LXIV Congreso Nacional SEHH
XXXVIII Congreso Nacional SETH
38th World Congress of the International Society of Hematology (ISH)
BARCELONA
6 - 8 | OCT | 2022
PALACIO DE CONGRESOS DE BARCELONA

ASPEN: Long-Term Follow-Up Results of a Phase 3 Randomized Trial of Zanubrutinib vs Ibrutinib in Patients with Waldenström Macroglobulinemia (WM)

Ramon Garcia-Sanz[1], Constantine S. Tam[2,3], Stephen Opat[3], Shirley D'Sa[4], Wojciech Jurczak[5], Hui Lee[6], Gavin Cull[7], Roger G. Owen[8], Paula Marlton[9], Bjorn E. Wahlin[10], Alessandra Tedeschi[11], Jorge J. Castillo[12], Tanya Siddiqi[13], Christian Buske[14], Veronique Leblond[15], Wai Y. Chan[16], Jingjing Schneider[16], Aileen Cohen[16], and Meletios Dimopoulos[17]

[1]Hospital Universitario de Salamanca, Salamanca, Spain; [2]The Alfred Hospital, Melbourne, VIC, Australia; [3]Monash University, Clayton, VIC, Australia; [4]Centre for Waldenström's Macroglobulinemia and Associated Disorders, University College London Hospital Foundation Trust, London, UK; [5]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [6]Flinders Medical Centre, Adelaide, SA, Australia; [7]Sir Charles Gairdner Hospital, University of Western Australia Perth, WA, Australia; [8]St. James University Hospital, Leeds, UK; [9]Princess Alexandra Hospital, Brisbane, QLD, Australia; [10]Karolinska Universitetssjukhuset and Karolinska Institutet, Stockholm, Sweden; [11]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [12]Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [13]City Of Hope National Medical Center, Duarte, CA, USA; [14]CCC Ulm - Universitätsklinikum Ulm, Ulm, Baden-Württemberg, Germany; [15]Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [16]BeiGene USA, Inc., San Mateo, CA, USA; and [17]National and Kapodistrian University of Athens, Athens, Greece

Disclosures for Ramon Garcia-Sanz

Consulting at Janssen; Travel expense from Janssen and Takeda; Royalties from BIOMED 2 primers; Honoraria from Janssen, Takeda, Amgen, BeiGene, Novartis, and Astellas Pharma; Research funding from Gilead Sciences, Incyte, and Astellas Pharma.

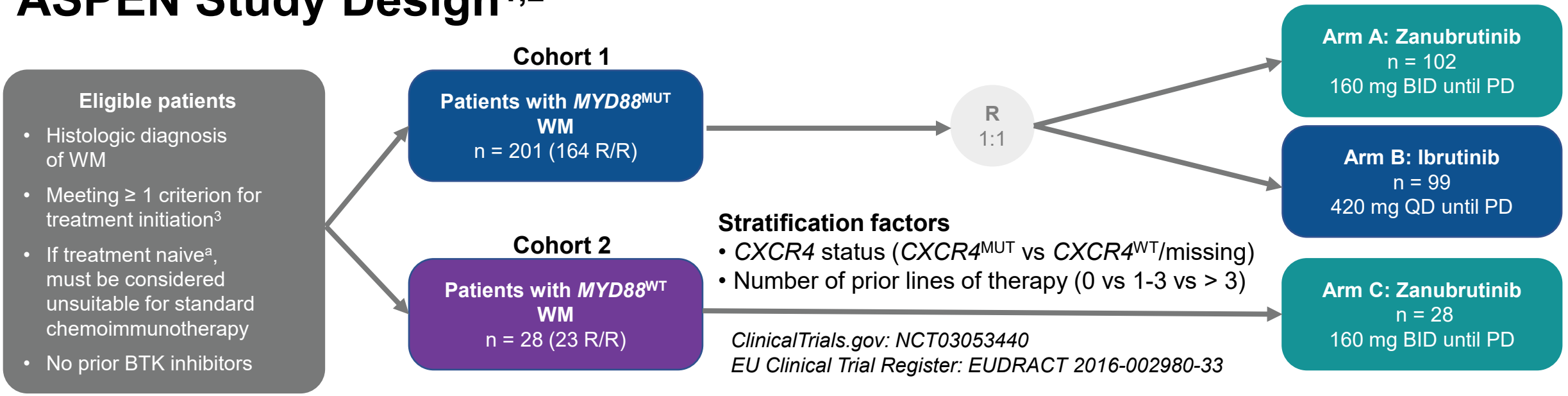
Background

- Zanubrutinib is a potent, selective, and irreversible next-generation BTK inhibitor designed to maximize BTK occupancy and minimize inhibition of off-target kinases[1]
- Zanubrutinib has demonstrated a complete and sustained BTK occupancy in peripheral blood mononuclear cells and lymph nodes[2]
- Zanubrutinib has shown equipotency against BTK compared with ibrutinib; it has high selectivity for BTK and minimal off-target inhibition of TEC and EGFR family kinases[1]
- Favorable drug interaction properties allow coadministration with strong or moderate CYP3A inhibitors (eg, antifungals) at a reduced dose, PPIs, acid-reducing agents, and antithrombotic agents[3,4]

BTK, Bruton tyrosine kinase; CYP3A, cytochrome P450 3A; EGFR, epidermal growth factor receptor; PPI, proton pump inhibitor; TEC, tyrosine kinase expressed in hepatocellular carcinoma.

1. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940; 2. Tam C, et al. *Blood.* 2019;134(11):851-859; 3. Mu S, et al. *Cancer Chemother Pharmacol.* 2020;85(2):391-399; 4. Ou Y, et al. *Clin Transl Sci.* 2021;14(2):764-772.

ASPEN Study Design[1,2]



- **Primary endpoint:** CR + VGPR rate in cohort 1
- **Secondary endpoints:** Efficacy, clinical benefit, antilymphoma effects, safety and tolerability of zanubrutinib vs ibrutinib
- **Exploratory endpoints:** Efficacy and safety of zanubrutinib in cohort 2, and efficacy of zanubrutinib vs ibrutinib according to *CXCR4* status

[a]Up to 20% of the overall population.
BID, twice daily; BTK, Bruton tyrosine kinase; *CXCR4*, C-X-C motif chemokine receptor type 4; MUT, mutant; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; R/R, relapsed/refractory; QD, once daily; VGPR, very good partial response; WM, Waldenström Macroglobulinemia; WT, wild type.
1. Tam C, et al. *Future Oncol.* 2018;14(22):2229-2237; 2. Tam C, et al. *Blood.* 2020;136(18):2038-2050; 3. Dimopoulos M, et al. *Blood.* 2014;124(9):1404-1411.

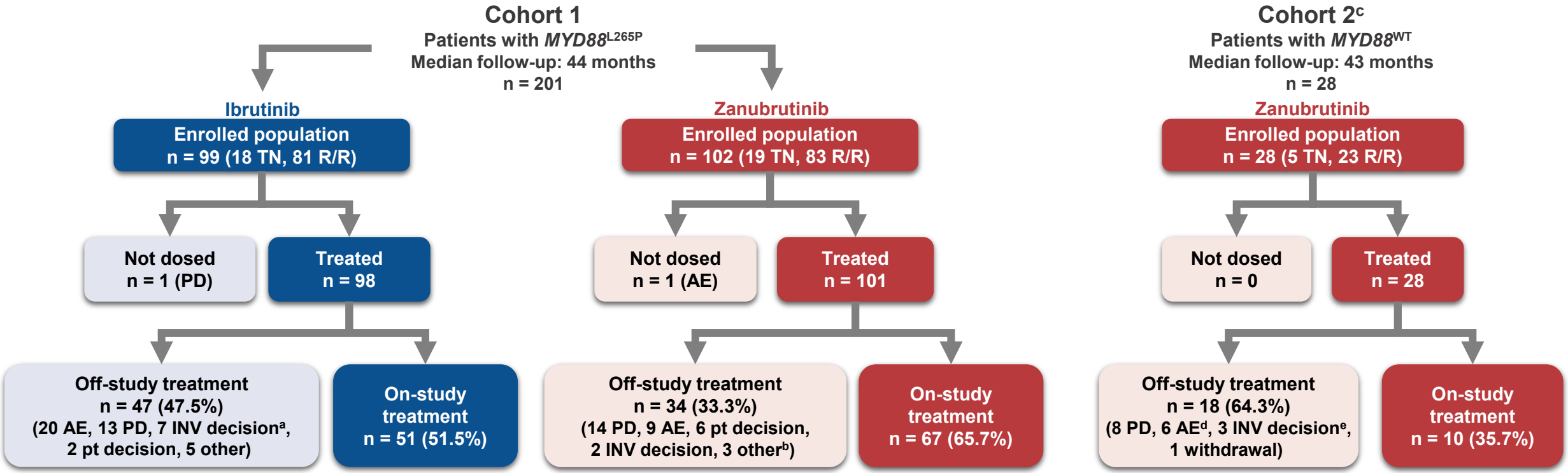
Baseline Demographics and Disease Characteristics

- 24 patients were enrolled across 8 sites in Spain

Characteristics	Cohort 1		Cohort 2
	Ibrutinib (n = 99)	**Zanubrutinib (n = 102)**	**Zanubrutinib (n = 28)**
Age, median (range), years	70 (38-90)	70 (45-87)	72 (39-87)
> 65 years, n (%)	**70 (70.7)**	61 (59.8)	19 (67.9)
> 75 years, n (%)	22 (22.2)	**34 (33.3)**	12 (42.9)
Male sex, n (%)	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, n (%)			
0	18 (18.2)	19 (18.6)	5 (17.9)
1-3	74 (74.7)	76 (74.5)	20 (71.4)
> 3	7 (7.1)	7 (6.9)	3 (10.7)
Genotype by NGS, n (%)			
CXCR4^{WT}	72 (72.7)	65 (63.7)	27 (96.4)
CXCR4^{MUT}	20 (20.2)	**33 (32.4)**	1 (3.6)
Unknown	7 (7.1)	4 (3.9)	0
IPSS WM, n (%)			
Low	13 (13.1)	17 (16.7)	5 (17.9)
Intermediate	42 (42.4)	38 (37.3)	11 (39.3)
High	44 (44.4)	47 (46.1)	12 (42.9)
Hemoglobin ≤ 110 g/L, n (%)	53 (53.5)	**67 (65.7)**	15 (53.6)
Baseline IgM, median (range), g/L, central lab	34.2 (2.4-108.0)	31.8 (5.8-86.9)	28.5 (5.6-73.4)
Bone marrow involvement, median (range), %	60 (0-90)	60 (0-90)	22.5 (0-50)
Extramedullary disease by investigator, n (%)	66 (66.7)	63 (61.8)	16 (57.1)

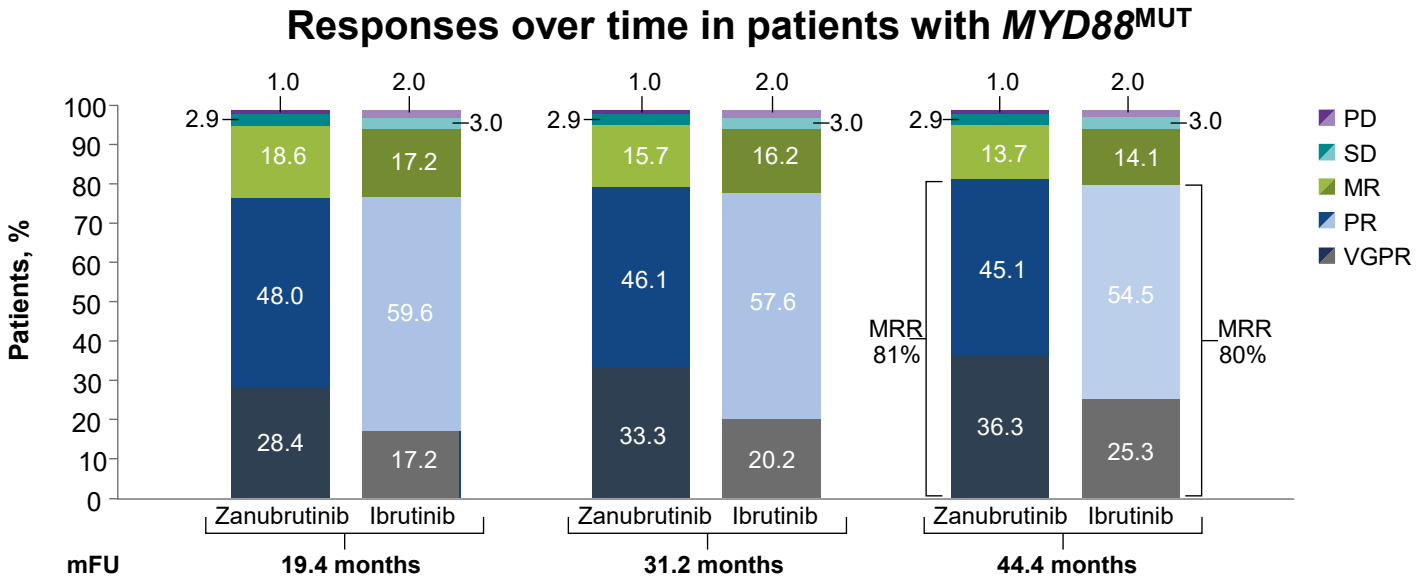
CXCR4, C-X-C motif chemokine receptor type 4; IgM, immunoglobulin M; IPSS, International Prognostic Scoring System; MUT, mutant; NGS, next-generation sequencing; WM, Waldenström macroglobulinemia.

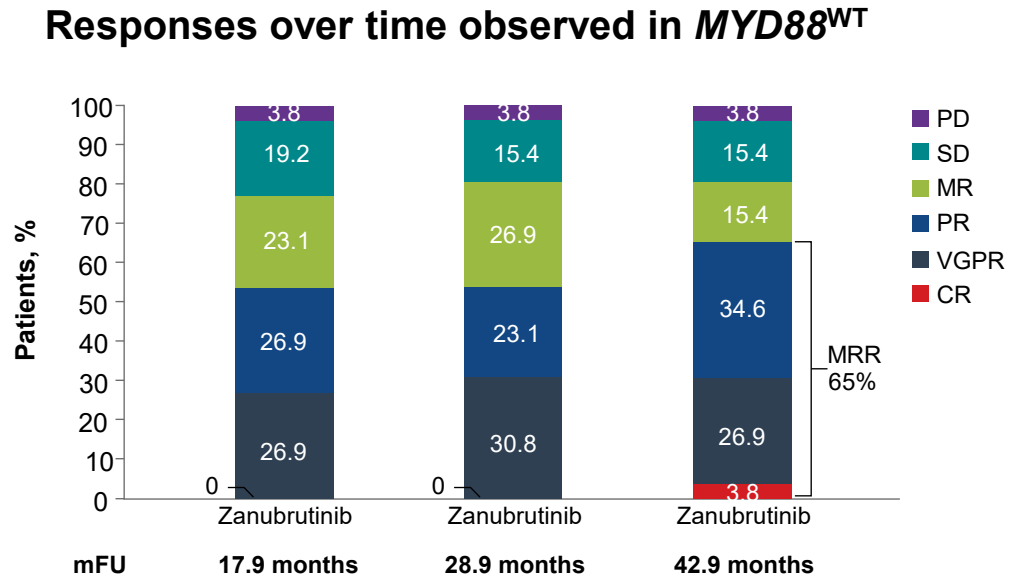
Patient Disposition



Data cutoff: October 31, 2021.
[a]One case related to COVID-19. [b]Radiotherapy for endometrial adenocarcinoma; patient started other anticancer therapy (rectal cancer); unwitnessed death (prior hospitalization for heart failure exacerbation but death not due to AE per site and no other information available). [c]In cohort 2 (n = 26 *MYD88*^{WT}; n = 2 *MYD88* mutation status unknown), the safety analysis set includes all 28 pts, and the efficacy analysis set includes 26 *MYD88*^{WT} patients, with a median treatment duration of 30 months. [d]One case related to COVID-19. [e]INV decision: palliative care; mycobacterium infection required prolonged antibiotics; treatment for skin scleroderma.
AE, adverse event; INV, investigator; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; pt, patient; R/R, relapsed/refractory; TN, treatment-naive; WT, wild type.

Best Overall Response by Investigator Over Time



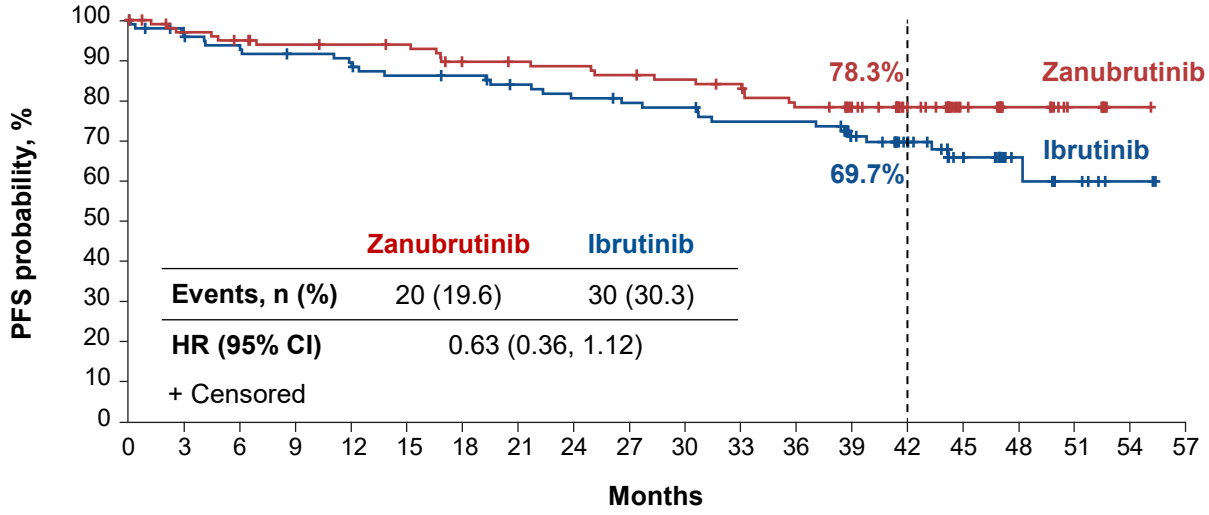


- Cohort 1 (*MYD88*^{MUT}): no CRs; at all time points, CR + VGPR response rate numerically higher with zanubrutinib vs ibrutinib
- Cohort 2 (*MYD88*^{WT}): for zanubrutinib, 1 CR and 31% CR + VGPR overall

Data cutoff: October 31, 2021.
CR, complete response; mFU, median follow-up; MR, major response; MUT, mutant; *MYD88*, myeloid differentiation primary response gene 88; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

PFS and OS in ITT population (Cohort 1)

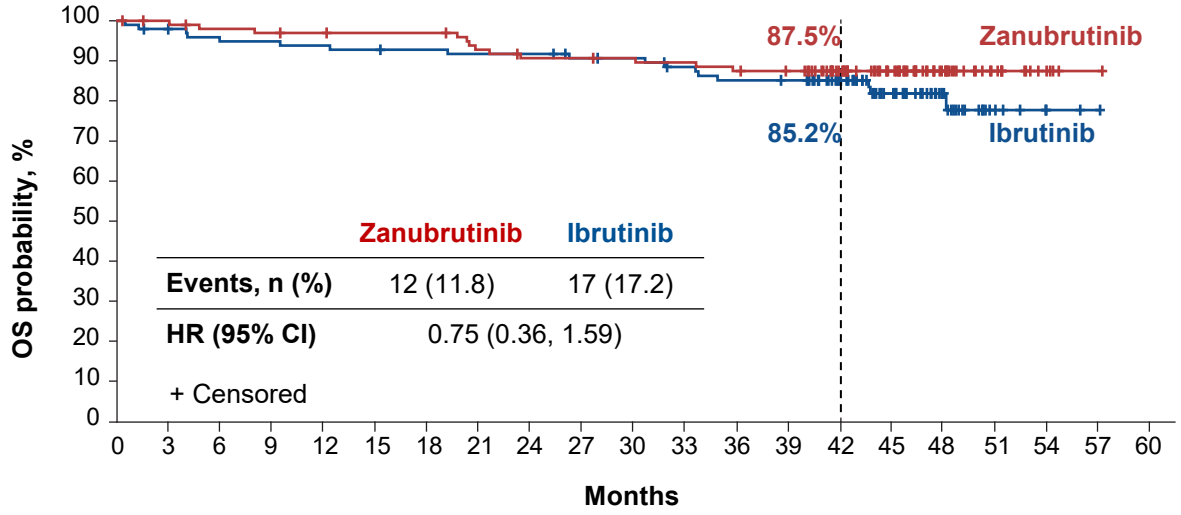
PFS[a]



No. of Patients at Risk:

Zanubrutinib	102	96	93	90	89	88	82	81	80	78	76	74	68	60	43	25	15	8	1	0
Ibrutinib	99	92	88	85	83	79	78	74	71	69	68	64	64	52	41	27	11	6	2	0

OS[a]



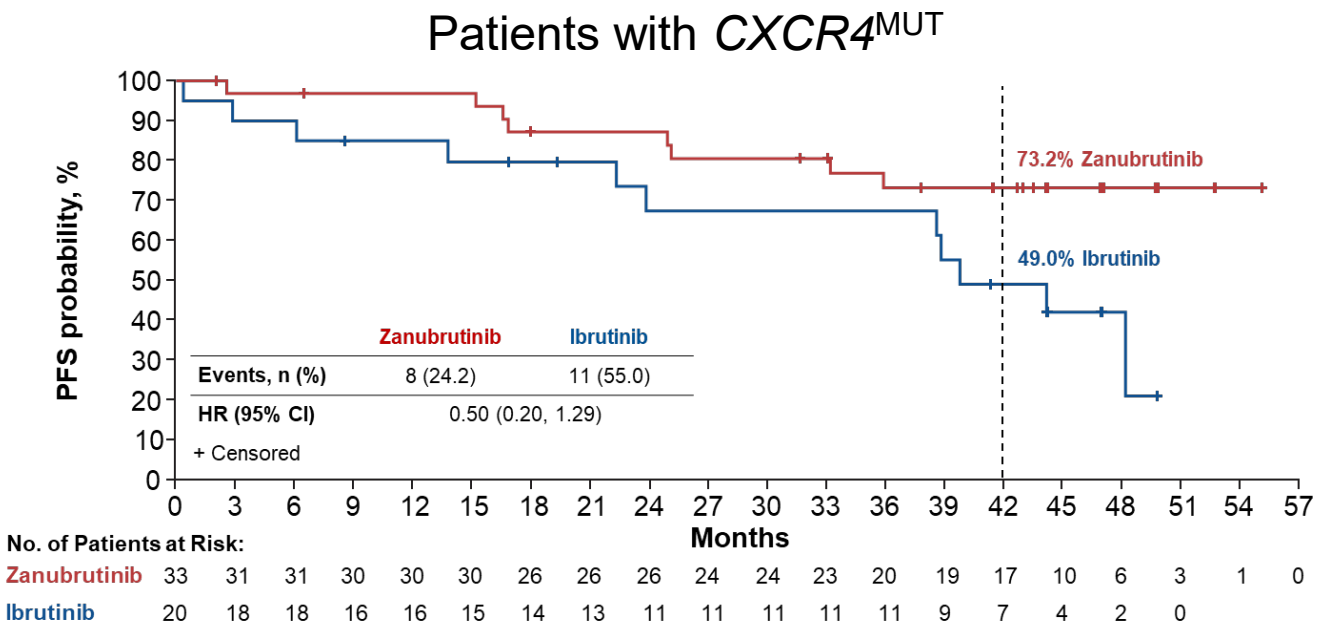
No. of Patients at Risk:

Zanubrutinib	102	100	97	96	95	94	94	89	86	86	85	84	82	80	65	49	27	13	5	1	0
Ibrutinib	99	96	93	92	91	90	89	88	88	85	84	80	77	76	62	43	21	7	3	1	0

- Median PFS and median OS were not yet reached; HR estimates favored zanubrutinib in cohort 1

Data cutoff: October 31, 2021
[a]By investigator assessment.
CI, confidence Interval; HR, hazard ratio; ITT, intent to treat; OS, overall survival; PFS, progression-free survival.

PFS and Response Assessment by *CXCR4* Status[a]



	*CXCR4*MUT		*CXCR4*WT	
	Ibrutinib (n = 20)	**Zanubrutinib (n = 33)**	**Ibrutinib (n = 72)**	**Zanubrutinib (n = 65)**
VGPR or better	2 (10.0)	**7 (21.2)**	22 (30.6)	**29 (44.6)**
Major response	13 (65.0)	**26 (78.8)**	61 (84.7)	54 (83.1)
Overall response	19 (95.0)	30 (90.9)	68 (94.4)	63 (96.9)
Time to major response, median (months)	6.6	3.4	2.8	2.8
Time to VGPR, median (months)	31.3	11.1	11.3	6.5

- Zanubrutinib demonstrated deeper and faster responses, as well as favorable PFS, compared with ibrutinib

Data cutoff: October 31, 2021. **Bold** values indicate > 10% difference between arms.
[a]*CXCR4* mutation determined by NGS. 92 ibrutinib patients and 98 zanubrutinib patients had NGS results available.
CI, confidence interval; *CXCR4*, C-X-C motif chemokine receptor type 4; HR, hazard ratio; MUT, mutant; PFS, progression-free survival; VGPR, very good partial response; WT, wild type.

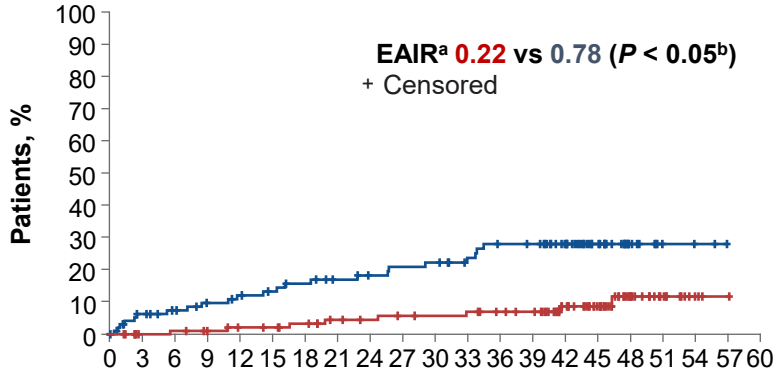
Overall Safety Summary and Treatment Discontinuation Due to AEs

Category, n (%)	Cohort 1		Cohort 2
	Ibrutinib (n = 98)	Zanubrutinib (n = 101)	Zanubrutinib (n = 28)
Patients with ≥ 1 AE	98 (100.0)	100 (99.0)	26 (92.9)
Grade ≥ 3	71 (72.4)	75 (74.3)	20 (71.4)
Serious	49 (50.0)	57 (56.4)	14 (50.0)
AE leading to death	5 (5.1)[a]	3 (3.0)[b]	3 (10.7)[c]
AE leading to treatment discontinuation	20 (20.4)[d]	9 (8.9)[e]	6 (21.4)[f]
AE leading to dose reduction	26 (26.5)	16 (15.8)	2 (7.1)
AE leading to dose held	62 (63.3)	63 (62.4)	18 (64.3)
COVID-19–related AE	4 (4.1)	4 (4.0)	2 (7.1)

Data cutoff: October 31, 2021.
[a]Cardiac failure acute, death (unexplained), pneumonia, sepsis (n = 2). [b]Cardiomegaly (cardiac arrest after plasmapheresis), metastatic malignant melanoma, subdural hematoma (after a fall). [c]Cardiac arrest, COVID-19 infection, lymphoma transformation. [d]Cardiac disorders (n = 4, includes 2 due to atrial fibrillation), infection and infestations (n = 4, pneumonia and sepsis, 2 each), respiratory, thoracic and mediastinal disorders (n = 3), second malignancy (n = 3), blood and lymphatic system disorders (n = 2), renal and urinary disorders (n = 1), death of unknown cause (n = 1), drug induced liver injury (n = 1), hepatitis (n = 1). [e]Second malignancy (n = 4, includes breast cancer, metastatic melanoma, multiple myeloma, and myelodysplastic syndrome, 1 each), cardiomegaly (n = 1), drug-induced liver injury (n = 1), neutropenia (n = 1), subdural hemorrhage (n = 1), worsening of chronic kidney disease (n = 1). [f]Cardiac arrest, COVID-19 infection, diarrhea, hepatitis B infection, squamous cell carcinoma of lung, subdural hemorrhage (after a fall).
AE, adverse event; COVID-19, coronavirus disease of 2019.

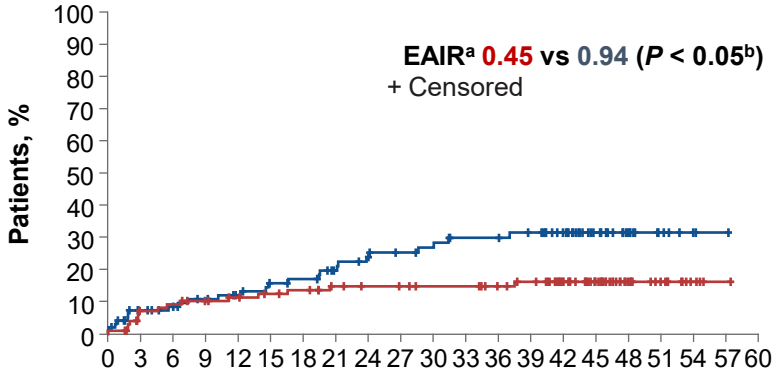
Time to AEs of Interest (Cohort 1)

Atrial fibrillation/flutter



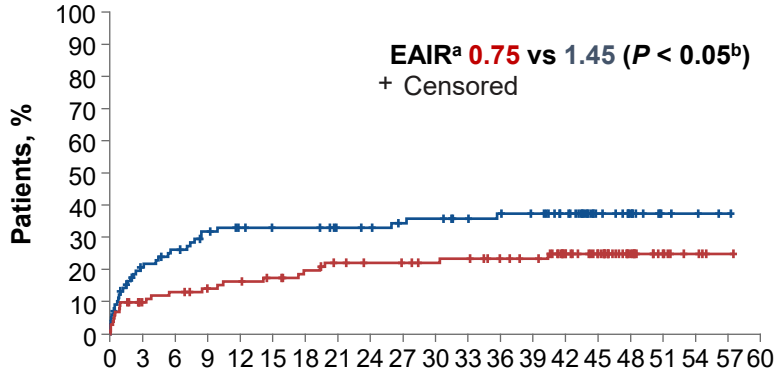
No. of Patients at Risk:																					
Zanubrutinib	101	95	94	92	89	87	84	79	77	75	74	74	70	68	52	41	22	11	4	1	0
Ibrutinib	98	87	83	78	74	71	68	64	62	59	58	54	49	48	40	25	10	4	2	0	

Hypertension



No. of Patients at Risk:																					
Zanubrutinib	101	89	87	83	80	77	75	70	68	67	65	65	61	58	46	34	17	11	14	1	0
Ibrutinib	98	84	80	75	71	66	64	58	52	50	47	44	43	41	34	22	10	6	1	0	

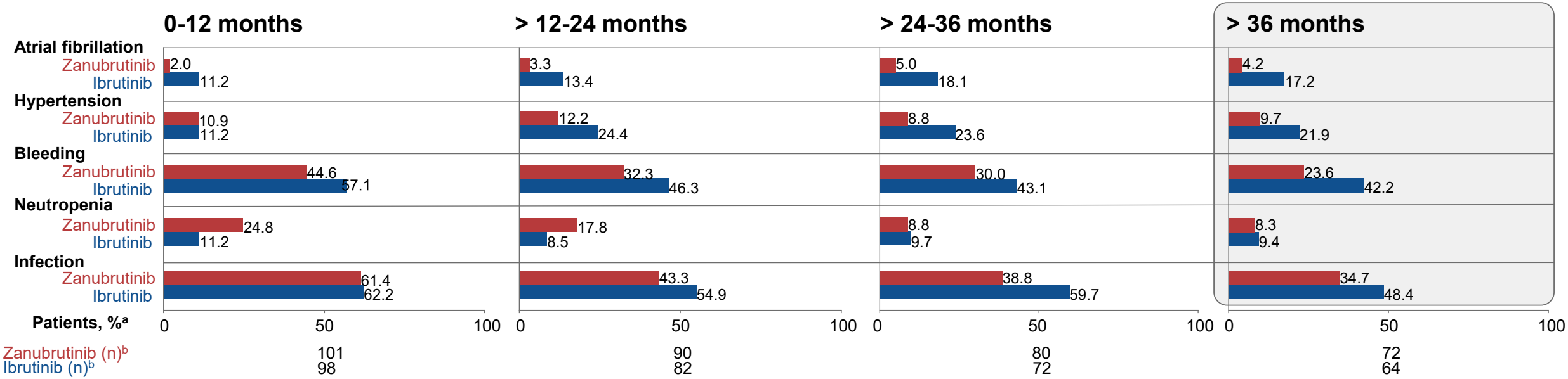
Diarrhea



No. of Patients at Risk:																					
Zanubrutinib	101	85	82	78	76	73	69	65	63	62	60	59	55	53	41	33	16	7	4	1	0
Ibrutinib	98	73	67	60	56	54	54	50	49	46	45	41	39	38	32	18	9	4	2	0	

Data cutoff: October 31, 2021.
[a]Descriptive purpose only, 2-sided *P* value; [b]Events of the same preferred term that occurred within 1 day of the previous event were combined as 1 event. Patients with ongoing or new events in the interval are counted.
AE, adverse event; EAIR, exposure-adjusted incidence rates (persons per 100 person-months).

Prevalence Analysis for AEs of Interest (Cohort 1)



Data cutoff: October 31, 2021.
[a]Percentage is based on N. [b]n is the number of patients who are on treatment in each time interval or who discontinued treatment but the time from first dose date to the earliest date (last dose date +30 days, initiation of new anticancer therapy, end of study, death or cutoff date) is within the time interval.
AE, adverse event.

Conclusions

- Zanubrutinib continued to demonstrate clinically meaningful efficacy in patients with WM
  - A consistent trend of deeper, earlier, and more durable responses CR + VGPR compared with ibrutinib was observed over time
    - Zanubrutinib provided faster and deeper responses in patients with *CXCR4*^{MUT}
    - PFS and OS continued to favor zanubrutinib treatment
    - Responses to zanubrutinib in patients with *MYD88*^{WT} (cohort 2) continued to deepen over time
- Safety advantages of zanubrutinib remained consistent with less off-target activity versus ibrutinib
  - Fewer AEs leading to treatment discontinuation, dose reductions, and deaths occurred in the zanubrutinib arm
  - Cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasm, and pneumonia were lower in patients receiving zanubrutinib
  - Despite a higher rate of neutropenia in the zanubrutinib arm, infection rates were similar and more patients in the ibrutinib arm had Grade ≥ 3 infections

Acknowledgments

We would like to thank the investigators, site support staff, and especially the patients and their caregivers for participating in this study.

This study was sponsored by BeiGene.

Editorial support was provided by Medical Expressions and funded by BeiGene.

Correspondence: rgarcias@usal.es