Updated Results of the ASPEN Trial From a Cohort of Patients With *MYD88* Wild-Type (*MYD88*^{WT}) Waldenström Macroglobulinemia (WM)

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48° CONGRESSO NAZIONALE SIE

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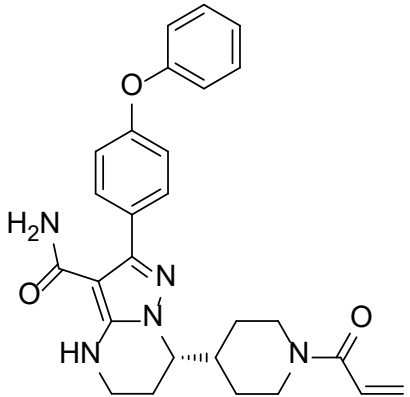
Disclosures of Pier Luigi Zinzani

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
VERASTEM			X		X	X	
CELLTRION					X	X	
GILEAD					X	X	
JANSSEN-CILAG					X	X	
BMS					X	X	
SERVIER					X	X	
SANDOZ						X	
MSD			X		X	X	
TG THERAP.					X	X	
TAKEDA					X	X	
ROCHE					X	X	
EUSAPHARMA			X		X	X	
KYOWA KIRIN					X	X	
NOVARTIS			X		X	X	
ADC THERAP.						X	
INCYTE					X	X	
BEIGENE					X	X	

BTK Inhibition in WM

- BTK plays a critical role in B-cell receptor signaling; this pathway is constitutively activated in WM (>90% with *MYD88* mutations), leading to malignant cell survival[1,2]
- BTK inhibition is a new standard of care for WM[3]
- Zanubrutinib is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC- and EGFR-family kinases
  - **Potent, selective, irreversible**
  - **Equipotent against BTK compared with ibrutinib;** fewer off-target effects due to higher selectivity for binding EGFR, ITK, JAK3, HER2, and TEC[4]
  - **Advantageous PK/pharmacodynamic properties**: complete and sustained BTK occupancy in PBMC and lymph nodes[5]
  - **Favorable drug-drug interaction properties:** can be coadministered with strong/moderate CYP3A inhibitors at a reduced dose, proton pump inhibitors, acid-reducing agents, and antithrombotic agents[6,7]

Zanubrutinib (BGB-3111)



1. Rickert RC. *Nat Rev Immunol*. 2013;13:578-591. 2. Argyropoulos KV, et al. *Leukemia*. 2016;30:1116-1125. 3. Treon SP, et al. *J Clin Oncol.* 2020;38:1198-1208. 4. Guo Y, et al. *J Med Chem.* 2019;62:7923-7940. 5. Tam CS, et al. *Blood*. 2019;134:851-859. 6. Mu S, et al. *Cancer Chemother Pharmacol.* 2020;85:391-399. 7. Data on file.

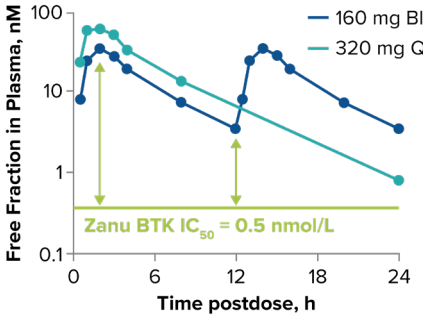
Abbreviations: BTK, Bruton tyrosine kinase; CYP3A, cytochrome P450, family 3, subfamily A; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; ITK, IL-2–inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; *MYD88*, myeloid differentiation primary response gene 88; PBMC, peripheral blood mononuclear cell; PK, pharmacokinetic; TEC, Tyrosine-protein kinase Tec; WM, Waldenström macroglobulinemia.

Zanubrutinib: A Potent and Selective BTK Inhibitor[1,2]

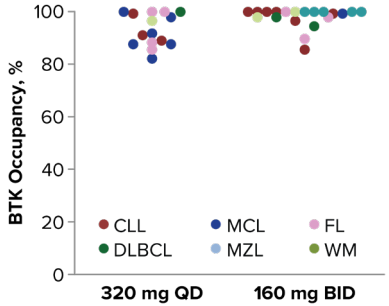
Potent, selective, irreversible; minimize off-target inhibition

	Targets	Assays	Zanubrutinib IC_{50} (nM)	Ibrutinib IC_{50} (nM)	Ratio (Zanubrutinib:Ibrutinib)
ON TARGET	BTK	BTK-pY223 Cellular Assay	1.8	3.5	0.5
		Rec-1 Proliferation	0.36	0.34	1.1
		BTK Occupation Cellular Assay	2.2	2.3	1
		BTK Biochemical Assay	0.22	0.2	1.1
OFF TARGET	EGFR	p-EGFR HTRF Cellular Assay	606	101	6
		A431 Proliferation	3210	323	9.9
	ITK	ITK Occupancy Cellular Assay	3265	189	17
		p-PLCγ1 Cellular Assay	3433	77	45
		IL-2 Production Cellular Assay	2536	260	9.8
		ITK Biochemical Assay	30	0.9	33
	JAK3	JAK3 Biochemical Assay	200	3.9	51
	HER2	HER2 Biochemical Assay	661	9.4	70
	TEC	TEC Biochemical Assay	1.9	0.8	2.4

C_{max} and C_{trough} > BTK IC_{50} Over 24 h



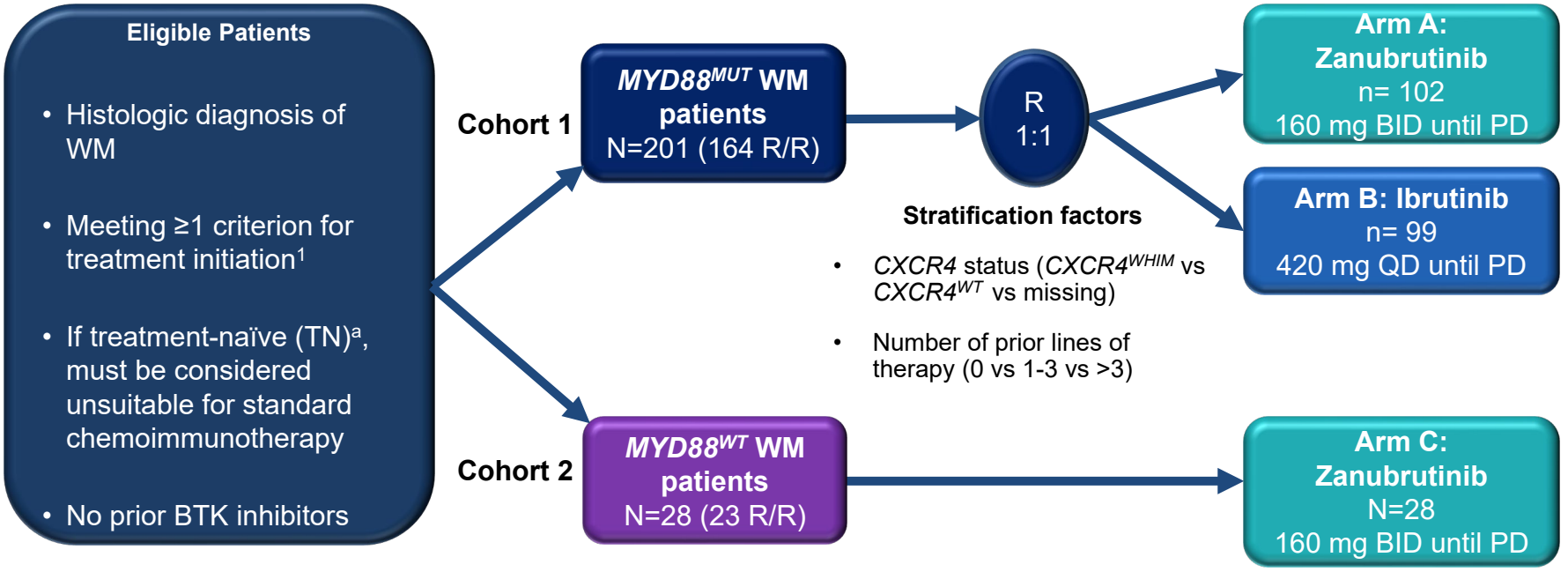
Complete, Sustained BTK Occupancy



1. Tam CS, et al. ICML Session 7, June 16, 2017 [abstr]. 2. Tam CS, et al. *Blood*. 2019;134:851-859.

Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; C_{max}, maximum concentration; C_{trough}, trough concentration; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; FL, follicular lymphoma; HER2, human epidermal growth factor receptor 2; HTRF, homogeneous time resolved fluorescence; IC_{50}, half maximal inhibitory concentration; ITK, IL-2–inducible T-cell kinase; JAK3, Janus-associated kinase 3; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; PLC, phospholipase C; TEC, Tyrosine-protein kinase Tec; QD, daily; WM, Waldenström macroglobulinemia; Zanu, zanubrutinib.

ASPEN Study Design: Zanubrutinib vs Ibrutinib in *MYD88*^{WT} WM



EUDRACT 2016-002980-33; NCT03053440

[a]Up to 20% of the overall population.

1. Dimopoulos MA, et al. *Blood*. 2014;124:1404-1411.

Abbreviations: BID, twice daily; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C motif chemokine receptor 4; *MYD88*, myeloid differentiation primary response gene 88; MUT, mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia; WT, wild-type.

ASPEN Cohort 2 Study Objectives

- **Main Objective**

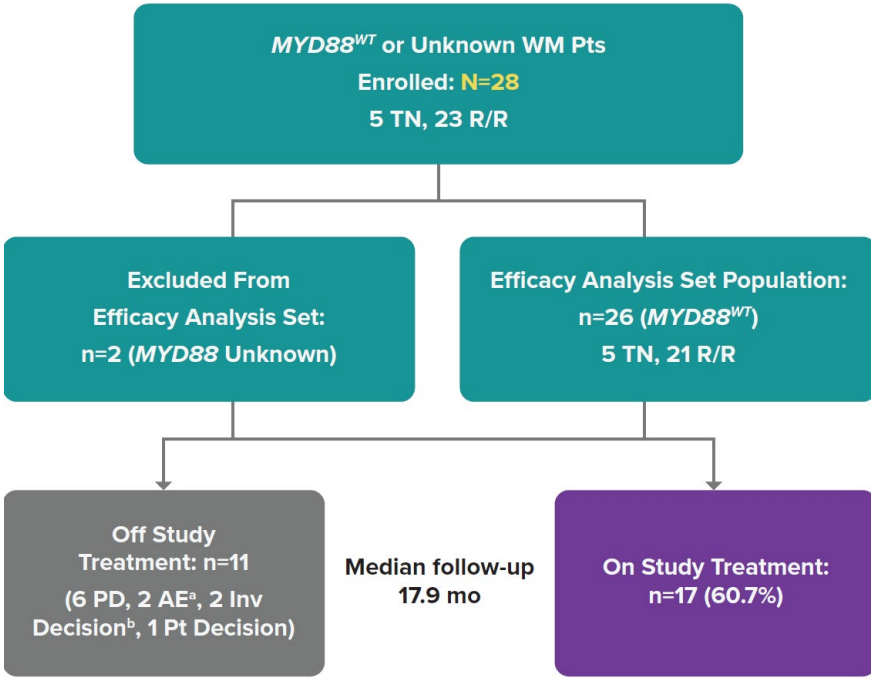
  To assess the safety and efficacy of zanubrutinib versus ibrutinib in WM patients with *MYD88*^{WT} (ASPEN; NCT03053440)

- **Exploratory Endpoints**
  - Responses were assessed monthly by IgM with extramedullary disease assessment every 3 months, according to response criteria in the National Comprehensive Cancer Network WM guidelines[1] and modified Owen criteria[2] as assessed by IRC
  - Efficacy: Response rates (overall and major response rate), progression-free survival, DoR, and OS; safety assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03)

1. National Comprehensive Cancer Network (NCCN). NCCN Guidelines: Lymphoplasmacytic Lymphoma/Waldenström's Macroglobulinemia. 2015; version 2. Owen RG, et al. *Br J Haematol*. 2013;160:171-176.

Abbreviations: DoR, duration of response; IgM, immunoglobulin M; IRC, independent review committee; *MYD88*, myeloid differentiation primary response gene 88; OS, overall survival; WM, Waldenström macroglobulinemia; WT, wild-type.

Disposition of Patients in Cohort 2



Data cutoff date: 31 August 2019.

[a]Grade 4 subdural hemorrhage; grade 3 diarrhea.

[b]Investigator decided no further treatment needed (n=1); patient discharged to hospice for palliative care (n=1).

Abbreviations: AE, adverse event; Inv, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; Pt, patient; R/R, relapsed/refractory; TN, treatment-naïve; WM, Waldenström macroglobulinemia; WT, wild-type.

Patient and Disease Characteristics

Characteristic	Total (N=28)
Age, median (range), y	70.1 (39-87)
>65 years, n(%)	19 (67.9)
>75 years, n(%)	12 (42.9)
Sex, n (%)	
Men	14 (50)
Women	14 (50)
IPSSWM, n (%)	
Low	5 (17.9)
Intermediate	11 (39.3)
High	12 (42.9)
Prior treatment status	
Treatment naïve, n (%)	5 (17.9)
R/R, n (%)	23 (82.1)
No. of prior therapies for R/R patients, median (range)	1 (1-5)
Extramedullary disease present at baseline by IRC, n (%)	21 (75.0)
Genotype, n (%)	
MYD88^{WT}/*CXCR4*^{WT}	23 (82.1)
MYD88^{WT}/*CXCR4*^{WHIM}	1 (3.6)
MYD88^{WT}/*CXCR4* unknown	2 (7.1)
MYD88 unknown/*CXCR4* unknown	2 (7.1)
Hemoglobin ≤110 g/L, n (%)	15 (53.6)

Abbreviations: *CXCR4*, C-X-C motif chemokine receptor 4; IPSSWM, International Prognostic Scoring System Waldenström macroglobulinemia; IRC, independent review committee; *MYD88*, myeloid differentiation primary response gene 88; R/R, relapsed/refractory; WT, wild-type.

Adverse Event (AE) Overview (N=28)

Treatment Emergent AE	n (%)
Patients with ≥1 AE grade ≥3	18 (64.3)
Patients with ≥1 serious AE	11 (39.3)
AE leading to death	0
AE leading to treatment discontinuation	2[a] (7.1)
AE leading to dose reduction	2[b] (7.1)

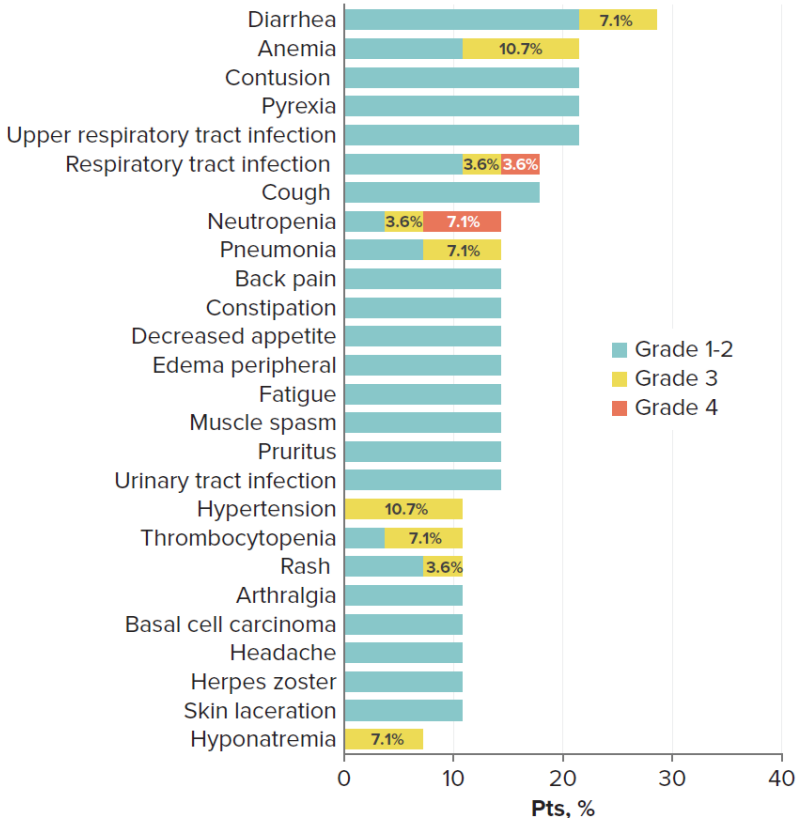
[a]Grade 4 subdural hemorrhage (related) and grade 3 diarrhea (related).
[b]Grade 3 pneumonitis resolved and followed by grade 2 pneumonia (n=1); grade 1 diarrhea (n=1).
Abbreviation: AE, adverse event.

AE Categories of Interest (BTKi Class AEs)

AE Categories (Pooled Terms), n (%)	All Grade	Grade ≥3
Atrial fibrillation/flutter	1 (3.6)	0
Diarrhea (PT)	8 (28.6)	2 (7.1)
Hemorrhage	11 (39.3)	2 (7.1)
Major hemorrhage[a]	2 (7.1)	2 (7.1)
Hypertension	3 (10.7)	3 (10.7)
Neutropenia[b]	5 (17.9)	3 (10.7)
Infection	21 (75.0)	8 (28.6)
Second malignancy[c]	4 (14.3)	0

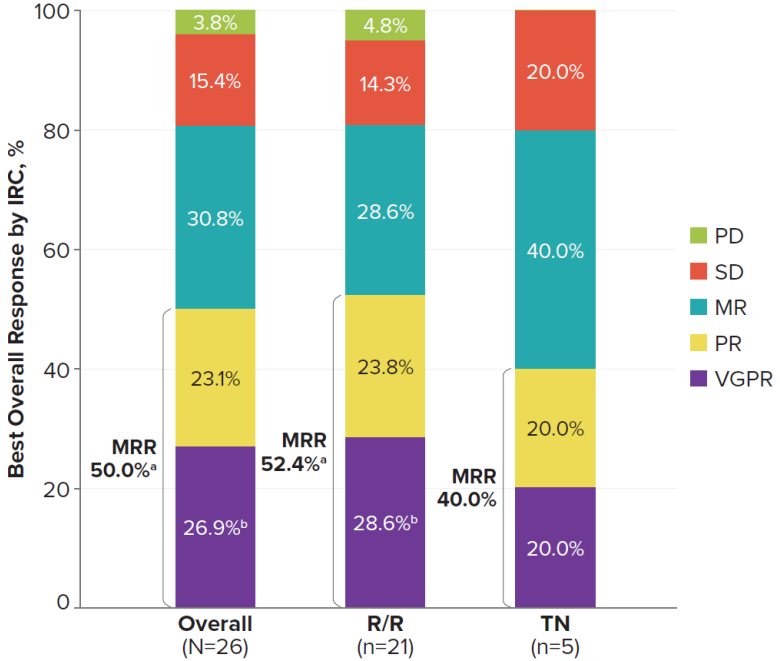
No tumor lysis syndrome or opportunistic infection was reported.
[a]Defined as any grade ≥3 hemorrhage or any grade central nervous system hemorrhage: gastric ulcer hemorrhage; and one patient had periorbital hematoma, subdural hematoma, and subdural hemorrhage.
[b]Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection, and neutropenic sepsis.
[c]Basal cell carcinoma (n=3) and Queyrat erythroplasia (n=1).
Abbreviations: AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.

Common AEs (Any Grade >10% or Grade ≥3 in >1 Patient), Regardless of Causality



Abbreviation: AE, adverse event; Pts, Patients.

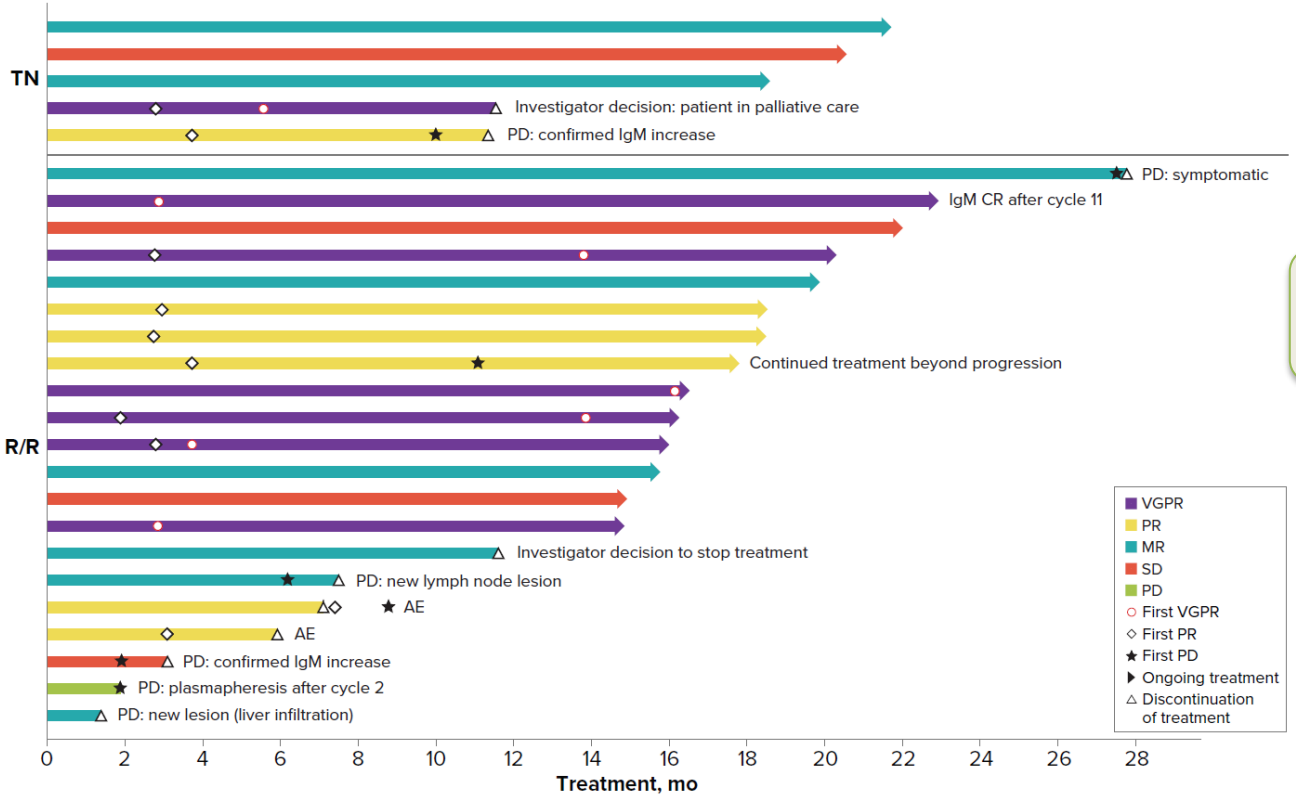
Best Responses by IRC in Patients With *MYD88*^{WT} WM



- One patient achieved IgM complete response[b]

[a]Including patients confirmed by next-generation sequencing of no other activating *MYD88* mutations.
[b]Normalized IgM and negative immunofixation since cycle 11, with bulky extramedullary disease improving.
Abbreviations: IgM, immunoglobulin M; IRC, independent review committee; MR, minor response; MRR, major response rate (≥PR); *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR; WM, Waldenström macroglobulinemia; WT, wild-type.

Responses Over Time on Treatment

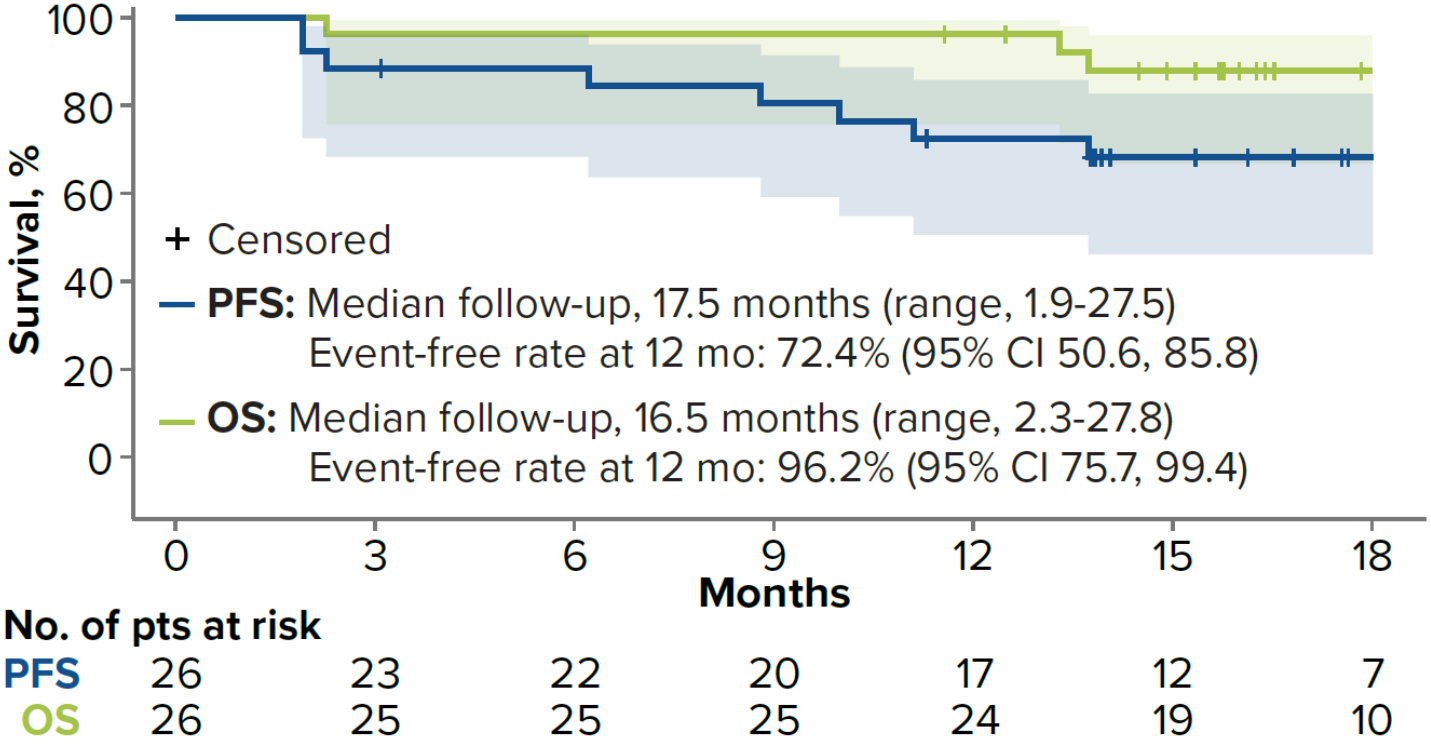


Median time to first major response was 2.9 months (range, 1.9-16.1)

Color of bars represents the best response for each patient.

Abbreviations: AE, adverse event; CR, complete response; IgM, immunoglobulin M; MR, minor response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; TN, treatment-naïve; VGPR, very good PR.

Progression-Free and Overall Survival



Shaded areas show the 95% CI.

Abbreviations: CI, confidence interval; OS, overall survival; PFS, progression-free survival; pts, patients.

Conclusions

- Largest cohort of patients with WM with confirmed *MYD88*^{WT} (n=26) studied in terms of safety and efficacy of BTK inhibitor treatment
- Single-agent zanubrutinib resulted in major responses (including very good partial response)
  - Major response rate of 50.0% including 26.9% with very good partial response
  - IgM complete response achieved in one patient
  - Median time to first major response was 2.9 months (range, 1.9-16.1)
- Zanubrutinib was well tolerated
  - Discontinuation due to AEs occurred in 7.1% of patients (2/28)
  - Primary reason for discontinuation was progressive disease (3 of 6 within first 3 cycles)
  - No fatal AEs reported
  - Low incidence of atrial fibrillation
- AE profile is consistent with Cohort 1 finding in the ASPEN study

Abbreviations: AE, adverse event; BTK, Bruton tyrosine kinase; IgM, immunoglobulin M; *MYD88*, myeloid differentiation primary response gene 88; WM, Waldenström macroglobulinemia; WT, wild-type.

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