, 2021

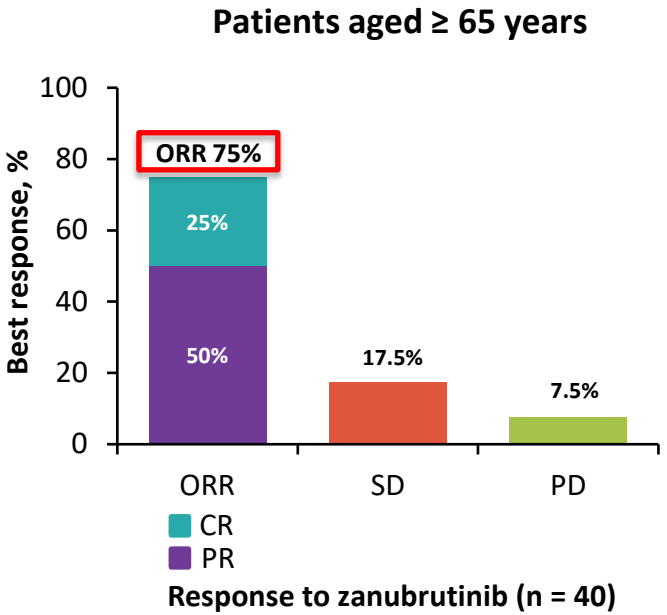
[a]Two patients discontinued due to fatal AEs: myocardial infarction in a patient with pre-existing cardiovascular disease, and COVID-19 pneumonia; [b]One patient discontinued per the investigator's discretion (required prohibited medications).
AE, adverse event; COVID-19, coronavirus disease of 2019; PD, progressive disease.

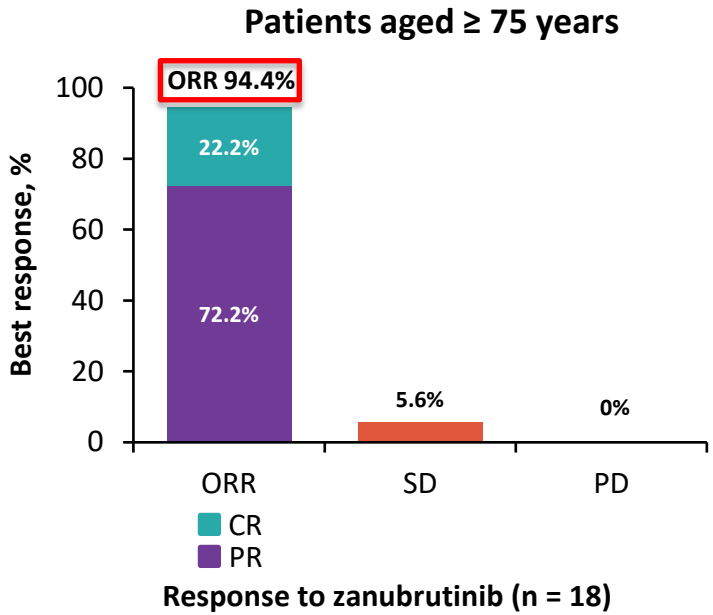
Patient and Disease Characteristics in Patients Aged ≥ 65 Years

Characteristic	Total (n = 40)
Age, median (range), years	**73 (65-85)**
Age category, n (%)	
≥ 65 and < 75 years	22 (55.0)
≥ 75 years	18 (45.0)
Male, n (%)	23 (57.5)
ECOG PS, n (%)	
0-1	35 (87.5)
2	5 (12.5)
Disease status, n (%)	
Relapsed	29 (72.5)
Refractory	10 (25.0)
MZL subtypes, n (%)	
Extranodal	17 (42.5)
Nodal	14 (35.0)
Splenic	8 (20.0)
Unknown[a]	1 (2.5)
Lymphoma involvement in bone marrow, n (%)	18 (45.0)
Prior lines of systemic therapy, median (range)	2 (1-6)

[a]One patient presented with both nodal and extranodal lesions; investigator was unable to classify the MZL subtype.
ECOG PS, Eastern Cooperative Oncology Group performance status; MZL, marginal zone lymphoma.

Best Overall Response by Independent Review





Median follow-up = 15.8 months

CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Best Overall Response by Independent Review and MZL Subtypes in Patients Aged ≥ 65 Years

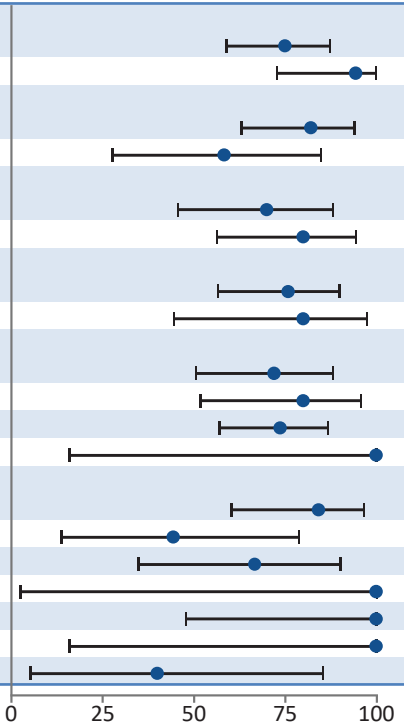
Best response, n (%)	Extranodal (n = 17)	Nodal (n = 14)	Splenic (n = 8)	Unknown (n = 1)	Total (N = 40)
ORR (CR or PR)	12 (70.6)	12 (85.7)	6 (75.0)	0	30 (75.0)
95% CI[a]	44.0, 89.7	57.2, 98.2	34.9, 96.8	0.0, 97.5	58.8, 87.3
Complete response	7 (41.2)	3 (21.4)	0	0	10 (25.0)
Partial response	5 (29.4)	9 (64.3)	6 (75.0)	0	20 (50.0)
Stable disease	4 (23.5)	2 (14.3)	1 (12.5)	0	7 (17.5)
Progressive disease	1 (5.9)	0	1 (12.5)	1 (100.0)	3 (7.5)

[a]Two-sided Clopper-Pearson 95% CI.

CI, confidence interval; CR, complete response; MZL, marginal zone lymphoma; ORR, overall response rate; PR, partial response.

Subgroup Analysis of ORR by IRC

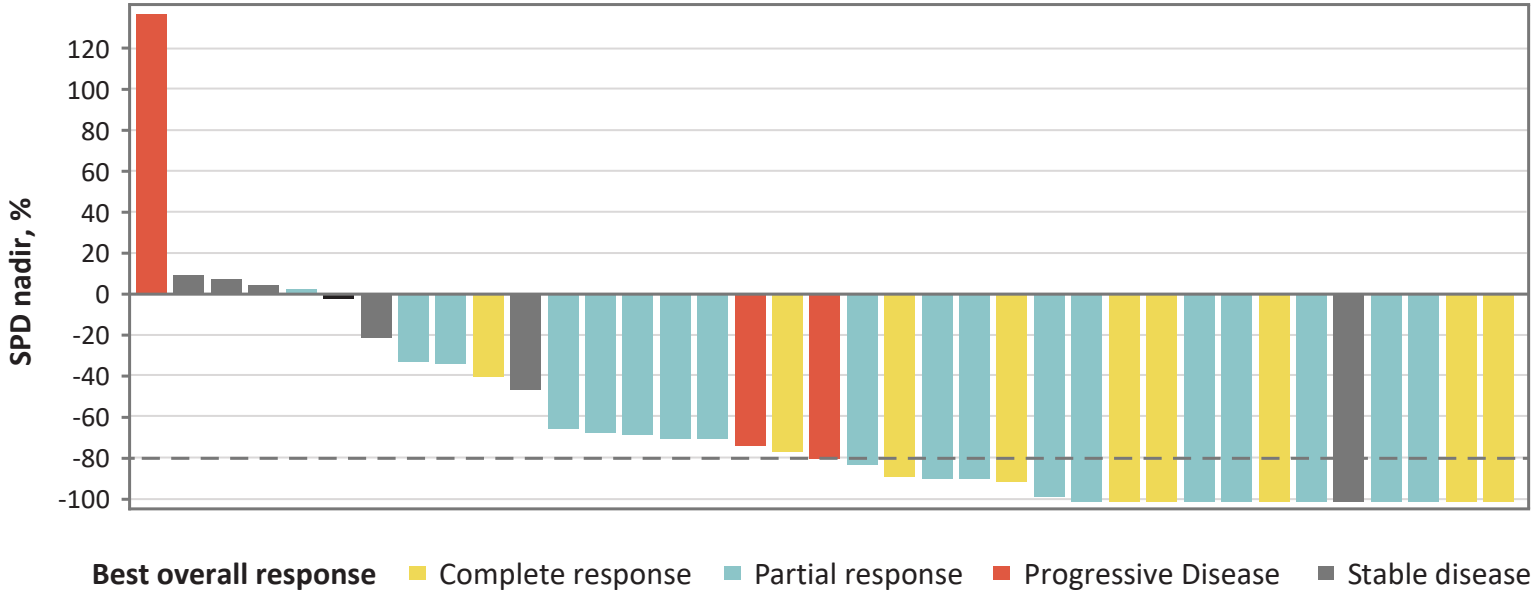
Subgroup	Patients/n	ORR (95% CI),[a] %
Age group		
≥ 65 years	30/40	75.0 (58.8, 87.3)
≥ 75 years	17/18	94.4 (72.7, 99.9)
Prior lines of systemic therapy		
< 3	23/28	82.1 (63.1, 93.9)
≥ 3	7/12	58.3 (27.7, 84.8)
Time since last antilymphoma therapy		
≤ 2 years	14/20	70.0 (45.7, 88.1)
> 2 years	16/20	80.0 (56.3, 94.3)
Disease status		
Relapsed	22/29	75.9 (56.5, 89.7)
Refractory	8/10	80.0 (44.4, 97.5)
Bulky disease		
LDi ≤ 5 cm	18/25	72.0 (50.6, 87.9)
LDi > 5 cm	12/15	80.0 (51.9, 95.7)
LDi ≤ 10 cm	28/38	73.7 (56.9, 86.6)
LDi > 10 cm	2/2	100.0 (15.8, 100.0)
Prior treatment		
RCVP	16/19	84.2 (60.4, 96.6)
RCHOP	4/9	44.4 (13.7, 78.8)
BR	8/12	66.7 (34.9, 90.1)
R-lenalidomide	1/1	100.0 (2.5, 100.0)
Rituximab monotherapy	5/5	100.0 (47.8, 100.0)
CHOP	2/2	100.0 (15.8, 100.0)
R-chlorambucil	2/5	40.0 (5.3, 85.3)



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

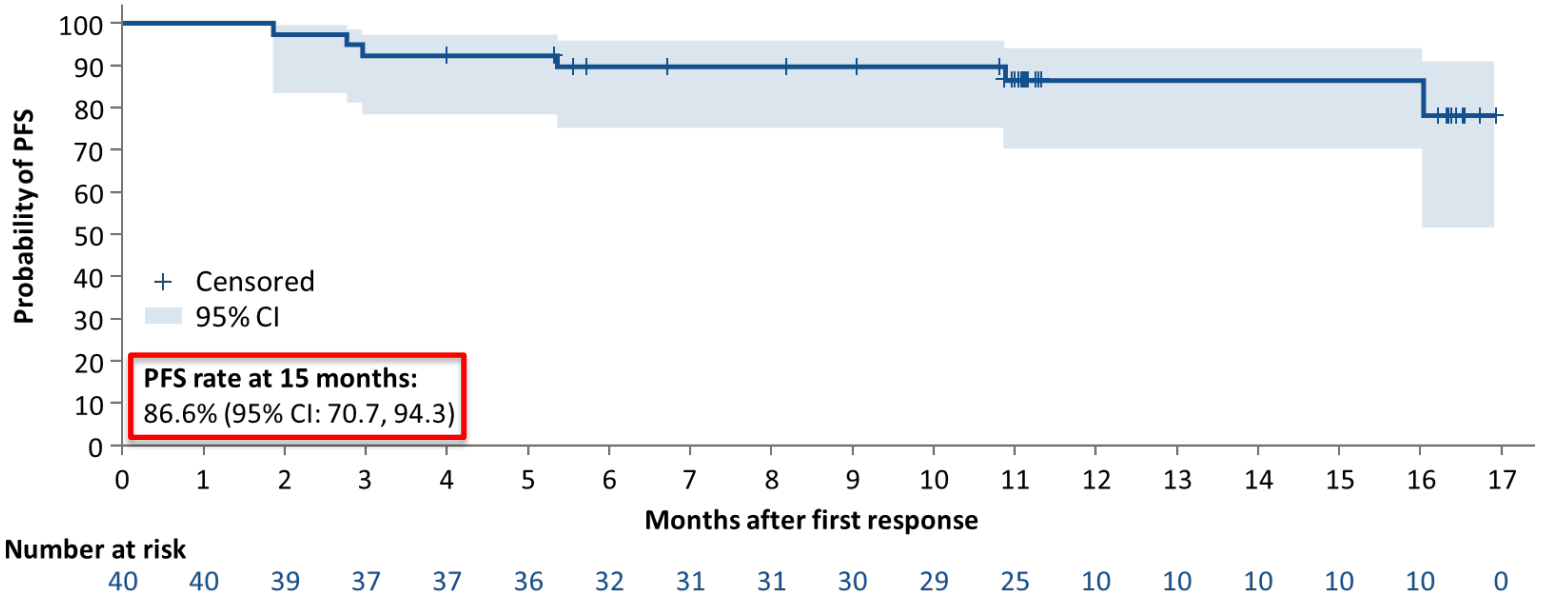
BR, bendamustine/rituximab; CHOP, cyclophosphamide/doxorubicin/vincristine/prednisone; CI, confidence interval; IRC, independent review committee; LDi, longest diameter; ORR, overall response rate; R, rituximab; RCHOP, rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone; RCVP, rituximab/cyclophosphamide/vincristine/prednisone.

Best Change in Target Lesion SPD from Baseline by IRC in Patients Aged ≥ 65 Years[a]



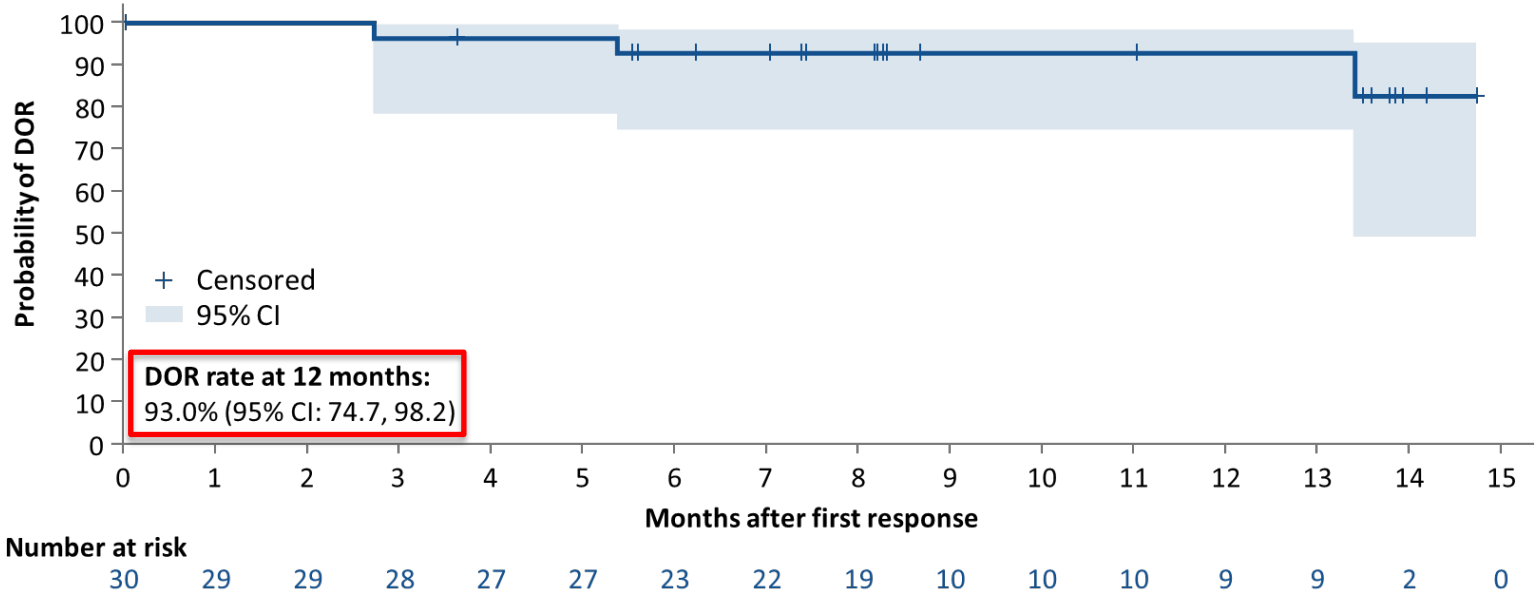
[a]Data cutoff: 18 January 2021. Only patients with nonmissing best overall response and SPD percent changes were included (n = 37). Dashed line = median reduction in SPD (−80%).
IRC, independent review committee; SPD, sum of products of perpendicular diameters.

Progression-Free Survival by IRC in Patients Aged ≥ 65 Years



CI, confidence interval; IRC, independent review committee; PFS, progression-free survival.

Duration of Response by IRC in Patients Aged ≥ 65 Years



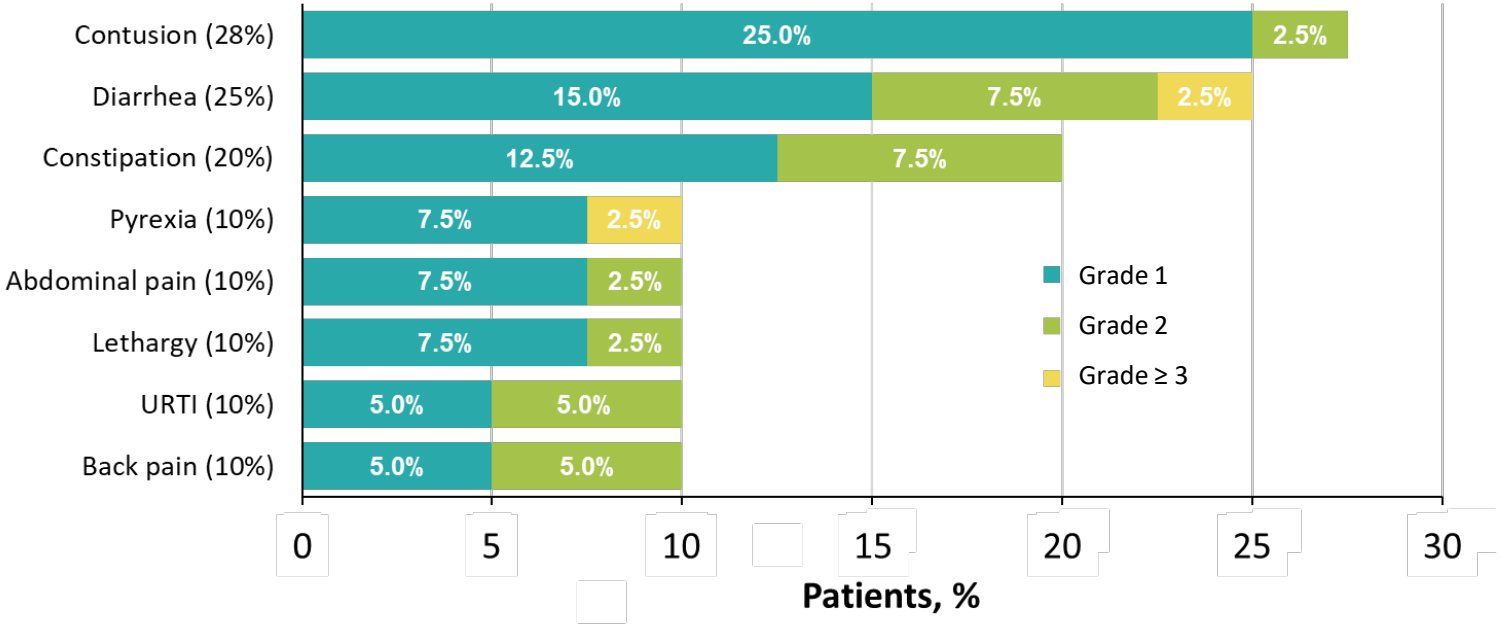
CI, confidence interval; DOR, duration of response; IRC, independent review committee.

Safety Summary in Patients Aged ≥ 65 Years

TEAEs, n (%)	n = 40
Patients with ≥ 1 TEAE	37 (92.5)
Grade ≥ 3	18 (45.0)
Serious TEAE	16 (40.0)
Leading to dose interruption	13 (32.5)
Leading to study drug discontinuation	2 (5.0)[a]
Leading to death	2 (5.0)[a]
Leading to dose reduction	0

[a]Two fatal unrelated adverse events: myocardial infarction, and COVID-19 pneumonia.
COVID-19, coronavirus disease of 2019; TEAE, treatment-emergent adverse event.

TEAEs occurring in ≥ 10% of Patients Regardless of Causality in Patients Aged ≥ 65 Years



TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

TEAEs of Interest in Patients Aged ≥ 65 Years

TEAE of interest	All-grade (n = 40)	Grade ≥ 3 (n = 40)
Patients with ≥ 1 TEAE of interest, n (%)	30 (75.0)	10 (25.0)
Hemorrhage	19 (47.5)	0
Infection[a]	18 (45.0)	5 (12.5)
Diarrhea	10 (25.0)	1 (2.5)
Thrombocytopenia[b]	5 (12.5)	1 (2.5)
Neutropenia[c]	5 (15.2)	3 (7.5)
Second primary malignancy[d]	3 (7.5)	1 (2.5)
Atrial fibrillation/flutter[e]	2 (5.0)	1 (2.5)
Hypertension[f]	2 (5.0)	1 (2.5)
Anemia	1 (2.5)	0
Major hemorrhage	0	0

- Atrial fibrillation/flutter and hypertension occurred in 2 patients (5%) each and did not lead to zanubrutinib discontinuation; no patients had major or serious hemorrhage

[a]Includes 2 patients with COVID-19 infection and 2 patients with COVID-19 pneumonia; [b]Combined terms thrombocytopenia and platelet count decreased; [c]Combined terms neutropenia and neutrophil count decreased; [d]Includes basal cell and squamous cell carcinoma (in 2 patients with history of skin cancer); grade 3 recurrent bladder cancer (in 1 patient with history of bladder cancer); [e]Includes atrial flutter (n = 1) which occurred 238 days after treatment start and atrial fibrillation (n = 1) in a patient with pre-existing atrial fibrillation (21 days after end of treatment due to disease progression); [f]Combined terms hypertension and prehypertension. TEAE, treatment-emergent adverse event.

Conclusions

- Zanubrutinib was well tolerated and highly effective in patients aged ≥ 65 years with R/R MZL
- After a median study follow-up of 15.8 months:
  - High ORR of 75% and complete response rate of 25% by IRC
    - Responses were observed in all MZL subtypes
  - Median PFS and median DOR not reached
    - 93% of responders were progression free/alive 12 months after initial response
    - PFS rate was 86.6% at 15 months
  - Treatment discontinuation due to unrelated fatal AEs in 2 patients (myocardial infarction and COVID-19 pneumonia)
  - No TEAEs led to dose reduction
  - Atrial flutter/fibrillation (n = 2) and hypertension (n = 2); did not lead to treatment withdrawal
  - No major hemorrhage was reported
- These results were consistent with previously published results: Opat et al. *Clin Cancer Res* 2021;27(23):6323-6332.
- Final analysis with longer study follow-up is planned

Acknowledgments

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Correspondence: alessandra.tedeschi@ospedaleniguarda.it