BTK Inhibitors

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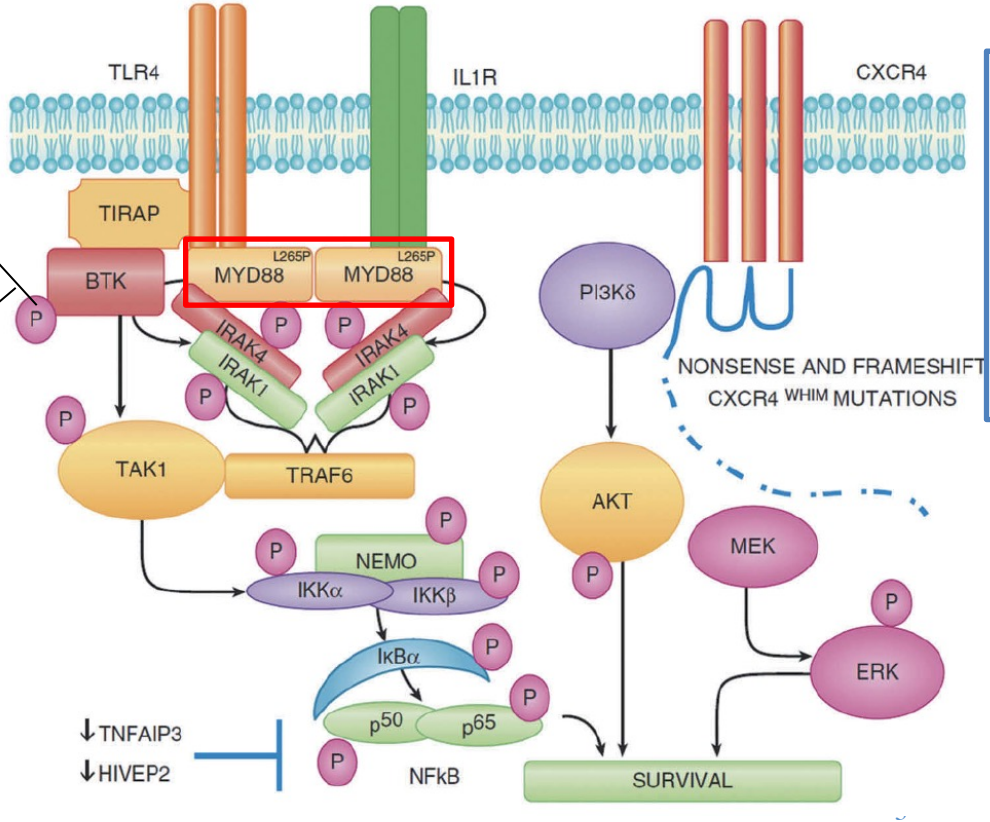
Disclosures of Beatrice Casadei

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Kite-Gilead					x	x	
Novartis					x	x	
Celgene-BMS					x	x	
Janssen						x	
Abbvie					x		
Beone					x		
Lilly					x		
Takeda						x	
Roche					x	x	

Signaling Pathways in Waldenström Macroglobulinemia

- 95-97% MYD88^{L265P}
- 5% MYD88WT

Ibrutinib
Zanubrutinib
Acalabrutinib
Tirabrutinib
Orelabrutinib
Pirtobrutinib
Nemtabrutinib



- 30-40% CXCR4 mutated.
- >40 different CXCR4 mutations (NS vs FS)
- The most frequent mutated region is the aminoacid S338X (both NS and FS mut).

TP53 alterations:
5-15% TN pts
25-30% RR pts

Del6q:
50% (heterozygous loss) in TN

Hunter et al, Blood 2013 ; Treon, et al. N Engl J Med. 2012; Cao et al, Leukemia 2014; Castillo JJ. Expert Rev Hematol, 2019

BTK-Inhibitors Trials in WM

Study	Cohort	Agent (s)	N	Time to Major Resp.	ORR/MRR (%)	≥VGPR (%)	PFS (%)
Ibrutinib							
Pivotal Study	R/R	Ibrutinib	63	2 mo.	91 / 79	30	54 @ 60 mo.
INNOVATE (c)	R/R	Ibrutinib	31	2 mo.	87 / 77	29	40 @ 60 mo.
Phase 2	TN	Ibrutinib	30	1.9 mo.	100 / 87	30	76 @ 48 mo.
INNOV							
Phase 2							
ASPEN- (MYD8							
ASPEN-							
Phase 2							@ 66 mo
Phase 2	TN, R/R	Tirabrutinib	27	1.9 TN; 2.1 R/R	96 / 93	33	93 @ 24 mo.
Phase 2	R/R	Pirtobrutinib	80	N/A	81/ 67 (prior cBTKi) 88/ 88 (cBTKi naïve)	24 (prior cBTKi) 29 (cBTKi naïve)	57 @ 18 mo (prior cBTKi) N/A for cBTKi naïve.

Median ORR: 93%
Major RR: 81%
Median time to major response: 2 mo
≥VGPR: 30%
PFS 76% @ 4 yrs

Treon SP et al, N Engl J Med 2015; Treon SP et al, J Clin Oncol 2021; Trotman J et al, CCR 2021; Castillo JJ et al, Leukemia 2021; Buske C et al, J Clin Oncol 2022; Trotman J et al, Blood 2022; Dimopoulos MA. *J Clin Oncol*, 2023 ; Mato AR et al, Lancet 2021; Owen RG et al, Lancet Hematol 2020; Sekiguchi N et al, Cancer Sci 2022.

CXCR4 Impact on BTK-inhibitors Outcomes in WM

Study	Patient Population	Agent (s)	Time to Major Response ($CXCR^{Mut\ vs.\ WT}$)	Major Response Rate ($CXCR^{Mut\ vs.\ WT}$)	≥VGPR ($CXCR^{Mut\ vs.\ WT}$)	PFS ($CXCR^{Mut\ vs.\ WT}$)
						28% vs. 70%
Phase 2	R/R	Zanubrutinib	N/A	91% vs. 87%	27% vs. 59%	~78% vs.~90% (@ 42 mo.)
ASPEN Cohort 1	TN, R/R	Ibrutinib	6.6 vs. 2.8 mos.	65% vs. 82%	10% vs. 24%	49% vs. 75% (@ 42 mo.)
	TN, R/R	Zanubrutinib	3.4 vs. 2.8 mos.	70% vs. 82%	18% vs. 34%	73% vs. 81% (@ 42 mo.)

$CXCR4^{Mut}$ vs $CXCR4^{WT}$
Median Time to Major Response: (4.2 vs. 1.9 m)
Median Major RR: 71% vs. 87%
Median ≥VGPR: 14% vs. 41%
PFS: 59% vs. 75% @4 years

Treon SP et al, N Engl J Med 2015; Treon SP et al, J Clin Oncol 2021; Trotman J et al, CCR 2021; Castillo JJ et al, Leukemia 2021; Buske C et al, J Clin Oncol 2022; Trotman J et al, Blood 2022; Dimopoulos MA. *J Clin Oncol*, 2023 ; Mato AR et al, Lancet 2021; Owen RG et al, Lancet Hematol 2020; Sekiguchi N et al, Cancer Sci 2022.

Characteristic	All Patients With WM
No. of patients	63
Median age, years (range)	63 (44-86)
Sex	
Male	48 (76)
Female	15 (24)
IPSSWM score	
Low	14 (22)
Intermediate	27 (43)
High	22 (35)
Serum Igs, mg/dL	
Median IgM (range)	3,520 (724-8,390)
IgM > 4,000	26 (41)
Median IgA (range)	26 (0-125)
Median IgG (range)	381 (49-2,770)
Median ANC, μL (range)	3,180 (1,140-10,970)
Hemoglobin level, g/dL	
Median (range)	10.5 (8.2-13.8)
< 11	37 (59)
< 10	25 (40)
Platelet count, μ/L	
Median (range)	214,000 (24,000-459,000)
< 100,000/μL	7 (11)
Serum β_2-microglobulin, mg/L	
Median (range)	3.9 (1.3-14.2)
> 3	45 (71)
> 3.5	35 (56)
Median BM disease involvement	60 (3–95)
Extramedullary disease, cm	
Adenopathy > 1.5	37 (59)
Splenomegaly > 15	7 (11)
Prior treatment status	
Median prior therapies (range)	2 (1-9)
≥ 3 therapies	27 (43)
Refractory to previous therapy	25 (40)

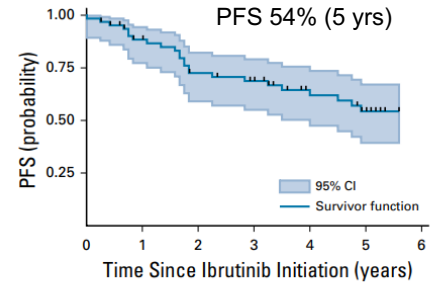
Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

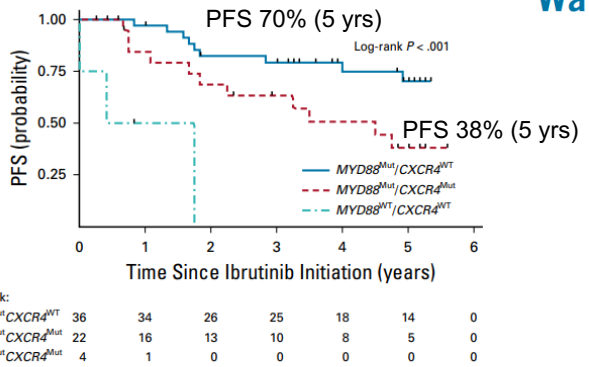
Variable	All	*MYD88*^{Mut} *CXCR4*^{WT}	*MYD88*^{Mut} *CXCR4*^{Mut}	*MYD88*^{WT} *CXCR4*^{WT}	*P*
No. of patients	63	36	22	4	
Overall response rate	57 (90.5)	36 (100.0)	19 (86.4)	2 (50.0)	< .0100
Major response rate	50 (79.4)	35 (97.2)	15 (68.2)	0 (0.0)	< .0001
Categorical responses					
No response	6 (9.5)	0 (0.0)	3 (13.6)	2 (50.0)	< .0001
Minor response	7 (11.1)	1 (2.8)	4 (18.2)	2 (50.0)	
Partial response	31 (49.2)	18 (50.0)	13 (59.1)	0 (0.0)	
Very good partial response	19 (30.2)	17 (47.2)	2 (9.1)	0 (0.0)	
Median time to response, months					
Major response (≥ partial response)	1.8	1.8	4.7	NA	.0200

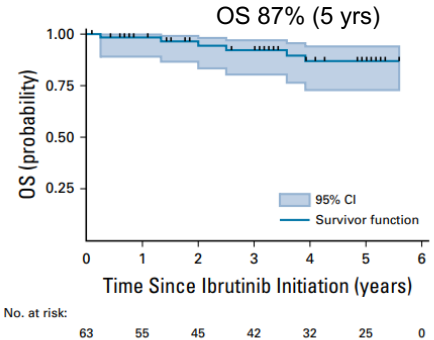
CXCR4 mutational status impacts ORR, MRR, deep of response (VGPR) and the time to MR

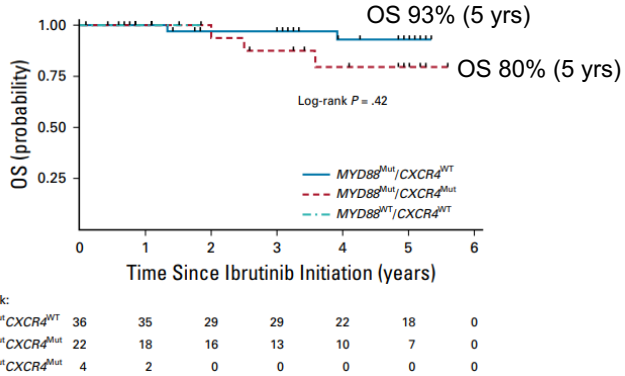
Treon SP. *N Engl J Med*, 2015; 372: 1430-1440 — Treon SP. *J Clin Oncol*, 2021; 39: 565-575

Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia







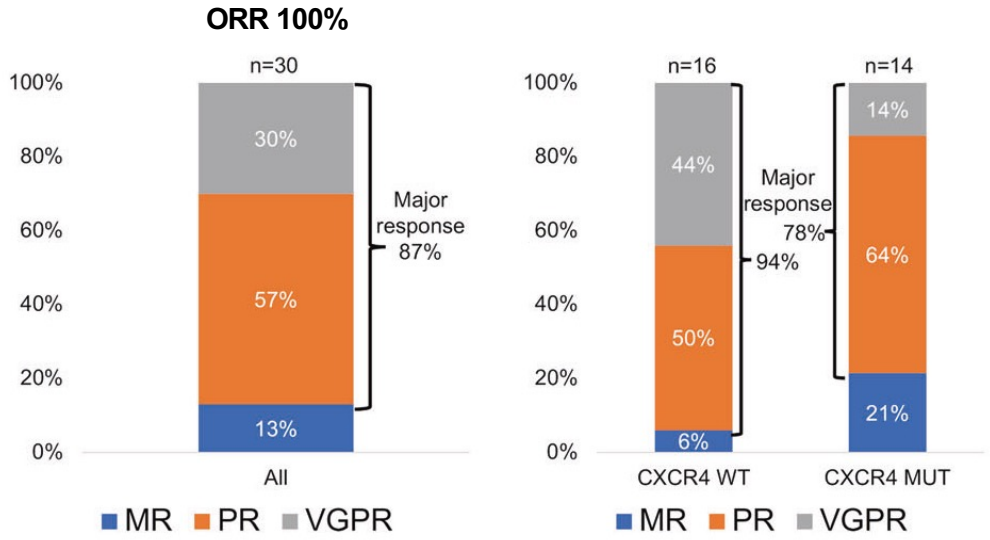


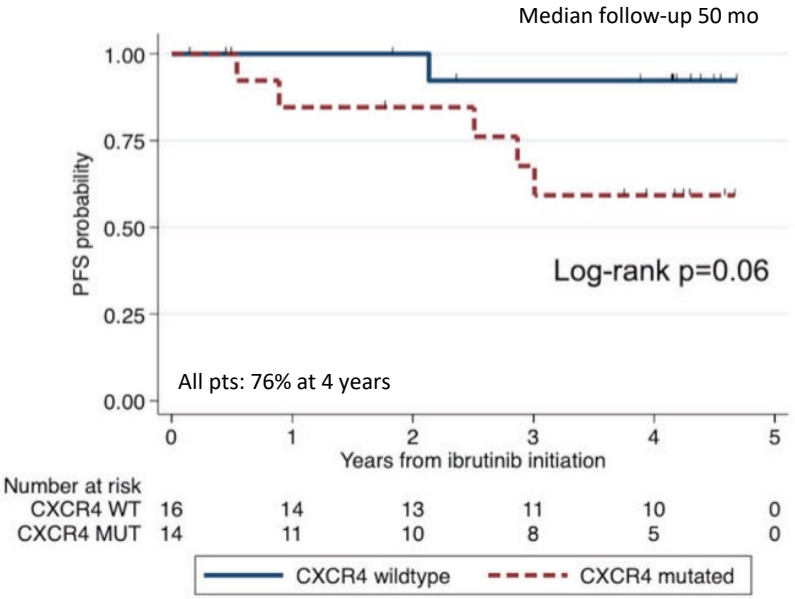
CXCR4 and MYD88 mutational status have an impact on PFS in pts treated with Ibrutinib

Median follow-up: 59 mo

Treon SP. *J Clin Oncol*, 2021; 39: 565-575

Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia





Also in first line CXCR4 mutational status impacts on VGPR, time to MRR and PFS

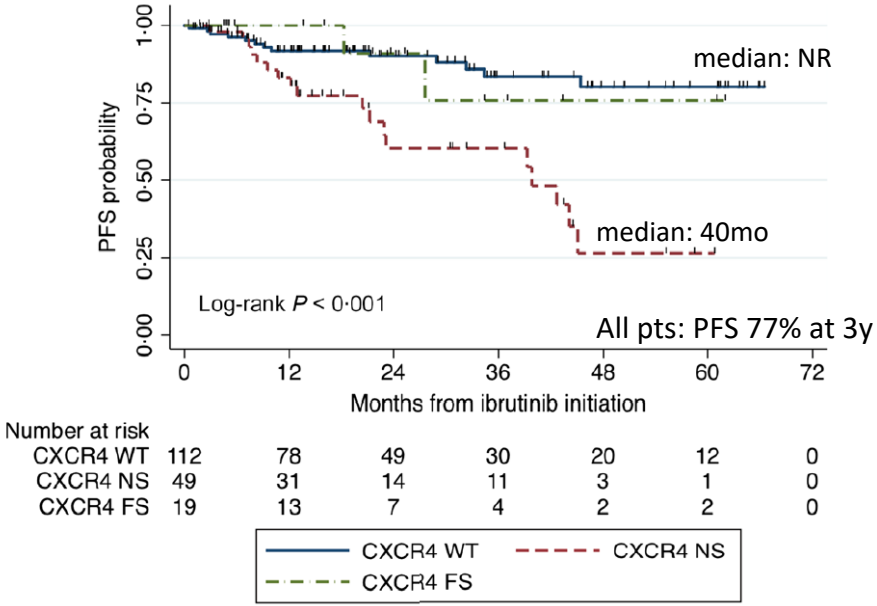
Castillo JJ. *Leukemia*, 2022

180 treated patients (pretreated + untreated):
100% MYD88^{L265P}
38% *CXCR4*^{mut}
27% *CXCR4*^{NS} (nonsense)
11% *CXCR4*^{FS} (frameshift)

CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenström macroglobulinaemia treated with ibrutinib

	Total	*CXCR4*^{WT}	*CXCR4*^{NS}	*CXCR4*^{FS}	*P*-value
All patients					
Very good partial response	44 (25%)	36 (33%)	3 (6%)	5 (26%)	<0·001
Partial response	90 (51%)	56 (52%)	24 (49%)	10 (53%)	
Minor response	31 (18%)	13 (12%)	16 (33%)	2 (11%)	
No response	11 (6%)	3 (3%)	6 (12%)	2 (11%)	
Major response (≥partial)	134 (76%)	92 (85%)	27 (55%)	15 (79%)	<0·001
Previously treated					
Very good partial response	33 (26%)	28 (36%)	2 (6%)	3 (21%)	0·002
Partial response	61 (49%)	37 (44%)	15 (45%)	19 (64%)	
Minor response	23 (18%)	11 (14%)	11 (33%)	1 (7%)	
No response	8 (6·4)	2 (3%)	5 (15%)	1 (7%)	
Major response (≥partial)	94 (75%)	65 (83%)	17 (51%)	12 (86%)	0·001
Previously untreated					
Very good partial response	11 (20%)	8 (24%)	1 (6%)	2 (40%)	0·28
Partial response	30 (55%)	20 (59%)	9 (56%)	1 (20%)	
Minor response	10 (18%)	4 (12%)	5 (31%)	1 (20%)	
No response	4 (7%)	2 (6%)	1 (6%)	1 (20%)	
Major response (≥partial)	41 (75%)	28 (82%)	10 (63%)	3 (60%)	0·24

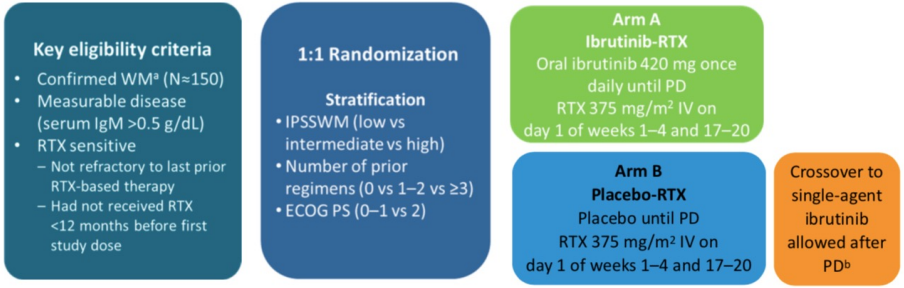
CXCR4^{WT}, *CXCR4* wild type; *CXCR4*^{NS}, *CXCR4* nonsense mutation; *CXCR4*^{FS}, *CXCR4* frameshift mutation.



Median follow-up 25 mo

Castillo JJ. Br J Haematol, 2019

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study



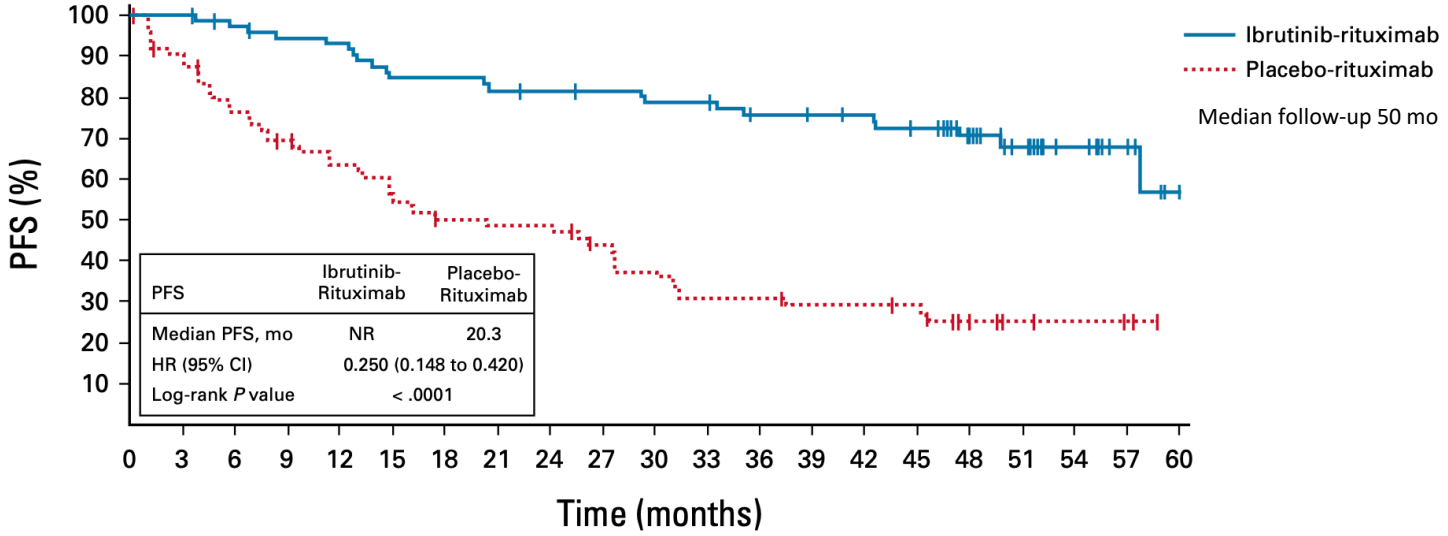
- **Endpoints:** PFS and response rates by IRC, OS, Hgb improvement, TTNT, safety
- At study closure, patients without PD could continue ibrutinib in an extension program

TABLE 1. Demographics and Clinical Characteristics of Patients at Baseline

Characteristic	Ibrutinib-Rituximab (n = 75)	Placebo-Rituximab (n = 75)
Median age, years (range)	70 (36-89)	68 (39-85)
Male, No. (%)	45 (60)	54 (72)
IPSSWM, No. (%)		
Low	15 (20)	17 (23)
Intermediate	33 (44)	28 (37)
High	27 (36)	30 (40)
Median Hgb, g/dL (range)	10.5 (6.9-15.5)	10.0 (6.6-16.1)
Baseline Hgb ≤ 11.0 g/dL, No. (%)	44 (59)	50 (67)
Median serum IgM, g/L (range)	33 (6-78)	32 (6-83)
No. of prior systemic therapies, No. (%)		
0	34 (45)	34 (45)
1-2	34 (45)	36 (48)
≥ 3	7 (9)	5 (7)
Genotype, No. (%)		
MYD88^{L265P}/*CXCR4*^{WT}	32 (43)	35 (47)
MYD88^{L265P}/*CXCR4*^{WHIM}	26 (35)	23 (31)
MYD88^{WT}/*CXCR4*^{WT}	11 (15)	9 (12)
Unknown[a]	6 (8)	8 (11)
Bone marrow infiltration: percentage of cellularity, median (range)	80 (25-100)	80 (2-100)

Buske C. J Clin Oncol, 2022

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

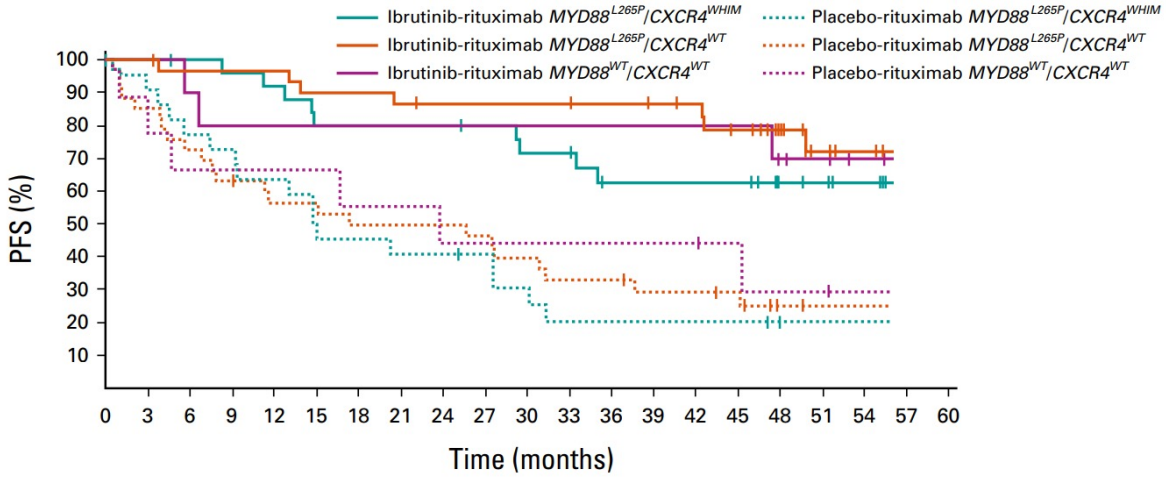


No. at risk:

Ibrutinib-rituximab	75	73	69	67	66	60	60	58	57	56	54	54	46	48	47	44	32	22	15	7
Placebo-rituximab	75	64	54	48	43	39	33	32	31	27	23	19	19	17	17	15	7	4	3	2

Buske C. *J Clin Oncol*, 2022

Ibrutinib Plus Rituximab Versus Placebo Plus Rituximab for Waldenström's Macroglobulinemia: Final Analysis From the Randomized Phase III iNNOVATE Study

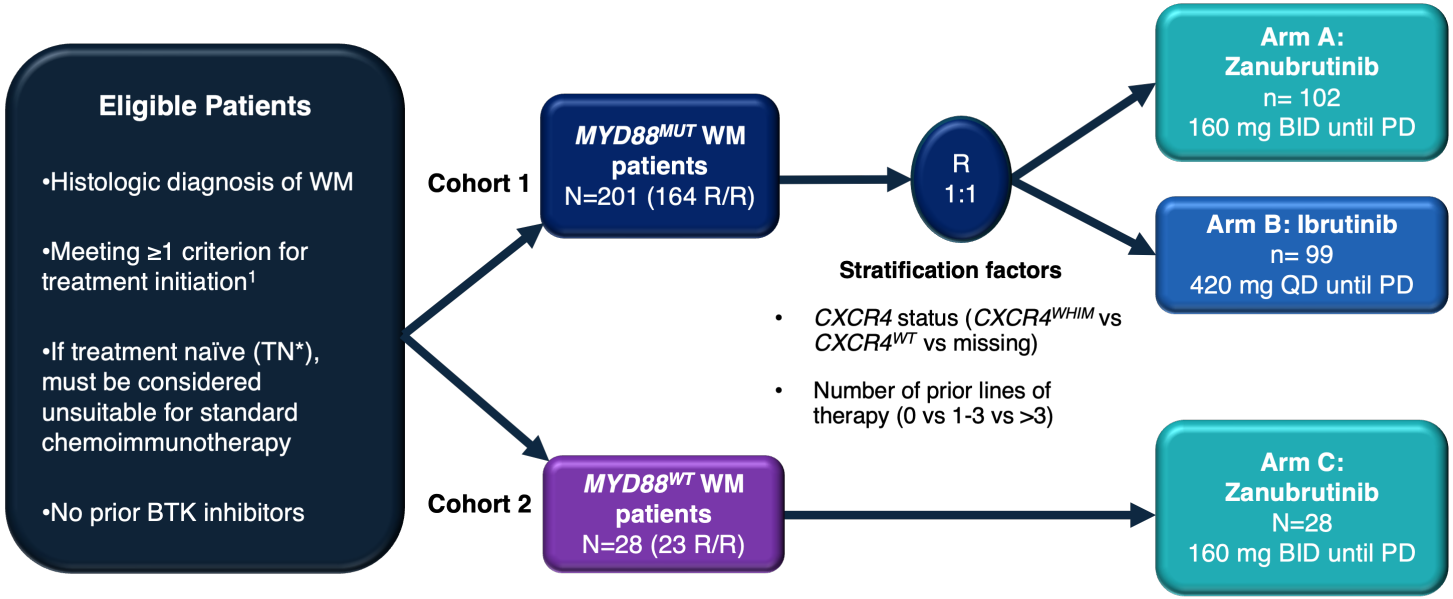


No. at risk:

Ibrutinib-rituximab $MYD88^{L265P}/CXCR4^{WHIM}$	26	26	25	24	23	20	20	20	20	19	17	17	13	13	13	13	8	7	5	2	0
Ibrutinib-rituximab $MYD88^{L265P}/CXCR4^{WT}$	32	31	29	29	29	27	27	26	25	25	25	25	24	23	22	19	15	8	5	3	0
Ibrutinib-rituximab $MYD88^{WT}/CXCR4^{WT}$	11	10	9	8	8	8	8	8	8	8	8	8	8	8	8	8	6	5	3	2	0
Placebo-rituximab $MYD88^{L265P}/CXCR4^{WHIM}$	23	20	17	16	14	11	10	9	9	8	6	4	4	4	4	4	2	1	1	1	0
Placebo-rituximab $MYD88^{L265P}/CXCR4^{WT}$	35	28	23	20	17	17	15	15	15	14	12	10	10	8	8	7	3	1	1	1	0
Placebo-rituximab $MYD88^{WT}/CXCR4^{WT}$	9	8	6	6	6	36	5	5	4	4	4	4	4	4	4	3	2	2	1	0	

Buske C. *J Clin Oncol*, 2022

Zanubrutinib Versus Ibrutinib in Symptomatic Waldenström Macroglobulinemia: Final Analysis From the Randomized Phase III ASPEN Study



EUDRACT 2016-002980-33; NCT03053440

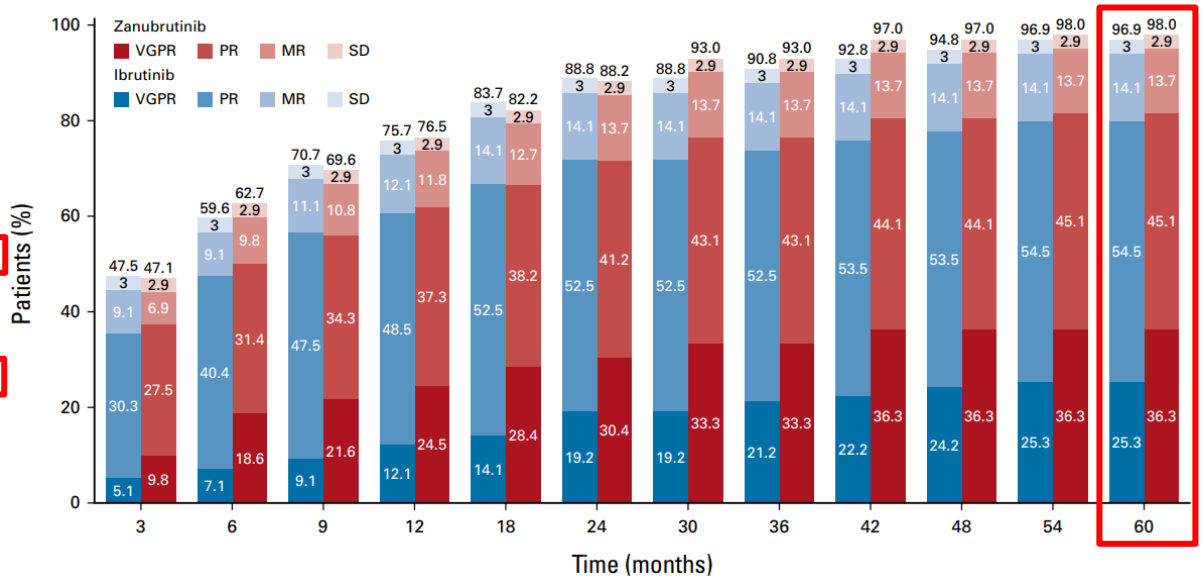
Primary endpoint:
CR or VGPR, per modified IWWM-6, by **independent review**

Secondary Endpoints:
1) MRR (≥PR)
2) PFS
3) Duration of response
4) Safety

median follow-up cohort 1: 44.4 mo and cohort 2: 42.9 mo

Dimopoulos MA. *J Clin Oncol*, 2023; Dimopoulos et al, IWWM-12, 2024

Characteristic	Cohort 1 (*) Ibrutinib (n = 99)	Cohort 1 (*) Zanubrutinib (n = 102)	Cohort 2 (**) Zanubrutinib (n = 28)
Age, median (range)	70 (38-90)	70 (45-87)	72 (39-87)
Age 65 years or older, No. (%)	70 (70.7)	61 (59.8)	19 (67.9)
Age 75 years or older, No. (%)	22 (22.2)	34 (33.3)	12 (42.9)
Male sex, No. (%)	65 (65.7)	69 (67.6)	14 (50.0)
Prior lines of therapy, No. (%)			
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, No. (%)			
CXCR4^{WT}	72 (72.7)	65 (63.7)	19 (67.9)
CXCR4^{MUT}	20 (20.2)	33 (32.4)	1 (3.6)
CXCR4^{FS}	7 (7.1)	19 (18.6)	1 (3.6)
CXCR4^{NS}	13 (13.1)	14 (13.7)	0
Unknown[b]	7 (7.1)	4 (3.9)	8 (28.6)
IPSS WM, No. (%)			
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, No. (%)	53 (53.5)	67 (65.7)	15 (53.6)
Baseline IgM (g/L, central lab), median (range)	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 (0-90)
Extramedullary disease,[a] No. (%)	66 (66.7)	63 (61.8)	16 (57.1)



(ibrutinib - zanubrutinib) (zanubrutinib)

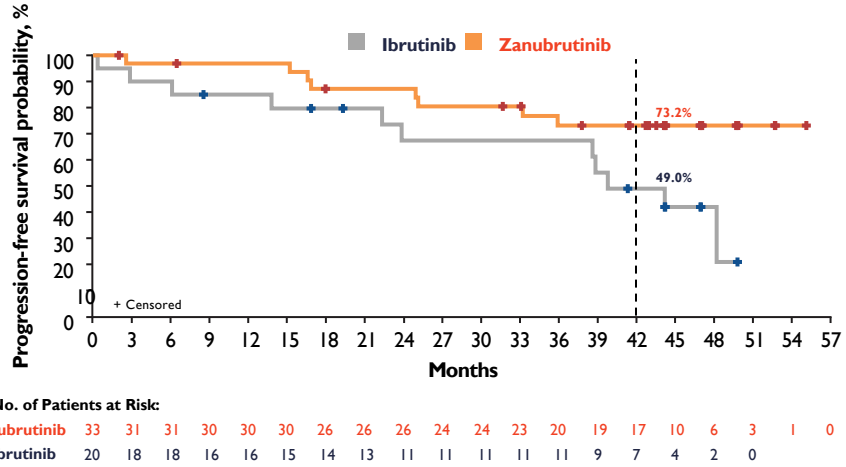
Cohort 1 best ORR: 94% - 95%
Cohort 1 best MRR: 80% - 81%
Cohort 1 best VGPR: 25% - 36%
Cohort 1 42 mo-PFS: 70% - 78%

Cohort 2 best ORR: 81%
Cohort 2 best MRR: 65%
Cohort 2 best VGPR: 30.8%
Cohort 2 42 mo-PFS: 54%

(*) All patients *MYD88*^{mut}
(**) All patients *MYD88*^{wt}

Dimopoulos MA. *J Clin Oncol*, 2023

Phase 3 ASPEN Trial: Focus on CXCR4^{mut}



	Zanubrutinib	Ibrutinib
Events, n (%)	8 (24.2)	11 (55.0)
HR (95% CI)	0.50 (0.20, 1.29)	

	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

In patients with *CXCR4^{MUT}* by NGS, zanubrutinib demonstrated deeper and faster responses, as well as favorable PFS, compared with ibrutinib

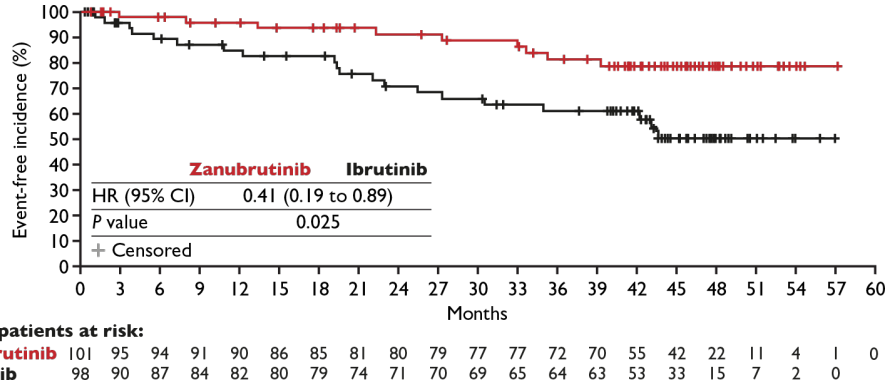
Dimopoulos MA. *J Clin Oncol*, 2023

Phase 3 ASPEN Trial: Focus on Safety

Overall Safety Summary

Category, n (%)	Cohort 1		Cohort 2
	Ibrutinib (n98)	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)	3 (3.0)	3 (10.7)
AE leading to tx 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)

Time to Treatment Discontinuations Due to AEs



Dimopoulos MA. *J Clin Oncol*, 2023

Most Common Adverse Events (Cohort 1)

	Any grades (≥20%)		Grade ≥3(≥5%)	
AEs,[a] n (%)	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Upper respiratory tract infection	32 (32.7)	33 (32.7)	1 (1.0)	0
Muscle spasms*	**28 (28.6)***	12 (11.9)	1 (1.0)	0
Contusion	27 (27.6)	19 (18.8)	0	0
Arthralgia	24 (24.5)	24 (23.8)	0	3 (3.0)
Hypertension	24 (24.5)	15 (14.9)	**19 (19.4)**	10 (9.9)
Peripheral edema	21 (21.4)	18 (17.8)	0	0
Epistaxis	21 (21.4)	17 (16.8)	0	1 (1.0)
Atrial fibrillation*	**21 (21.4)***	7 (6.9)	6 (6.1)*	2 (2.0)
Cough	20 (20.4)	19 (18.8)	0	0
Fatigue	19 (19.4)	26 (25.7)	1 (1.0)	1 (1.0)
Pneumonia*	**18 (18.4)***	5 (5.0)	**10 (10.2)***	1 (1.0)
Syncope	8 (8.2)	5 (5.0)	6 (6.1)	5 (5.0)

Bold text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms. *Descriptive purposes only, 1-sided P<0.025 in rate difference in all grades and/or grade ≥3. [a]Preferred terms by Medical Dictionary for Regulatory Activities v24.0; excluding cytopenia.

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Adverse Events of Interest (Cohort 1)

AEs,[a] n (%)	All grades		Grade ≥3	
	Ibrutinib (n=98)	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=101)
Infection	78 (79.6)	80 (79.2)	**27 (27.6)**	22 (21.8)
Bleeding	61 (62.2)	56 (55.4)	10 (10.2)	9 (8.9)
Diarrhea	**34 (34.7)**	23 (22.8)	2 (2.0)	3 (3.0)
Hypertension*	**25 (25.5)**	15 (14.9)	**20 (20.4)***	10 (9.9)
Atrial fibrillation/flutter*	**23 (23.5)***	8 (7.9)	**8 (8.2)***	2 (2.0)
Anemia	22 (22.4)	18 (17.8)	6 (6.1)	**12 (11.9)**
Neutropenia*[b]	20 (20.4)	**35 (34.7)***	10 (10.2)	**24 (23.8)***
Thrombocytopenia	17 (17.3)	17 (16.8)	6 (6.1)	11 (10.9)
Second primary malignancy/ Non-Skin Cancers	17 (17.3)/ 6 (6.1)	17 (16.8)/ 6 (5.9)	3 (3.1)/ 3 (3.1)	6 (5.9)/ 4 (4.0)

Bold text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
*Descriptive purposes only, 1-sided P<0.025 in rate difference in all grades and/or grade ≥3.
[a]AE categories (grouped terms) of preferred terms by Medical Dictionary for Regulatory Activities v24.0.
[b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsi

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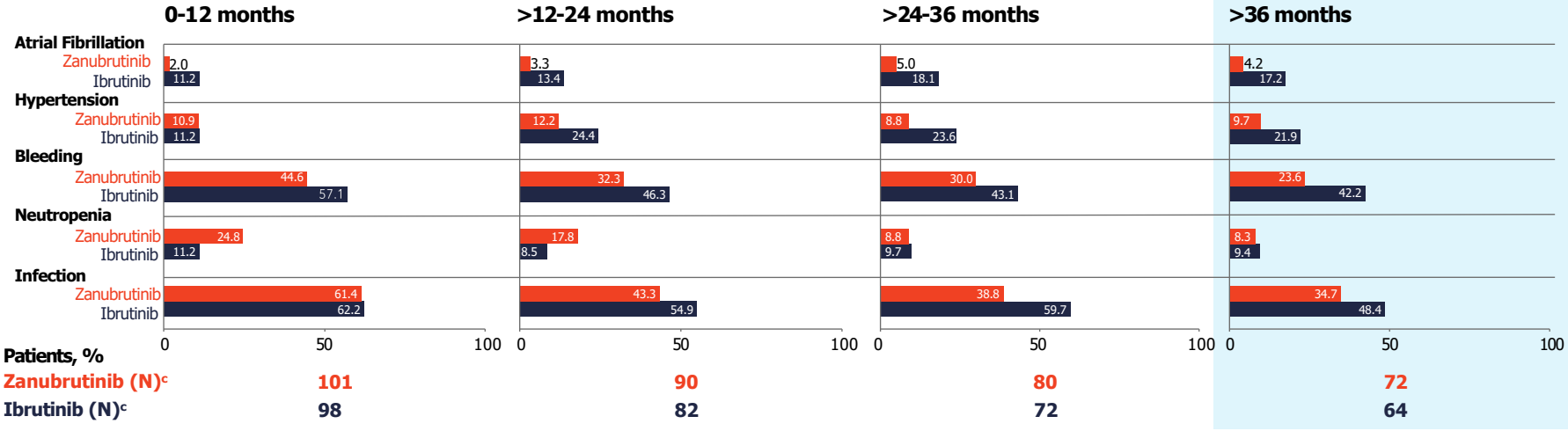
Prevalence Analysis for AEs of Interest



[a]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. [b]Percentage is based on N. [c]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.

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Real World Data on Zanubrutinib in WM

	US	ISRAEL	ITALY
N° of patients, n	50	13	99
Age, median (IQR)	72 (47-93)	71 (50–85)	77 (70-85)
R/R, n (%)	33 (66)	12 (92)	63 (64)
TN, n (%)	17 (34)	1 (8)	36 (36)
ORR, %	85	83	89.7
VPGR, %	28	8	23 (75 MRR)
Median FU, mo	12.9	19.6	15

Frustaci A et al, ASH2024, Castillo EJ et al, Hematol 2023; Itchaki, Acta Hematologica 2025

Conclusions

Zanubrutinib, with exploratory long-term follow-up, continued to demonstrate clinically meaningful efficacy in patients with WM

- Although **not statistically significant at primary analysis**, 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 CXCR4MUT
  - PFS and OS continued to favor zanubrutinib treatment
- At median follow-up of nearly 4 years, 66% of patients remain on treatment with zanubrutinib versus 52% with ibrutinib
- Responses to zanubrutinib in patients with MYD88WT (cohort 2) continued to deepen over time

With longer follow-up, safety advantages of zanubrutinib remained consistent with less off-target activity compared with ibrutinib

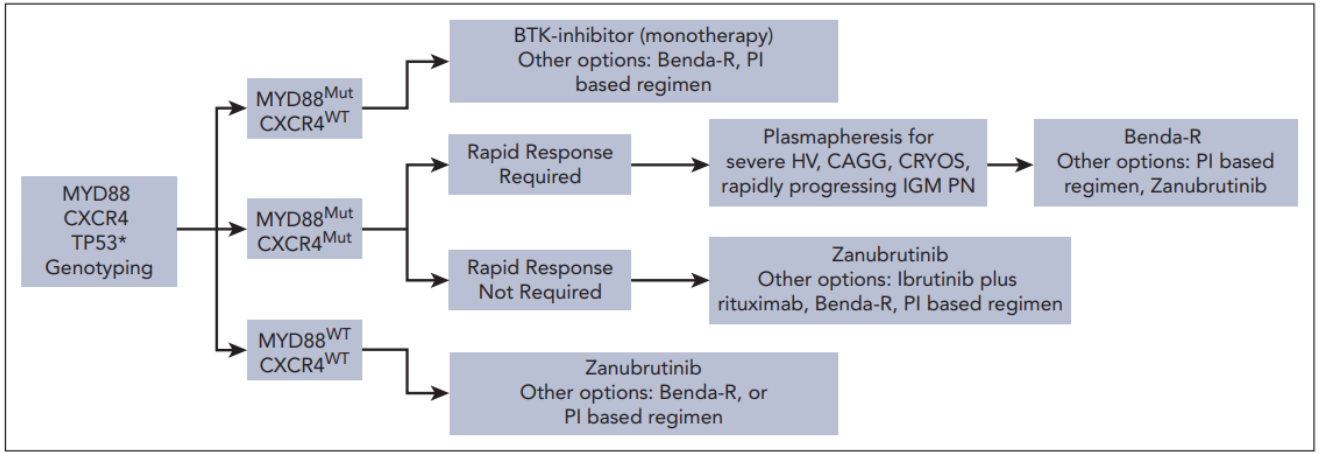
- Fewer AEs leading to treatment discontinuation, dose reductions, and deaths occurred in the zanubrutinib arm
- Cumulative incidences of atrial fibrillation, diarrhea, hypertension, muscle spasm, and pneumonia were lower in patients receiving zanubrutinib
- Despite a higher rate of neutropenia in the zanubrutinib arm, infection rates were similar and more patients in the ibrutinib arm had grade ≥3 infections

AE=adverse event, CR=complete response, CXCR4=C-X-C motif chemokine receptor 4, MUT=mutant, OS=overall survival, PFS=progression-free survival, VGPR=very good partial response, WM=Waldenström's macroglobulinemia, WT=wild type.

Summary

- **Targeted action**: BTKi act on BTK, directly activated by MYD88 mutations.
- **Rapid efficacy**: Improve hemoglobin, reduce IgM, and induce responses within 1–4 months.
- **Genetic sensitivity**: Most effective in MYD88mut / CXCR4wt subgroups.
- **Next-gen advantage**: Zanubrutinib overcomes ibrutinib limitations in MYD88wt / CXCR4mut cases.
- **Excellent tolerability**: High adherence, low discontinuation, reduced cardiovascular toxicity.
- **Age-inclusive**: Suitable for elderly and younger patients avoiding alkylator-related risks.
- **Safer than chemo**: Lower hematologic, infectious, and neurotoxic risks.
- **Key role**: Preferred option for relapse after frontline chemo-immunotherapy.

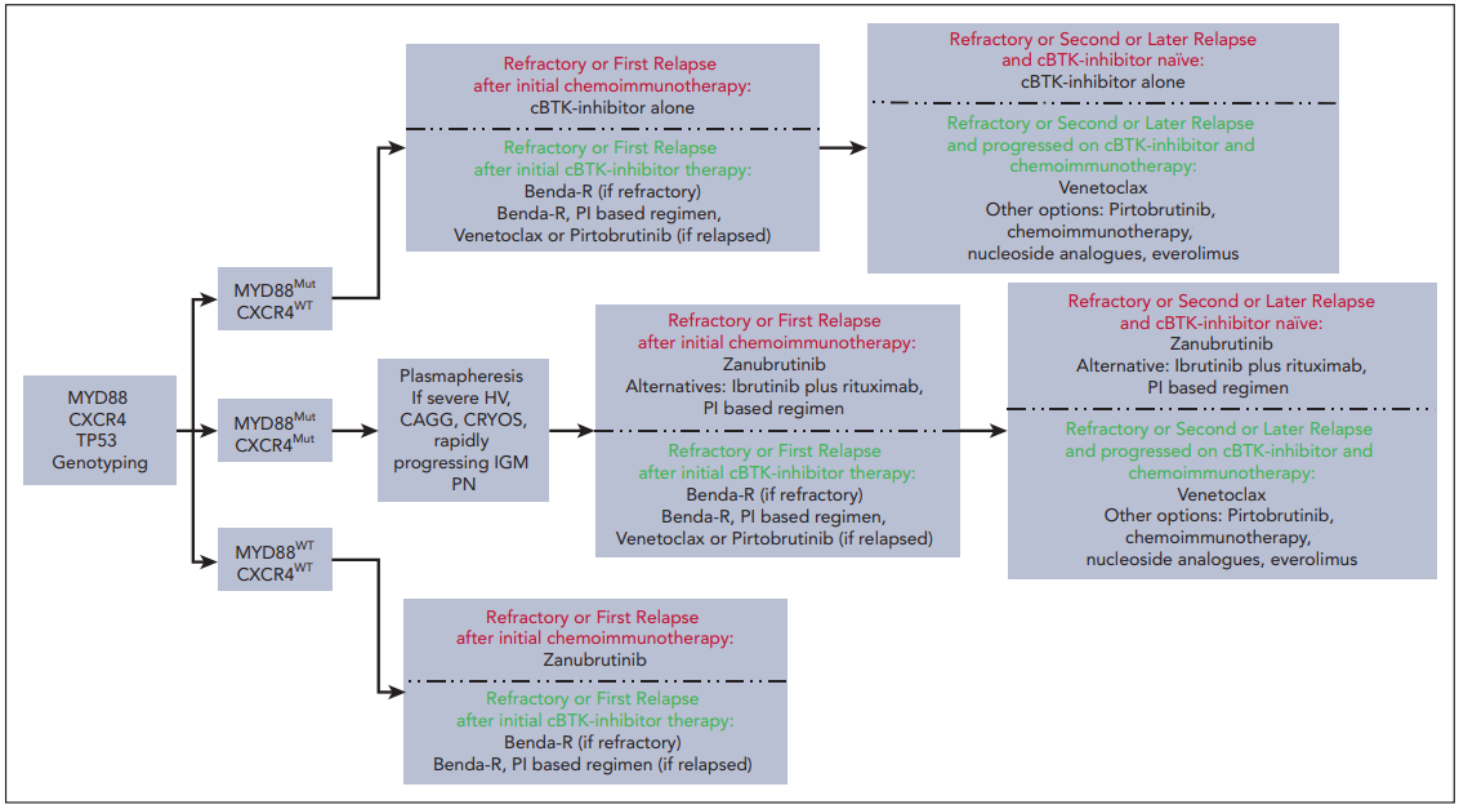
Choosing Treatment According to Presentation and Genotype: Frontline Options



	Preference	Alternative
BTKi options for initial therapy		
Convenience/compliance	Ibrutinib Zanubrutinib	Acalabrutinib
Deep IgM response needed (ie, IgM demyelinating neuropathy, cryoglobulinemia, and cold agglutinemia)	Zanubrutinib	Ibrutinib Acalabrutinib
BNS	Ibrutinib	Zanubrutinib
History or predisposition to arrythmia	Zanubrutinib	
History or predisposition to bleeding	Zanubrutinib	
Neutropenic or pancytopenic	Ibrutinib	
$MYD88^{WT}$	Zanubrutinib	
$CXCR4^{Mut}$	Zanubrutinib	Ibrutinib plus rituximab
TP53 alteration	Zanubrutinib	Ibrutinib
BTKi options for switchover		
Intolerant to ibrutinib for adverse events other than atrial fibrillation	Dose-reduction of Ibrutinib Zanubrutinib Acalabrutinib	Pirtobrutinib
Intolerant to ibrutinib due to atrial fibrillation	Zanubrutinib	Pirtobrutinib
Acquired resistance to a cBTKi	Pirtobrutinib	

Buske C. *Semin Hematol*, 2023; 60: 73-79 — Treon SP. *Blood*, 2024; 143: 1702-1712

Recommendations For Later Treatment Lines According To Previous Therapy



Buske C. *Semin Hematol*, 2023; 60: 73-79 — Treon SP. *Blood*, 2024; 143: 1702-1712

What’s Next?

TX NAÏVE:
Benda+Rit+Acala (Ph 2)
Benda+Rit+Zanu (Ph 2)
Ibrutinib + ixazomib

RR:
Pirtobrutinib (Ph 1/2)
Pirto+Ven(Ph 2)
Nemtabrutinib
Sonrotoclax+Zanu
Ibrutinib + ixazomib
Ibrutinib+ulocuplomab
BTK degrader