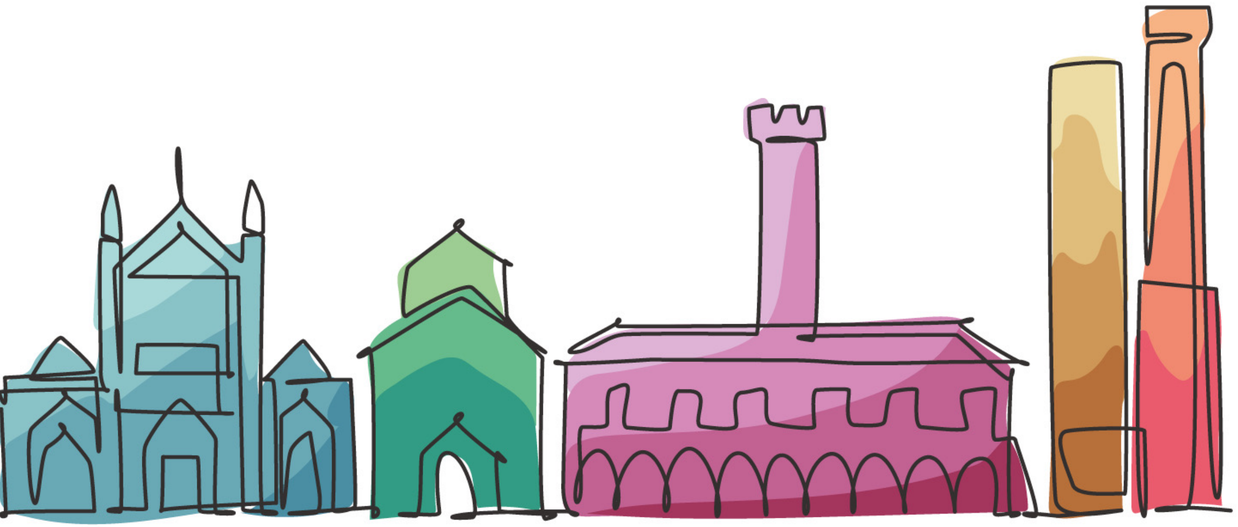
PRECEPTORSHIP



Un confronto sulla gestione delle malattie linfoproliferative al Sant'Orsola di Bologna

Bologna, NH DE LA GARE, 18 settembre 2025

Management ed approccio terapeutico dei pazienti con malattia di Waldenstrom e linfoma della zona marginale in prima linea e dei pazienti ricaduti/refrattari

Cinzia Pellegrini
IRCCS AOU Bologna

Disclosure

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche					**x**		**x**
Gilead					**x**		**x**
Takeda						**x**	
Janssen-Cilag						**x**	
Abbvie					**x**		**x**
Beigene					**x**		

Waldenstrom Macroglobulinemia: 2025 Update

MYD88 Directed Pro-survival Signaling in WM

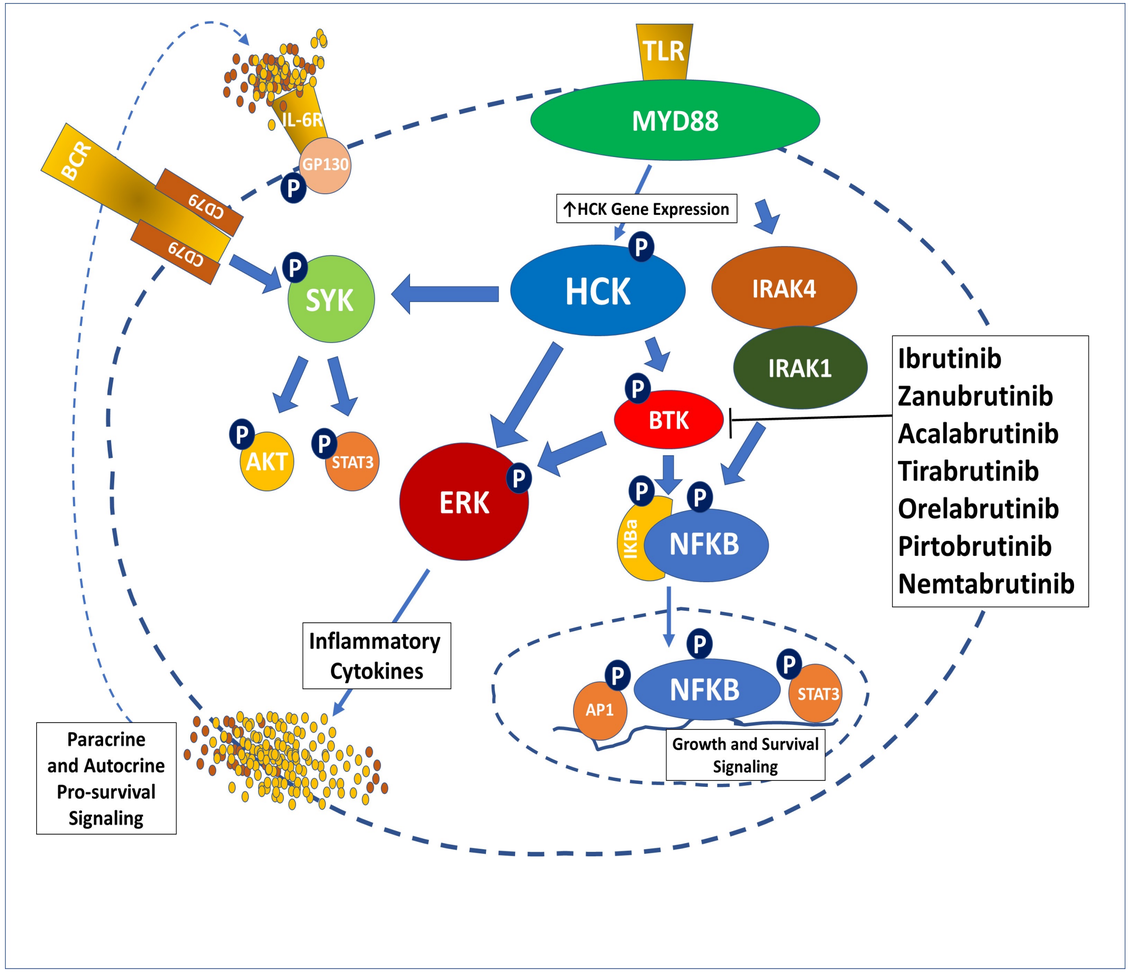
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D., Lian Xu, M.S., Guang Yang, Ph.D., Yangsheng Zhou, M.D., Ph.D., Xia Liu, M.D., Yang Cao, M.D., Patricia Sheehy, N.P., Robert J. Manning, B.S., Christopher J. Patterson, M.A., Christina Tripsas, M.A., Luca Arcaini, M.D., Geraldine S. Pinkus, M.D., Scott J. Rodig, M.D., Ph.D., Aliyah R. Sohani, M.D., Nancy Lee Harris, M.D., Jason M. Laramie, Ph.D., Donald A. Skifter, Ph.D., Stephen E. Lincoln, Ph.D., and Zachary R. Hunter, M.A.

MYD88 mutations occur in 95-97% WM Patients



Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

Plenary Paper

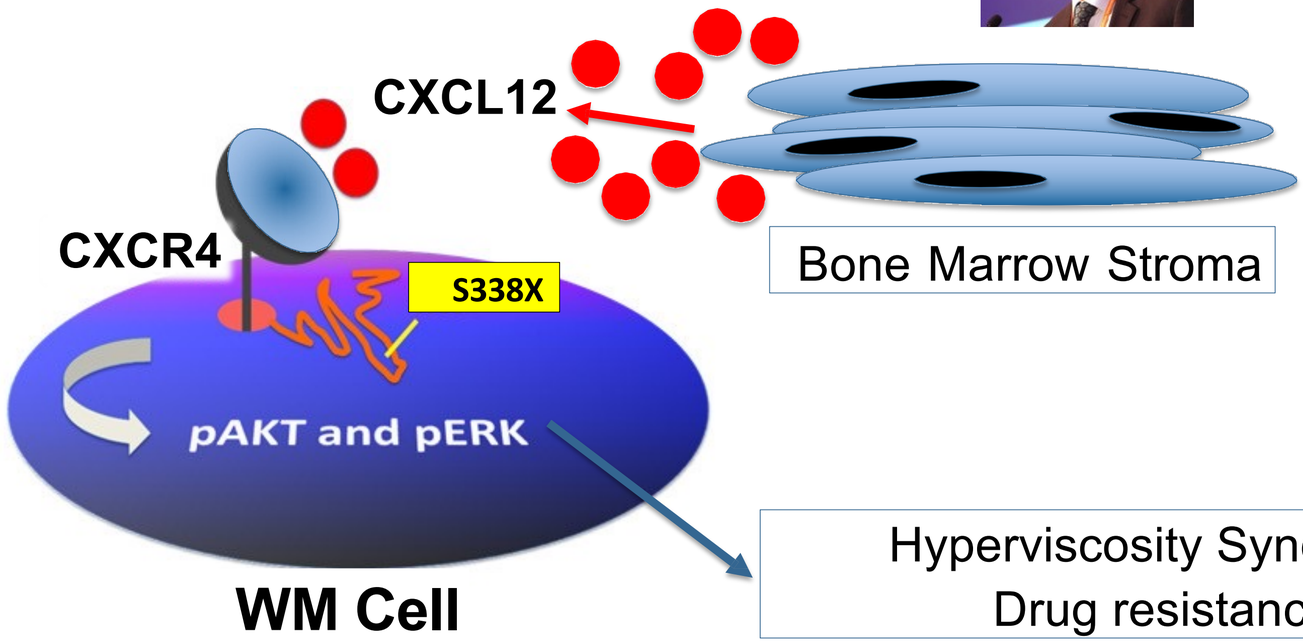
LYMPHOID NEOPLASIA

The genomic landscape of Waldenström macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis

Zachary R. Hunter,[1,2] Lian Xu,[1] Guang Yang,[1] Yangsheng Zhou,[1] Xia Liu,[1] Yang Cao,[1] Robert J. Manning,[1] Christina Tripsas,[1] Christopher J. Patterson,[1] Patricia Sheehy,[1] and Steven P. Treon[1,3]

[1]Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [2]Department of Pathology and Laboratory Medicine, Boston University School of Graduate Medical Sciences, Boston, MA; and [3]Harvard Medical School, Boston, MA

- 30-40% of WM patients have CXCR4 mutations
  - >40 different CXCR4 mutations, most common is S338X.



Hyperviscosity Syndrome
Drug resistance

Hunter et al, Blood 2013; Treon et al, Blood 2014; Roccarro et al, Blood 2014; Cao et al, Leukemia 2014.

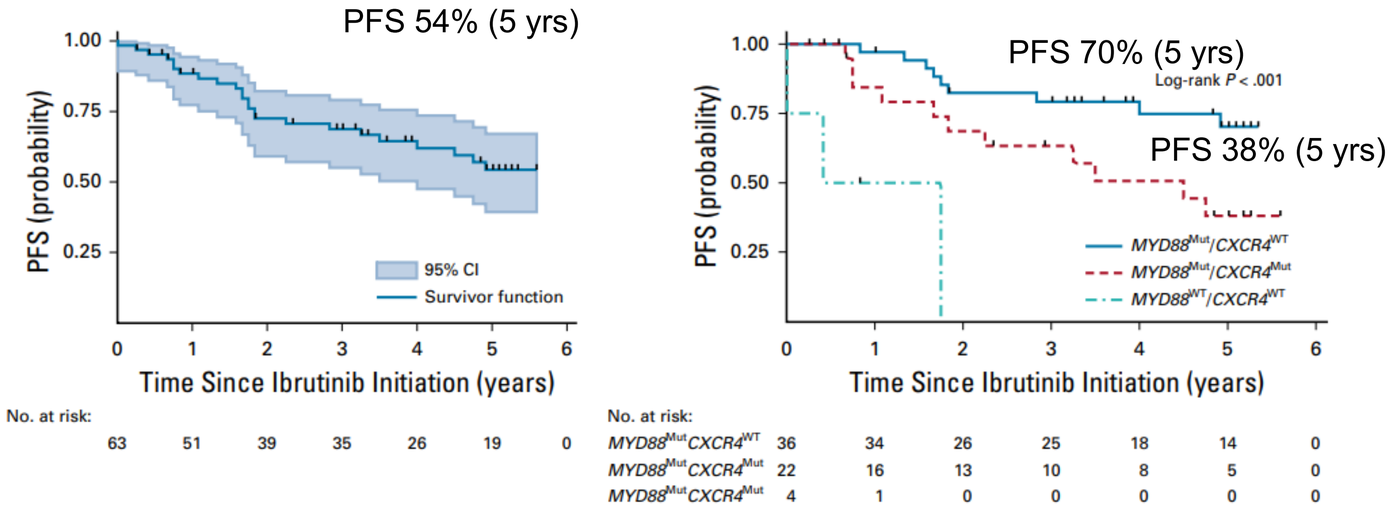
Characteristic	All Patients With WM
No. of patients	63
Median age, years (range)	63 (44-86)
Sex	
Male	48 (76)
Female	15 (24)
IPSSWM score	
Low	14 (22)
Intermediate	27 (43)
High	22 (35)
Serum Igs, mg/dL	
Median IgM (range)	3,520 (724-8,390)
IgM > 4,000	26 (41)
Median IgA (range)	26 (0-125)
Median IgG (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)

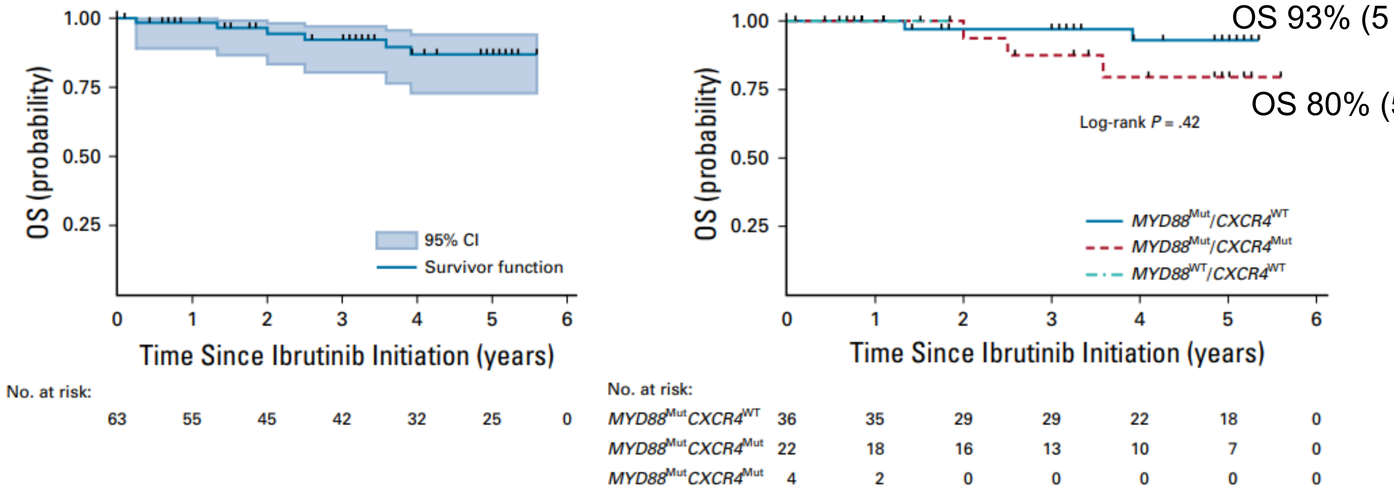
Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenström Macroglobulinemia

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

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

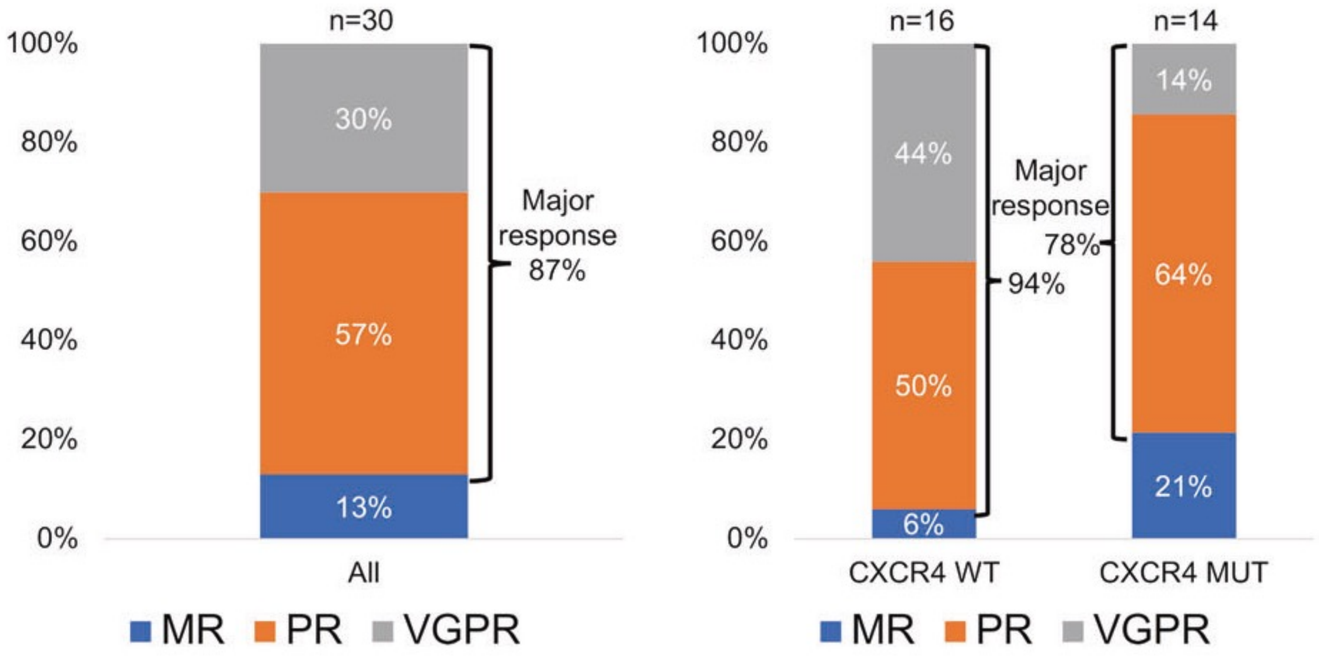


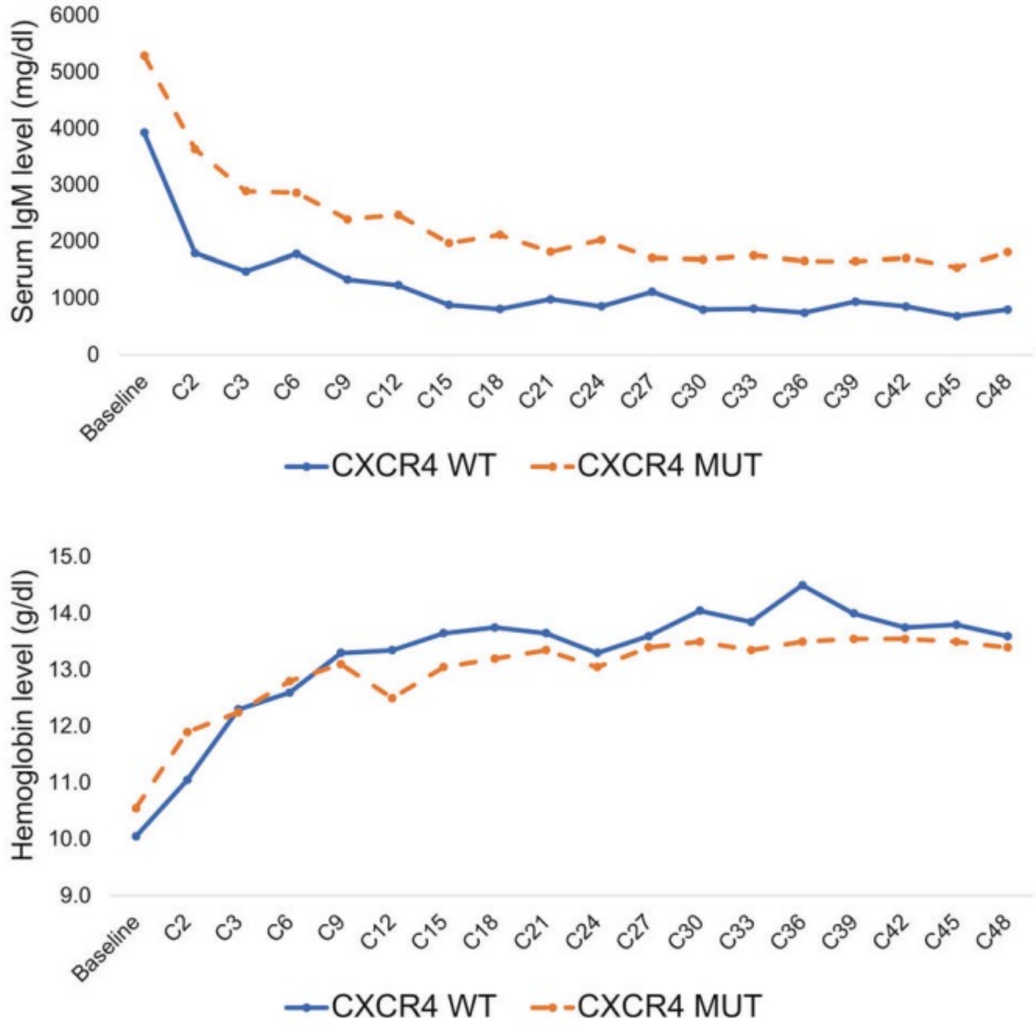


Treon SP. *J Clin Oncol*, 2021; 39: 565-575

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

ORR 100%

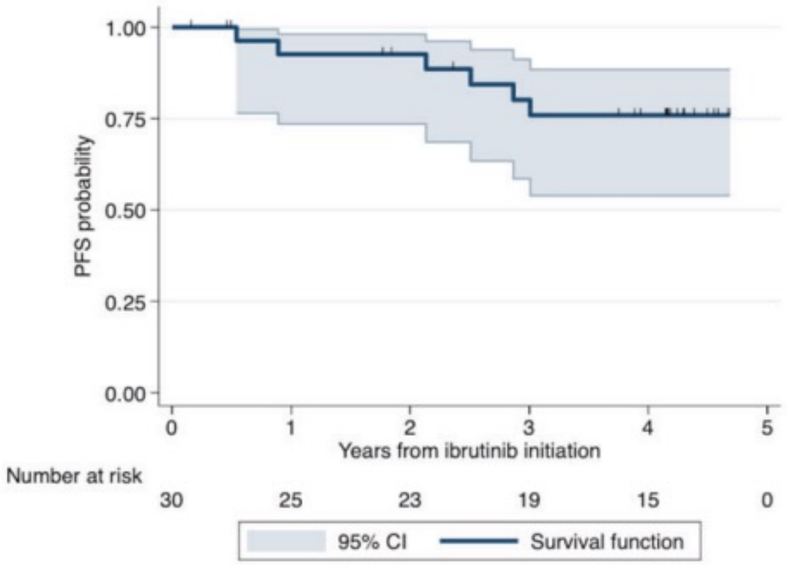


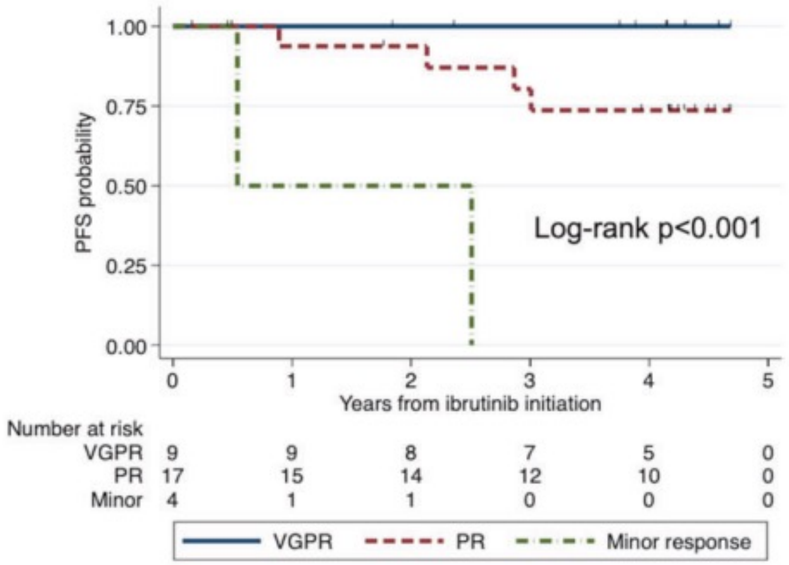


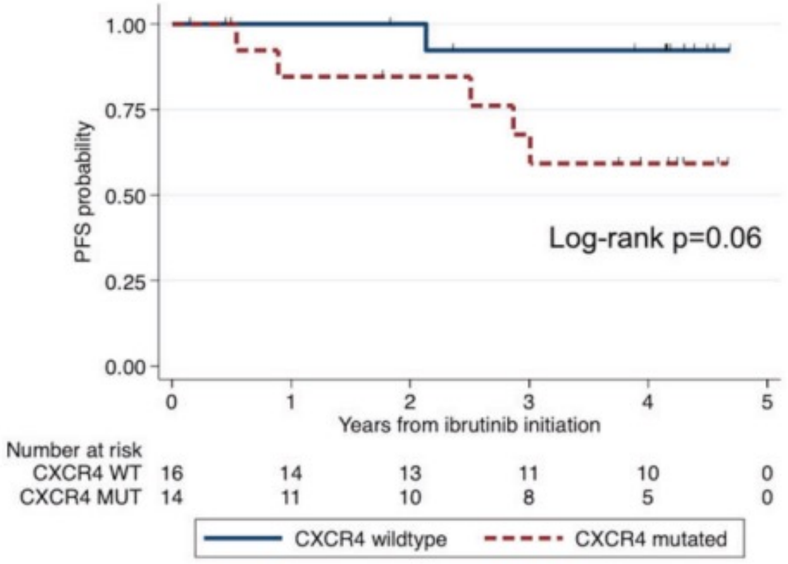
Castillo JJ. *Leukemia*, 2022; 36: 532-539

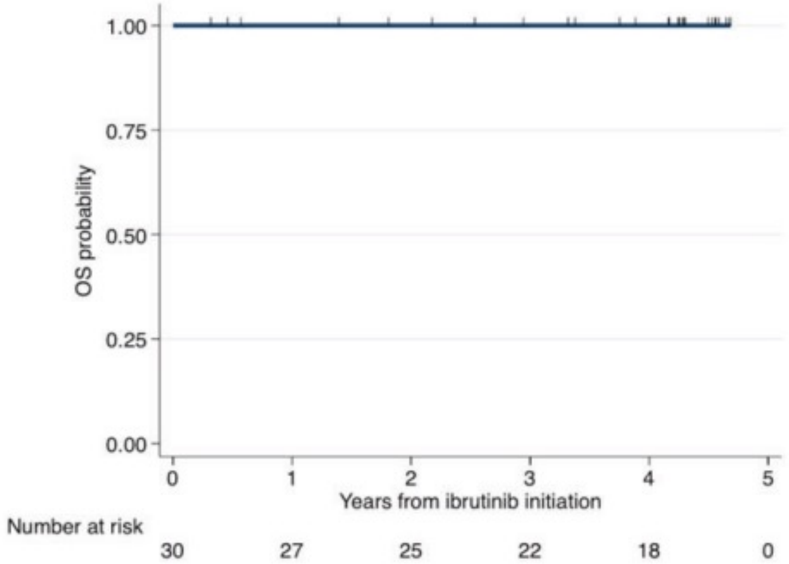
Long-term follow-up of ibrutinib monotherapy in treatment-naive patients with Waldenstrom macroglobulinemia

PFS 76% (4 yrs)









Castillo JJ. *Leukemia*, 2022; 36: 532-539

BTK-Inhibitor Trials in WM

Study	Patient population	Agent(s)	n	Time to minor/ major response	ORR (%)/ MRR (%)	≥VGPR rate (%)	PFS (%)
Pivotal study[39]	R/R	Ibrutinib	63	0.9 mo/2.0 mo	91/79	30	54 (60 mo)
INNOVATE arm C[40]	R/R	Ibrutinib	31	1 mo/2 mo	87/77	29	40 (60 mo)
Phase 2[41]	TN	Ibrutinib	30	0.9 mo/1.9 mo	100/87	30	76 (48 mo)
INNOVATE arms A, B[42]	TN, R/R	Ibrutinib Rituximab	150	1 mo/3 mo	92/76	31	68 (54 mo)
Phase 2[43]	TN, R/R	Zanubrutinib	77	N/A/2.8 mo	96/82	45	76 (36 mo)
ASPEN cohort 1 ($MYD88^{Mut}$)[44]	TN, R/R TN, R/R	Ibrutinib Zanubrutinib	99 102	1 mo/2.9 mo 1 mo/2.8 mo	94/80 95/81	25 36	85 (42 mo) 88 (42 mo)
ASPEN cohort 2 ($MYD88^{WT}$)[44]	TN, R/R	Zanubrutinib	28	1 mo/3.0 mo	78/63	27	84 (42 mo)
Phase 2[45]	TN, R/R	Acalabrutinib	106	1 mo/N/A	94/81	39	84 TN/52 R/R (66 mo)
Phase 2[46]	TN, R/R	Tirabrutinib	27	N/A 1.9 (TN) 2.1 (R/R)	96/93	33	93 (24 mo)
Phase 2[47,48]	R/R	Pirtobrutinib	80	N/A /N/A	81 and 67 (prior cBTKi) 88 and 88 (cBTKi naïve)	24 (prior cBTKi) 29 (cBTKi naïve)	57 (18 mo for prior cBTKi) N/A for cBTKi naïve

BTK-Inhibitor Trials in WM

Study	Patient population	Agent(s)	n	Time to minor/ major response	ORR (%)/ MRR (%)	≥VGPR rate (%)	PFS (%)
Pivotal study[39]	R/R	Ibrutinib	63	0.9 mo/2.0 mo	91/79	30	54 (60 mo)
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INNOVATE arms A, B[42]	TN, R/R	Ibrutinib Rituximab	150	1 mo/3 mo	92/76	31	68 (54 mo)
ASPEN cohort 2 ($MYD88^{WT}$)[44]	TN, R/R	Zanubrutinib	28	1 mo/3.0 mo	78/63	27	84 (42 mo)
Phase 2[45]	TN, R/R	Acalabrutinib	106	1 mo/N/A	94/81	39	84 TN/52 R/R (66 mo)
Phase 2[46]	TN, R/R	Tirabrutinib	27	N/A 1.9 (TN) 2.1 (R/R)	96/93	33	93 (24 mo)
Phase 2[47,48]	R/R	Pirtobrutinib	80	N/A /N/A	81 and 67 (prior cBTKi) 88 and 88 (cBTKi naïve)	24 (prior cBTKi) 29 (cBTKi naïve)	57 (18 mo for prior cBTKi) N/A for cBTKi naïve

Median ORR: 93%; Major RR: 81%; ≥ VGPR: 30%
PFS: 78% @4 years

Impact of CXCR4 Mutation Status in BTK-Inhibitor Studies in WM

Study	Patient population	Agent(s)	Time to major response ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	MRR (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	≥VGPR rate (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	PFS (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)
Pivotal study[39]	R/R	Ibrutinib	4.7 vs 1.8 mo	68 vs 97	9 vs 47	38 vs 70 (60 mo)
INNOVATE arm C[40]	R/R	Ibrutinib	3.6 vs 1.0 mo	71 vs 88	14 vs 41	18 mo vs NR (60 mo)
Phase 2[41]	TN	Ibrutinib	7.3 vs 1.8 mo	78 vs 94	14 vs 44	59 vs 92 (48 mo)
INNOVATE arms A, B[42]	TN, R/R	Ibrutinib Rituximab	3 vs 2 mo	77 vs 81	23 vs 41	63 vs 72 (54 mo)
Phase 2[49]	R/R	Zanubrutinib	N/A	91 vs 87	27 vs 59	~90 vs ~78 (42 mo)
ASPEN cohort 1[44]	TN, R/R TN, R/R	Ibrutinib Zanubrutinib	6.6 vs 2.8 mo 3.4 vs 2.8 mo	65 vs 85 79 vs 83	10 vs 31 21 vs 45	49 vs 75 (42 mo) 73 vs 81 (42 mo)

Impact of CXCR4 Mutation Status in BTK-Inhibitor Studies in WM

Study	Patient population	Agent(s)	Time to major response ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	MRR (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	≥VGPR rate (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)	PFS (%) ($CXCR^{Mut}$ vs $CXCR4^{WT}$)
cohort 1[44]	TN, R/R	Zanubrutinib	3.4 vs 2.8 mo	79 vs 83	21 vs 45	73 vs 81 (42 mo)

$CXCR4^{Mut}$ vs $CXCR4^{WT}$

Median Time to Major Response: (4.2 vs. 1.9 mos)

Median Major RR: 71% vs. 87%

Median ≥VGPR: 14% vs. 41%

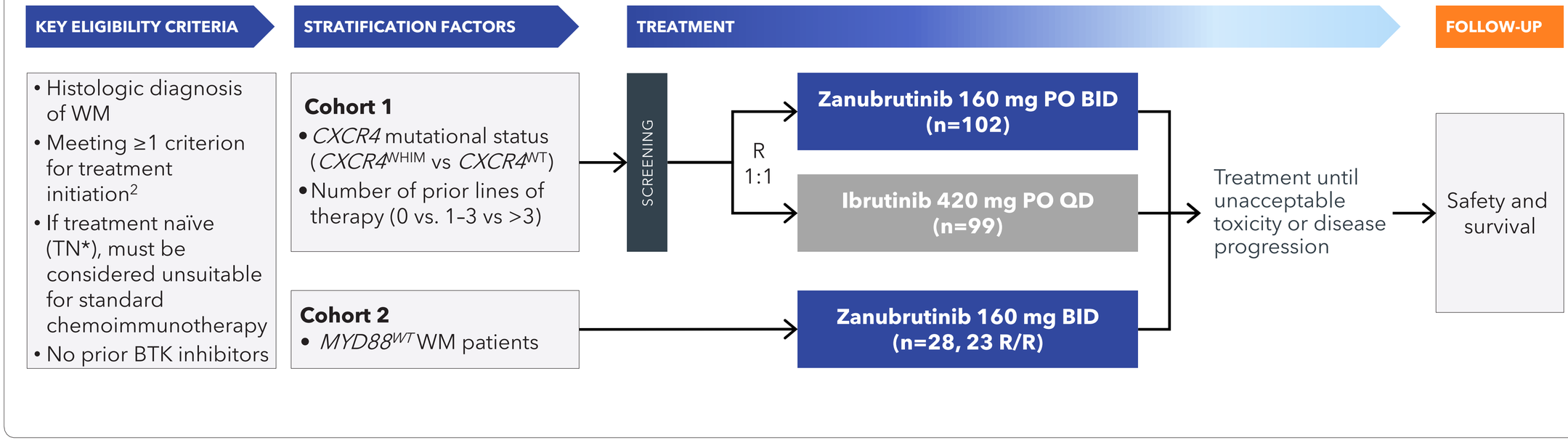
PFS: 59% vs. 75% @4 years

Phase 3 ASPEN Study Zanubrutinib vs. Ibrutinib in WM

PHASE 3

Study Identifier: BGB-3111-302, NCT03053440

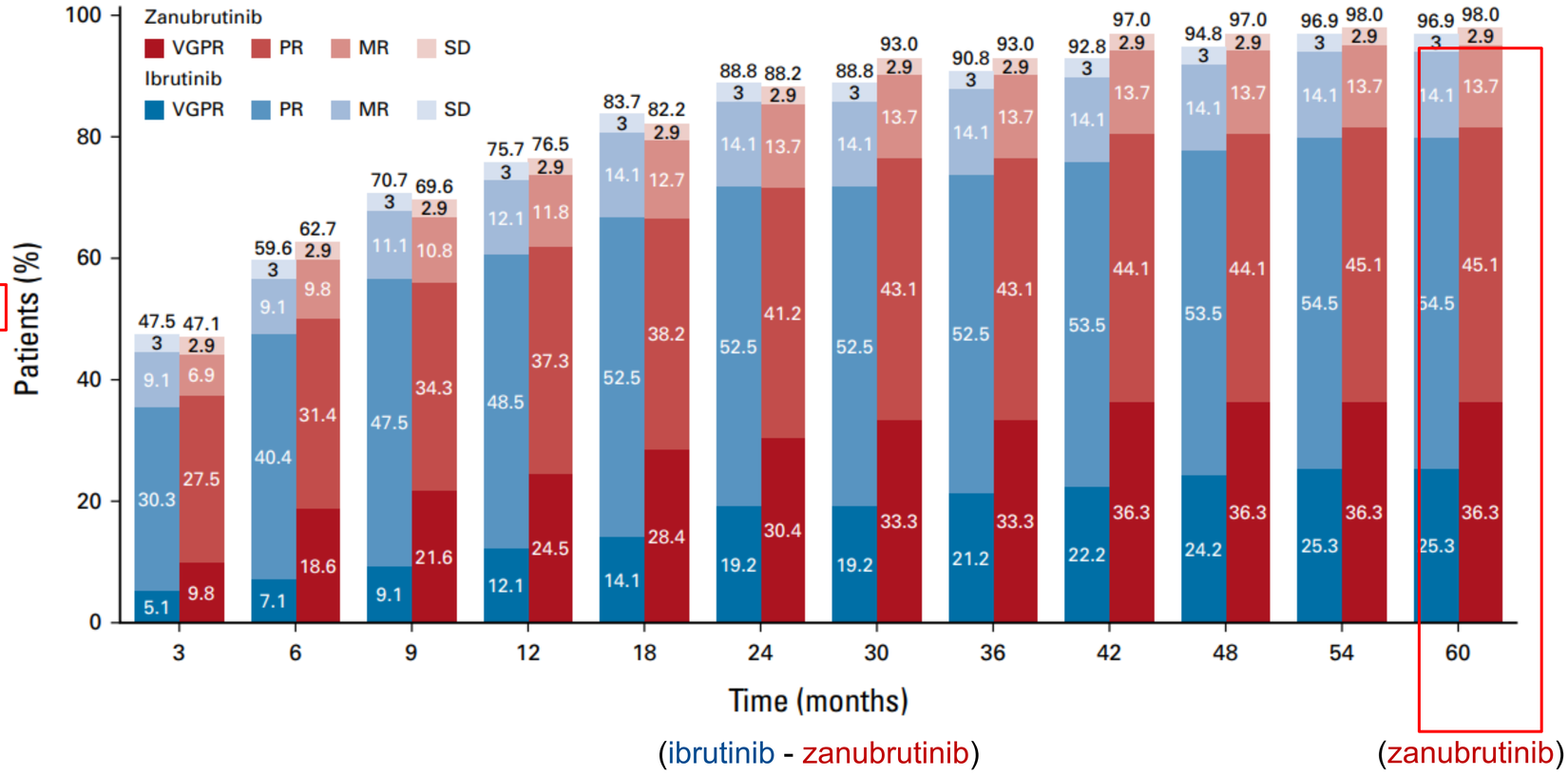
Primary Endpoint: CR/VGPR rate
Key Secondary Endpoints: MRR (≥PR), PFS, OS, DOR, symptom resolution, safety
Exploratory Endpoints: PK, QoL



Data cutoff: 31 January 2020. Median Follow-up: 19.4 months.
*Up to 20% of the overall population.
BID=twice daily, BTK=Bruton tyrosine kinase, CR=complete response, CXCR4=C-X-C motif chemokine receptor 4, DOR=duration of response, MRR=major response rate, MYD88MUT=myeloid differentiation primary response gene 88 mutant, PFS=progression-free survival, PK=pharmacokinetics, PO=per oral, PR=partial response, QD=once daily, QoL=quality of life, R=randomized, R/R=relapsed/refractory, TN=treatment-naïve, VGPR=very good partial response, WM=Waldenström's macroglobulinemia, WT=wild-type.

Tam CS et al. *Blood.* 2020;136(18):2038-2050. 2. Dimopoulos MA et al. Blood. 2014;124:1404-1411. 3.

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%

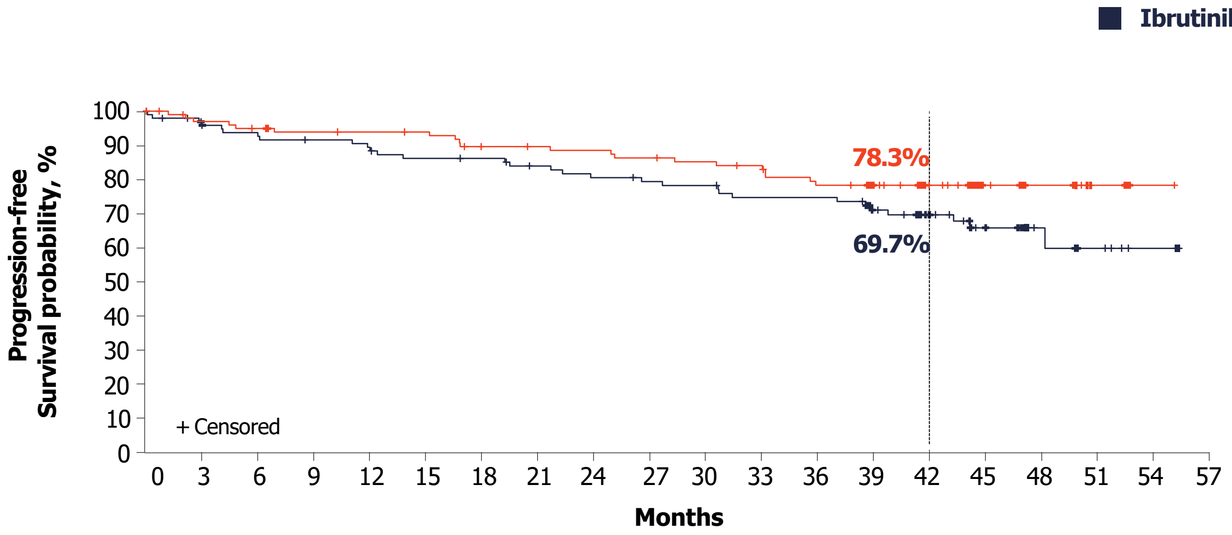
Cohort 2 best ORR: 81%
Cohort 2 best MRR: 65%
Cohort 2 best VGPR: 27%
Cohort 2 best CR: 4%

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

Dimopoulos MA. *J Clin Oncol*, 2023; 41: 5099-5106

Progression-Free and Overall Survivals in ITT Population

Progression-Free Survival[a]

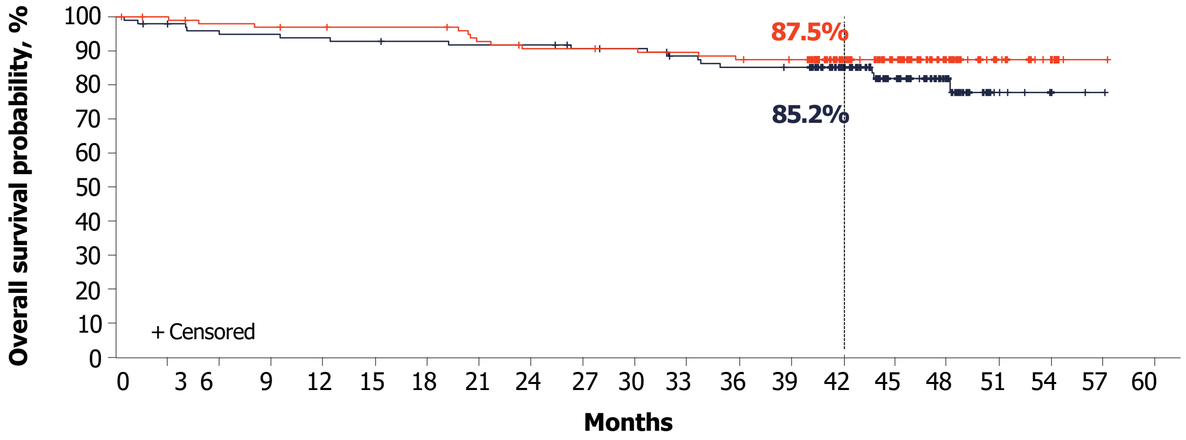


No. of Patients at Risk:

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

	Zanubrutinib	Ibrutinib
Events, n (%)	20 (19.6)	30 (30.3)
HR (95% CI)	0.63 (0.36, 1.12)	

Overall Survival[a]



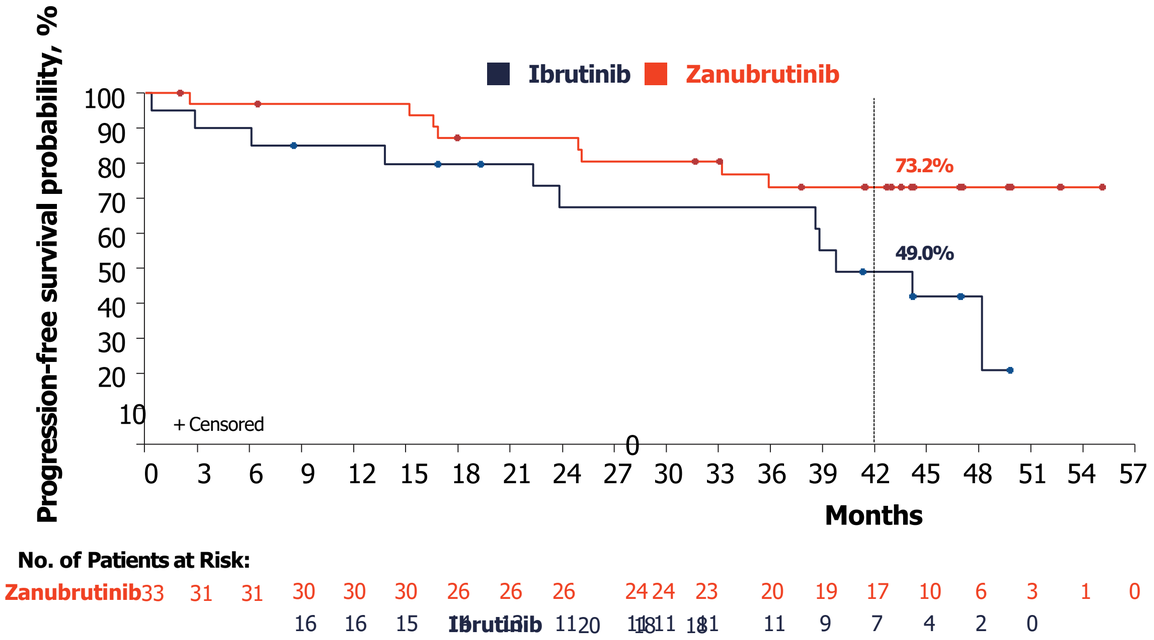
No. of Patients at Risk:

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

	Zanubrutinib	Ibrutinib
Events, n (%)	12 (11.8)	17 (17.2)
HR (95% CI)	0.75 (0.36, 1.59)	

Images adapted from Dimopoulos MA et al. JCO 2023
Data cutoff: October 31, 2021.
[a]By investigator assessment.
CI=confidence interval, HR=hazard ratio, ITT=intention-to-treat, OS=overall survival, PFS=progression-free survival.
Dimopolous MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

Progression-Free Survival in Patients With CXCR4MUT and Response



	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

Tam CS et al. Poster presented at ASCO 2022. Abstract 7521

Cumulative Event Rate and Treatment Discontinuations Due to AEs

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)[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)

Time to Treatment Discontinuations Due to AEs

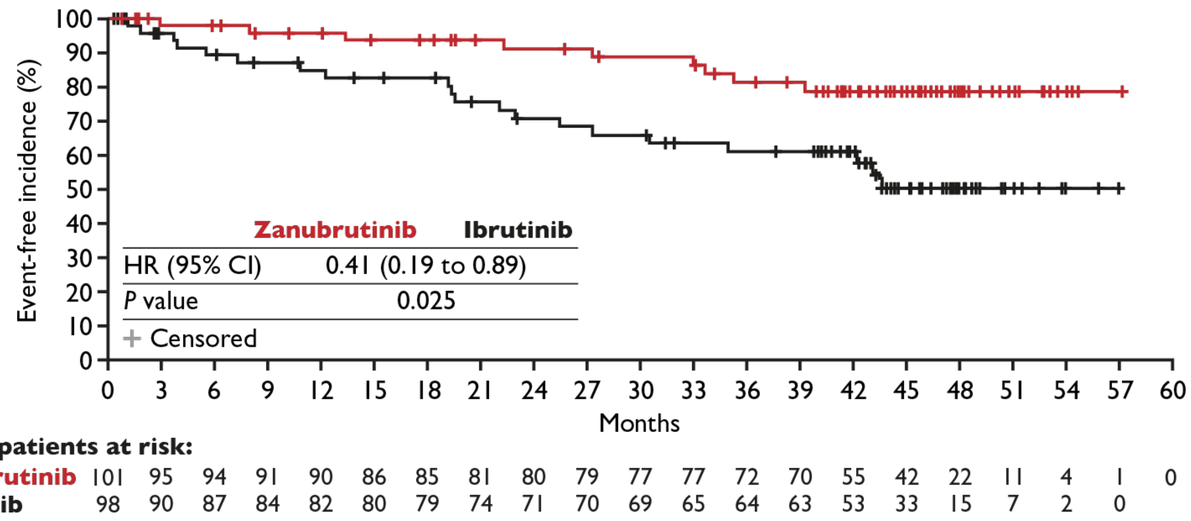


Image adapted from Tam CS et al. ASCO 2022

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=coronavirus disease.

Tam CS et al. Poster presented at ASCO 2022. Abstract 7521
Dimopolous MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

Most Common Adverse Events (Cohort 1)

AEs,[a] n (%)	All grades (≥20%)		Grade ≥3 (≥5%)	
	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.
Data cutoff: October 31, 2021.
*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.
AE=adverse event.
Dimopolous MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

Prevalence Analysis for AEs of Interest

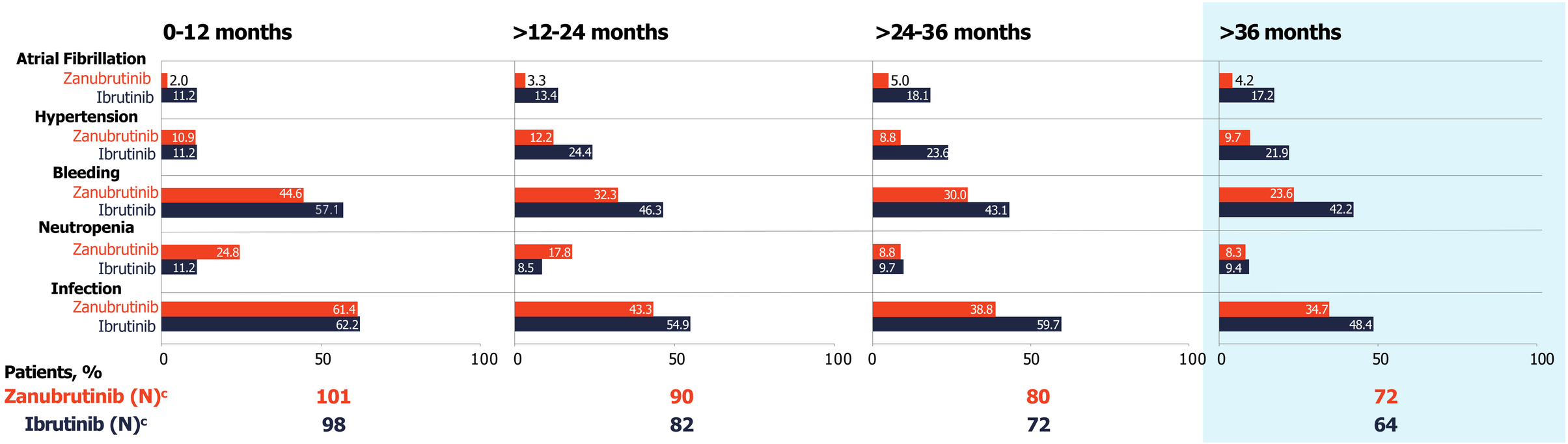


Image adapted from Dimopoulos MA et al. JCO 2023

Data cutoff: October 31, 2021.

[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.

AE=adverse event.

Dimopolous MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

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.

Tam CS et al. Poster presented at ASCO 2022. Abstract 7521
Dimopolous MA et al. JCO 2023 DOI: 10.1200/JCO.22.02830

Do we give BTK-inhibitors or chemoimmunotherapy to treatment-naïve patients?

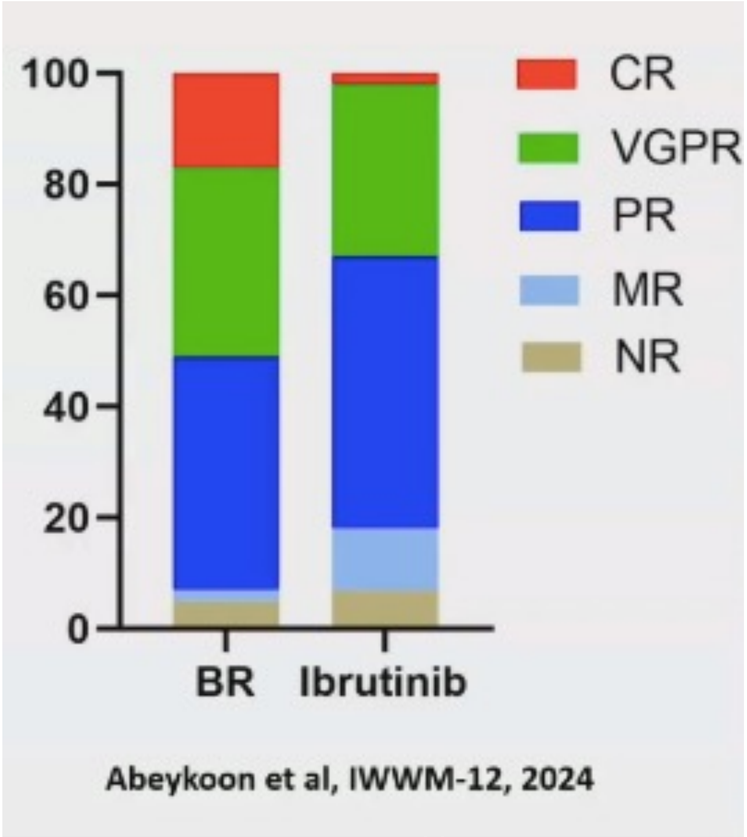
Summary of outcomes in frontline chemo- and BTKi-treated patients

	RB	RCD	BRD	Ibrutinib	Acalabrutinib	Zanubrutinib
ORR (%)	98	78	84	100	93	100
MRR (%)	96	53	68	87	79	88
Median PFS (years)	5.2	4.3	1.8	NR @ 4 yrs	NR @ 2 yrs	NR @ 3 yrs
Time to best response (months)	4.5	5.9	6.7	1.9	4.6	2.8
Median DOR (years)	NR @ 5 yrs	3.9	3.6	NR @ 4 yrs	NR @ 2 yrs	NR @ 4 yrs
4yr-OS (%)	90	87	87	100	91 @ 2 yrs	100 @ 2 yrs

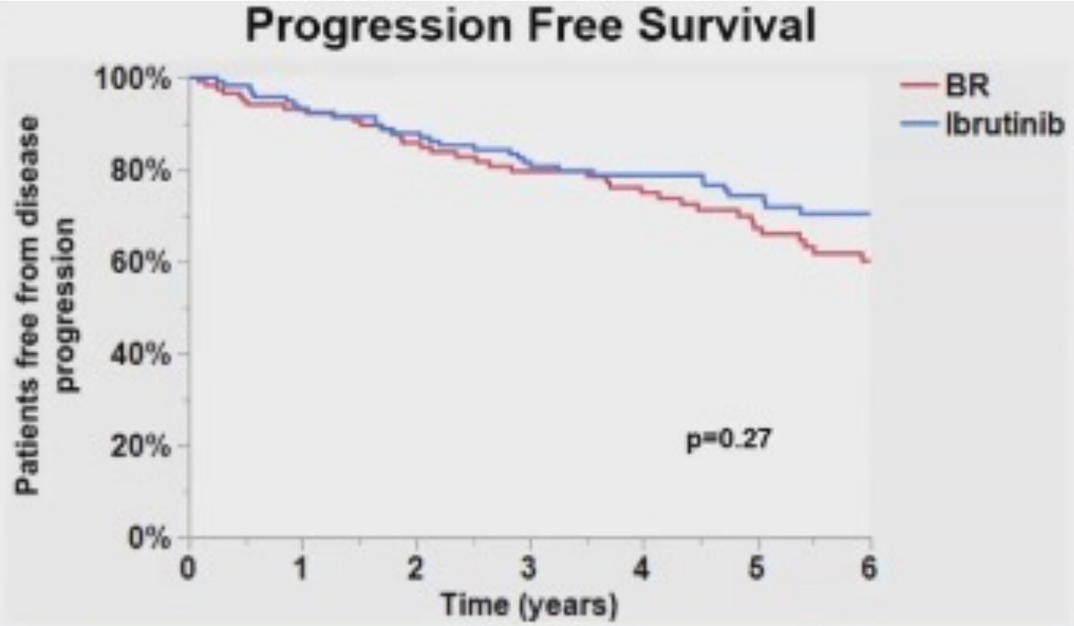
Abeykoon JP. *Am J Hematol*, 2021; 96: 945-953 — Castillo JJ. *Leukemia*, 2022; 36: 532-539
Owen RG. *Lancet Haematol*, 2020; 7: e112-e121 — Trotman J. *Blood*, 2020; 136: 2027-2037

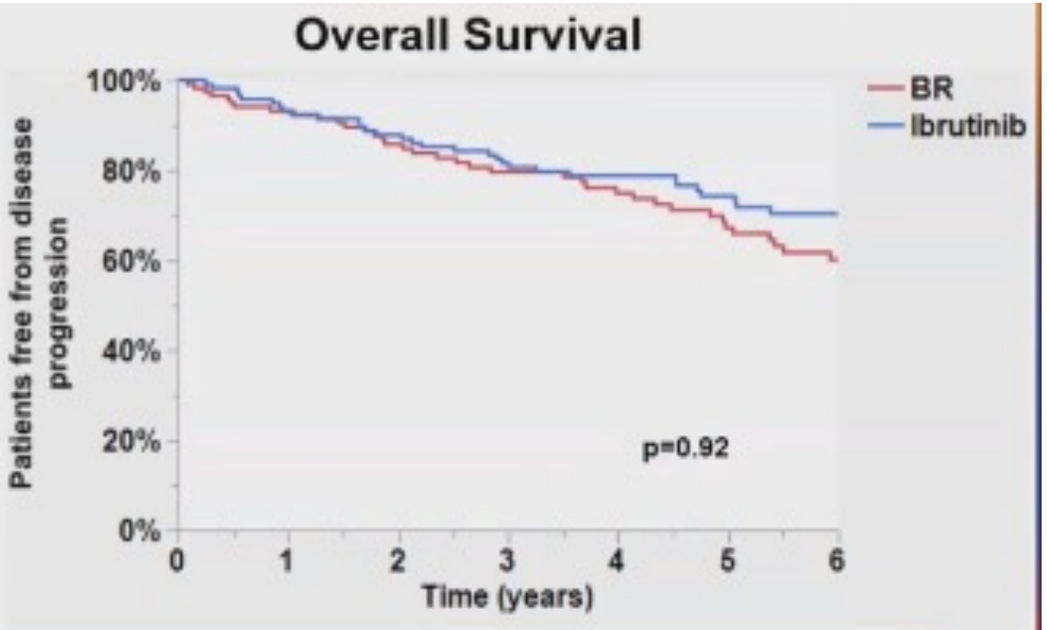
Comparative Efficacy of Bendamustine-Rituximab and Ibrutinib in Treatment-Naive WM (International Retrospective Study)

Variable	BR (n=123)	Ibrutinib (n=123)	p-value
Follow-up, median, 95%CI, y	6.0 (5.1-6.6)	6.0 (5.4-6.6)	0.89
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS, %			
Low	11	17	0.63
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 79%	54 (1-114)	
Overall response rate, %	95	93	0.47
Major response rate, %	93	82	**0.014**
Complete response, %	17	2	**<0.001**
≥VGPR, %	50	33	**0.008**



Benda-R versus Ibrutinib: Time-to-event analyses

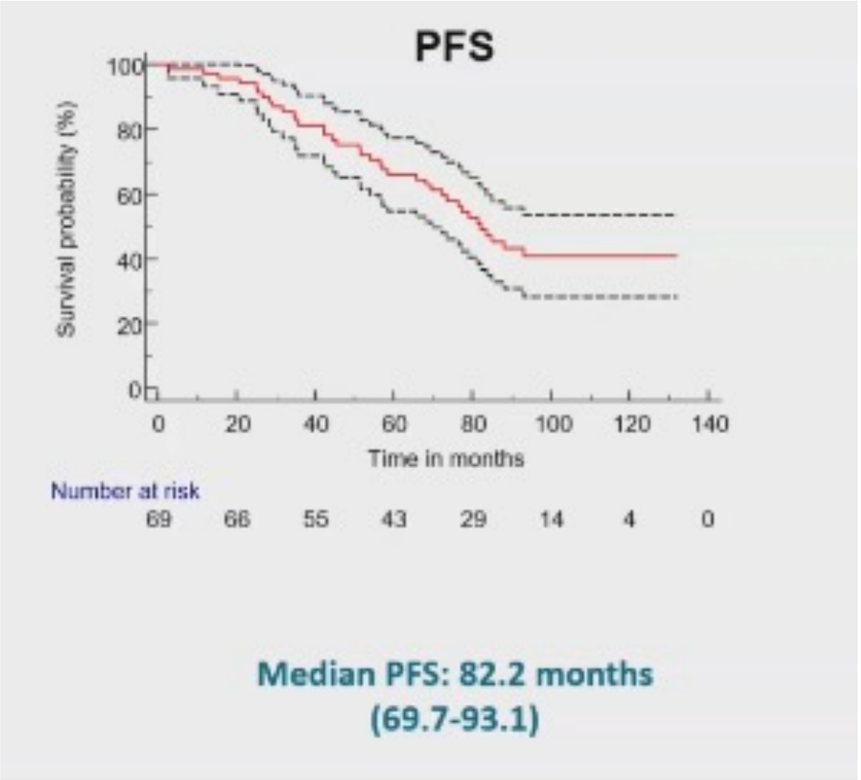




Variable	BR (n=123)	Ibrutinib (n=123)	p-value
6-year PFS, %	58	70	0.27
6-year OS, %	80.5	84	0.92

Long term responce data for benda-R (FILO)
69 patients, median age 71 years

Response	N	%	
Overall response	68/69	97%	
Major response	67/69	96%	
VGPR with negative immunofixation (IF)	13	19%	56%
VGPR with positive IF	26	37%	
Partial response	28	40%	
Minor response	1		
Stable disease	1		
Progression	0		



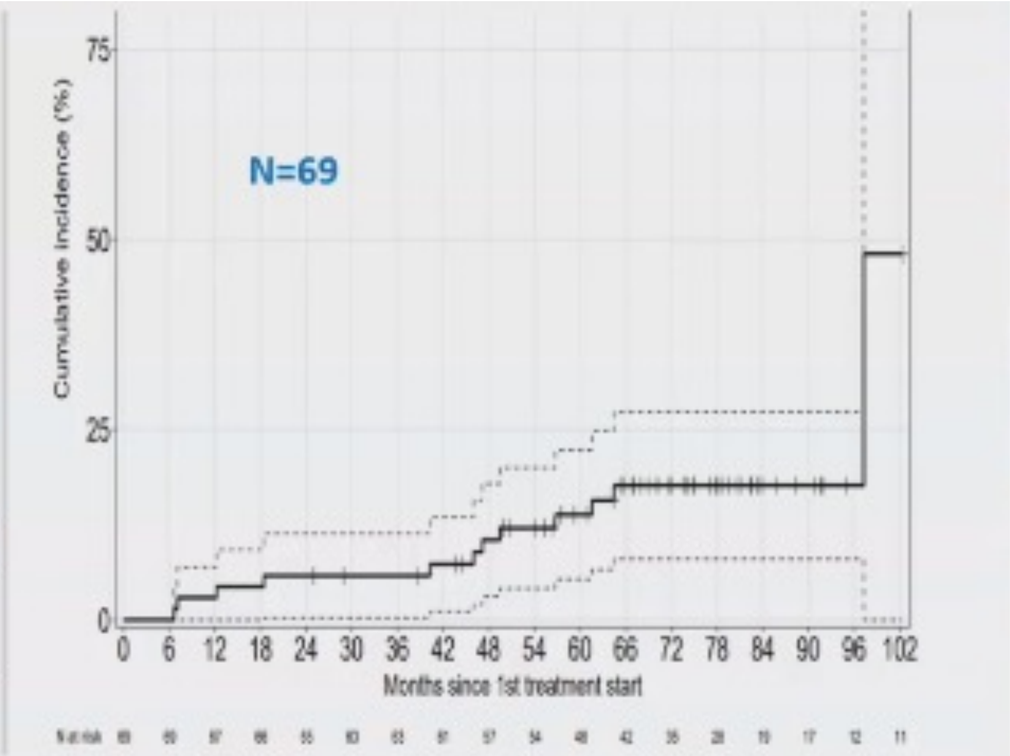
LeBlond et al. IWWM-12, 2024

Late- Onset Toxicities for Benda-R (FILO)

Type of Cytopenia	N	%	Duration (months) median (range)
Neutropenia	26	38%	9m (3-24)
Anemia	17	25%	6m (3-36)
Thrombocytopenia	11	16%	9m (3-36)

- Long–lasting cytopenia occurred in 35 patients (51%)

- **Second malignancies: 12 patients**
  - 9 solid tumors (2 pancreas , 2 gastric, 1 colic, 1 oesophagus 1 lung, 1 skin, 1 breast)
  - 3 myelodysplastic syndromes with 2 AML



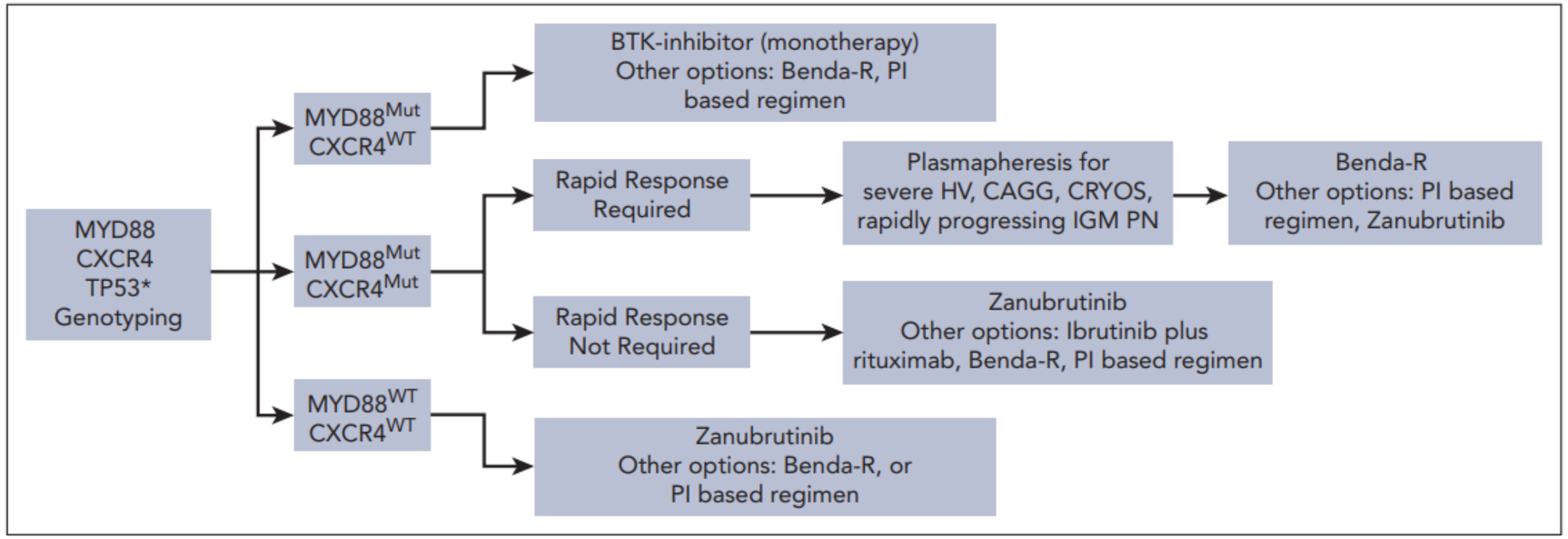
Cumulative incidence of second malignancies of 17.66% [7.99-27.64] at 66 months.

LeBlond et al. IWWM-12, 2024

General Consideration

- **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.

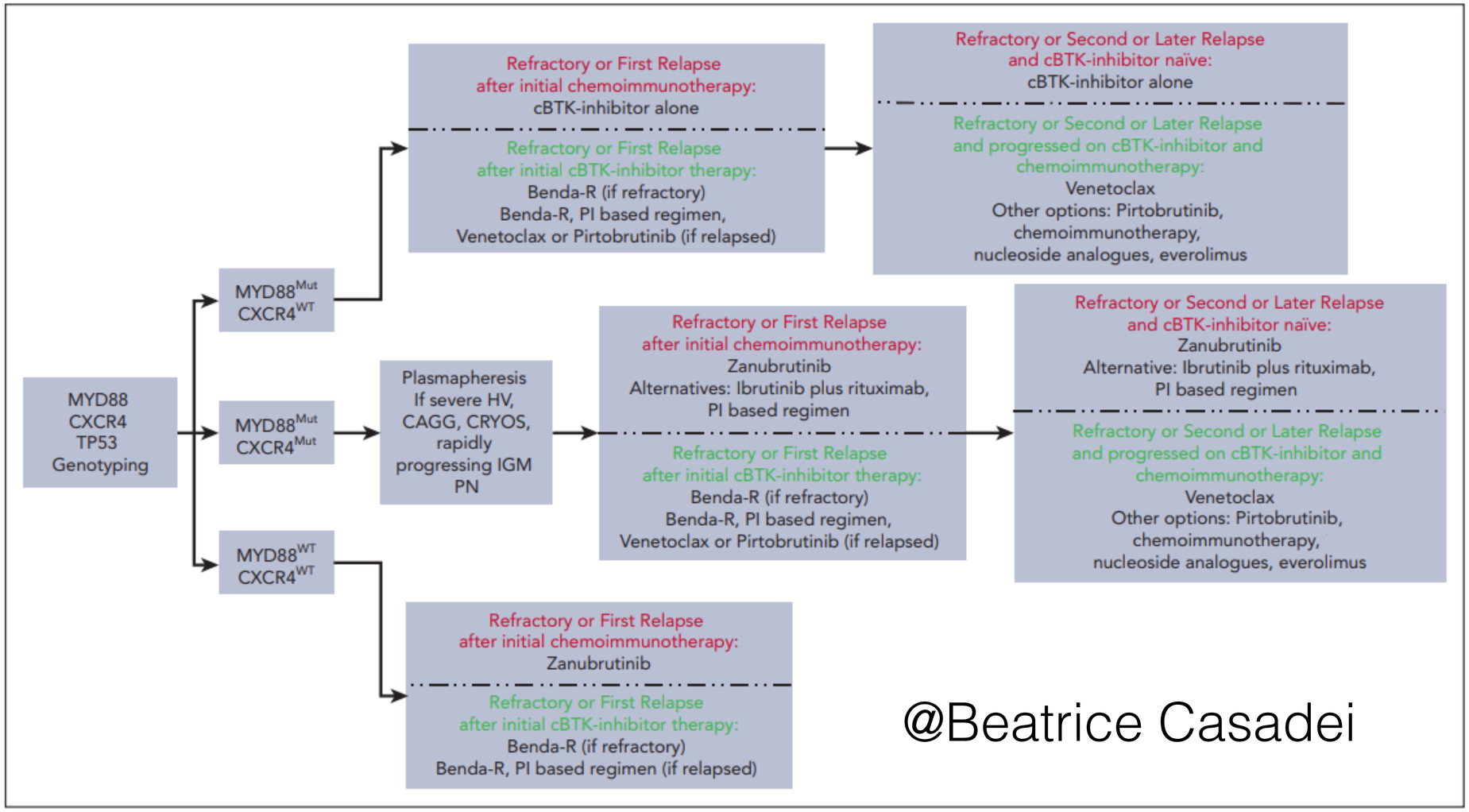
Choosing treatment wisely according to presentation and genotype: frontline options



	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

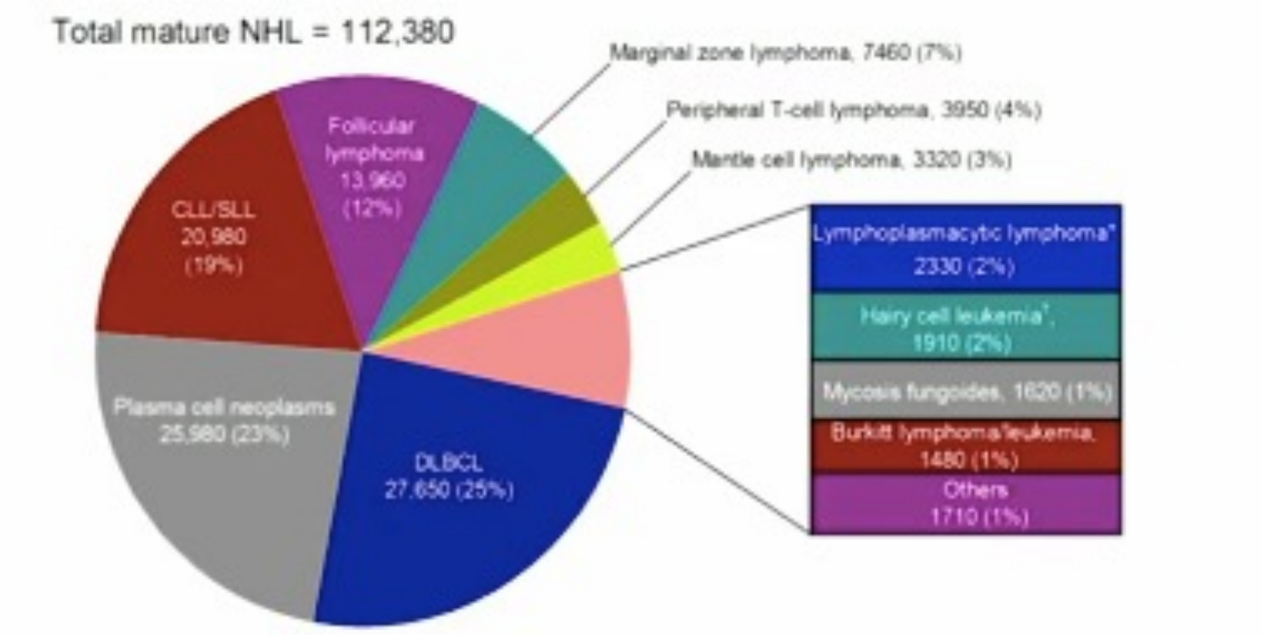
Recommendations for later treatment lines according to previous therapy

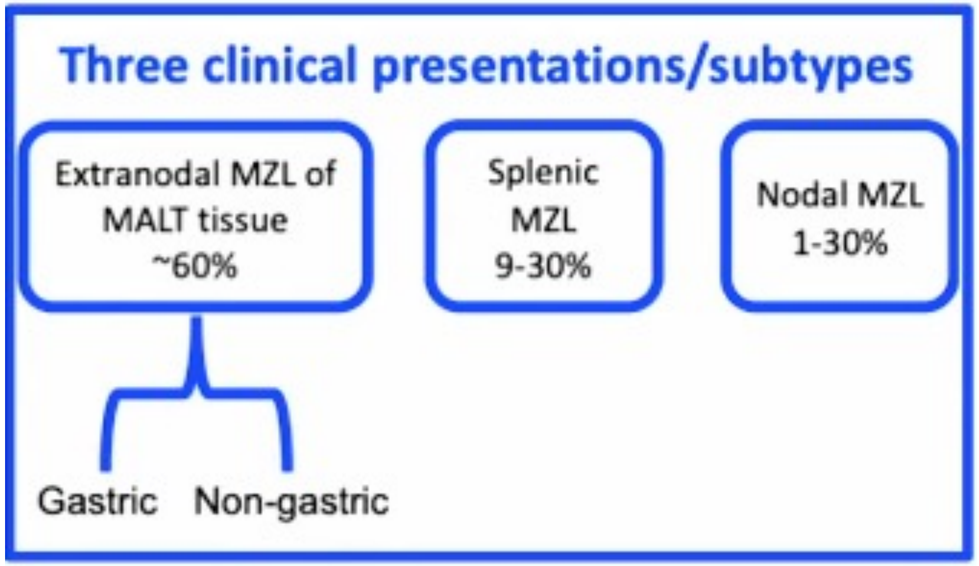


Buske C. *Semin Hematol*, 2023; 60: 73-79 — Treon SP. *Blood*, 2024; 143: 1702-1712

Marginal Zone Lymphoma

Epidemiology and clinical subtypes





- 3° most common mature B-NHL
- Frquent stage IE
- Indolent course
- 90% 5-yesr survival

Cerhan and Haberman Ann Lymphoma 2021 Mar:5:1
Teras et al. CA Cancer J Clin (2016) 66: 443-459

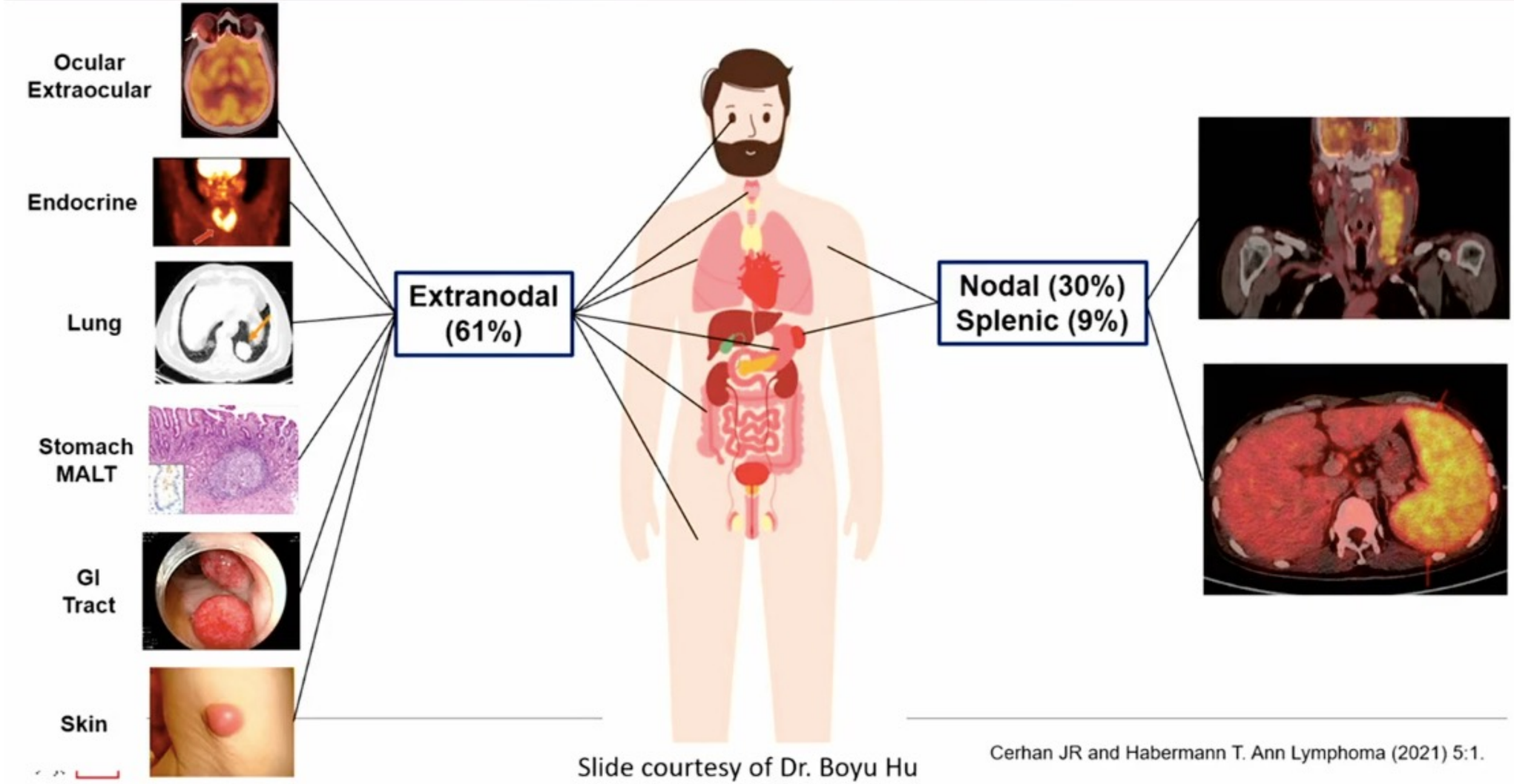
EN MZL disease site and common genetic alterations/balanced translocations

SITE	ANTIGENIC ASSOCIATION	GENETIC ALTERATION
Stomach	H. Pylori	*MALT1, FOXP1, BCL10, MALT1, TNFAIP3 inact*
Intestinal	Campylobacter jejuni	*MALT1, BCL10*
Cutaneous	Borrelia Burgdorferi	*FOXP1, MALT1,*
Ocular adnexal	Chlamydia psittaci	*FOXP1, MALT1, TNFAIP3 inact*
Pulmonary	Achromonas xylosoxidans	*MALT1, BCL10, TNFAIP3 inact*
Salivary gland	Sjogren's disease	*MALT1, BCL10, TNFAIP3 inact*
Thyroid	Hashimoto's thyroiditis	*FOXP1, MALT1, TNFAIP3 inact*

t (11;18); t (3;14); t (1;14)

Schrueder J. Hematop. 2017

Clinical Presentation



Slide courtesy of Dr. Boyu Hu

Cerhan JR and Habermann T. Ann Lymphoma (2021) 5:1.

Clinical Spectrum and other features

- **CBL-MZL**—premalignant clonal B-cell lymphocytosis of marginal zone origin
  - A systemic disorder with similarities to NMZL and SMZL
  - Precedes onset of MZL
- **Pediatric subtype of nodal MZL**
- **IPSID** (immunoproliferative small intestinal disease)
  - A form of MALT lymphoma
- **Relapsed/refractory MZL**
  - Plasmacytic differentiation
  - Frequent paraprotein production (~30% of SMZL will have Ig paraprotein)
  - paraneoplastic and autoimmune phenomena (20% of SMZL will have autoimmunity)
- **Transformation** of MZL to aggressive lymphoma (non-GC)
  - 5-10% incidence
  - Genomic classifiers suggest that molecular subgoups C1 and BN2 might represent transformed MZL (associated with NOTCH and BCL6 translocations)

Rossi D. N. Engl. J. Med. 2022

Staging—similar to other lymphomas with some special considerations

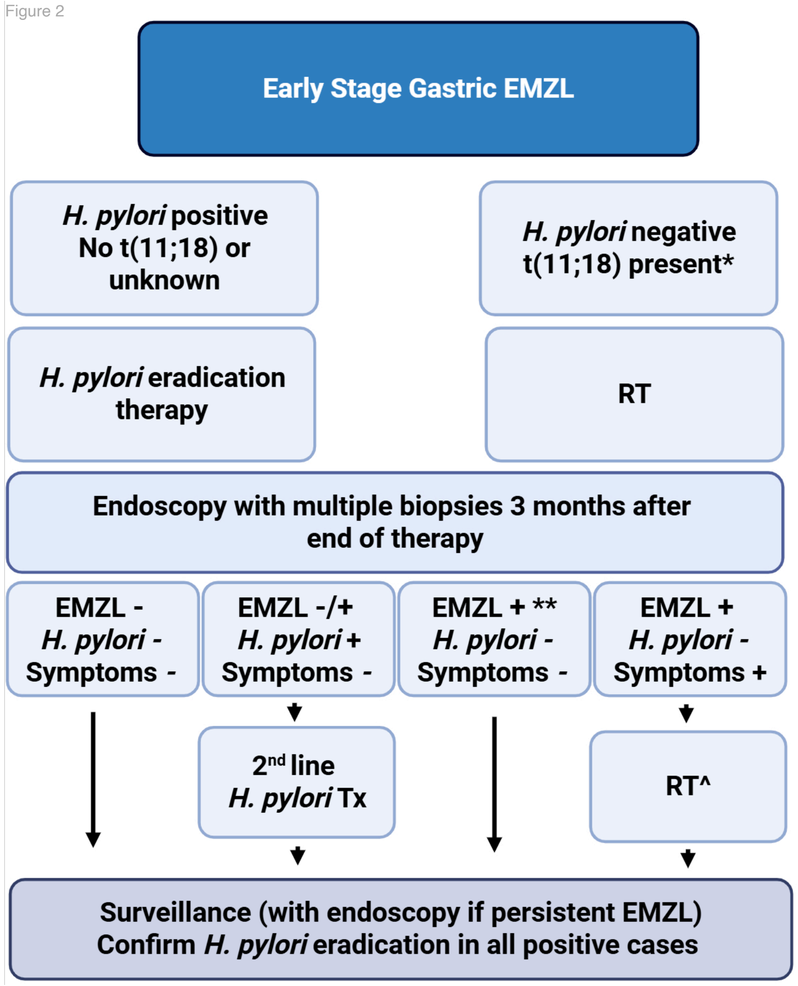
***Role of PET and PET/CT is evolving but is generally recommended if available

- Gastric EN MZL:
  - Mandatory: EGD, IHC for H.pylori
  - Optional: EUS to evaluate regional LNs and gastric wall infiltration may be helpful, FISH for t(11;18)
- Other EN MZL special assessments are site specific
  - Consider MRI for extraocular and salivary gland EN MZL
  - Colonoscopy for colonic EN MZL
  - PCR, IHC, or ISH for Campylobacter jejuni in IPSID biopsy specimen
- SMZL and NMZL: check HCV

NCCN_Guidelines 2025

The treatment of Marginal Zone Lymphoma

Figure 2

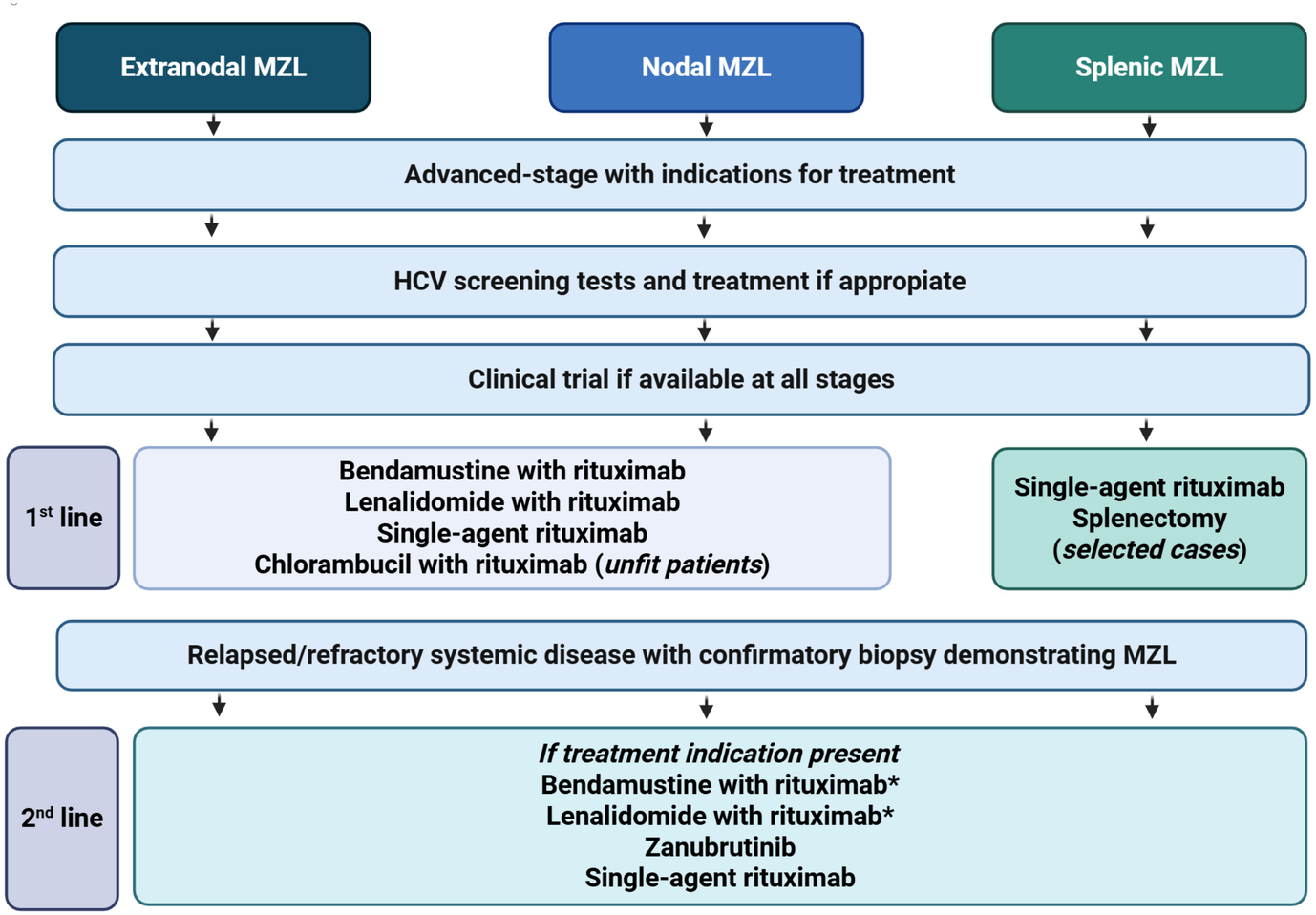


Early Stage Nongastric EMZL

RT
Single-agent rituximab
if RT not feasible

Alderuccio J.P. et al Blood 2025

The treatment of Marginal Zone Lymphoma

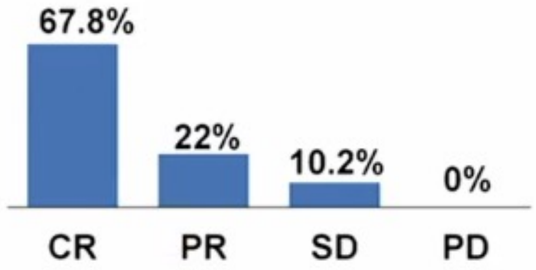


Alderuccio J.P. et al Blood 2025

Systemic therapy: some considerations

- Similar to others iNHL, treatment is based on GELF/NCCN criteria
  - Local symptoms / early satiety, pain) can drive treatment decisions
  - 20-30% of patients can have paraneoplastic symptoms
- Majority of data is derived from small datasets
- Very few trials are conducted specifically in patients with MZL
- Staging with PET-CT can miss mucosal or skin involvement

Rituximab monotherapy is active



4 doses of rituximab in EN MZL (n=59)

Table 3. Response to Treatment (n = 26)

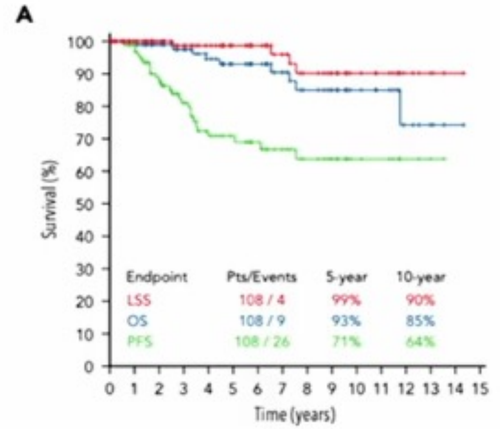
	Patients	
	No.	%
Complete response	12*	46
Partial response	8	31
Stable disease	6	23

*Eleven of 12 complete responders were in stage I/II_1 at study entry.

4 doses of rituximab in gastric EN MZL (n=27)

Response	No prior chemotherapy, n = 23	Prior chemotherapy, n = 11
ORR (%)	20 (87)†	5 (45)†
CR (%)	11 (48)	4 (36)
PR (%)	9 (39)	1 (9)
SD (%)	2 (9)	4 (36)
PD (%)	1 (4)	2 (18)

Decreased efficacy in relapsed disease



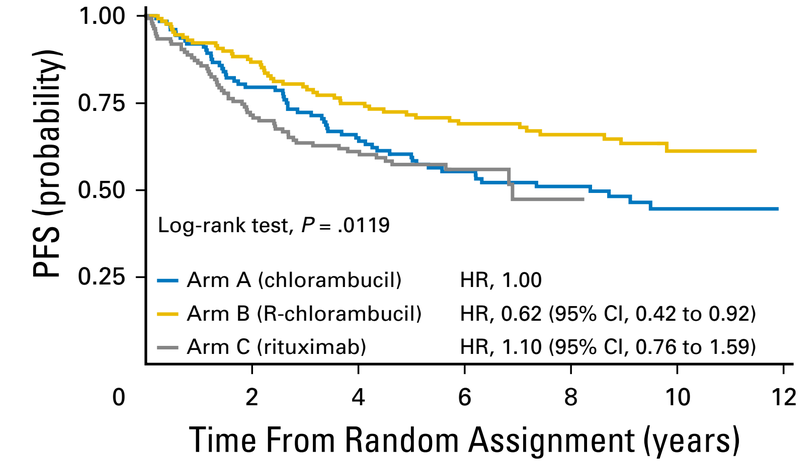
Rituximab monotherapy as a splenectomy-sparing approach

Conconi Blood (2003) 102 (8): 2741–2745; Kalpadakis Blood (2018) 132 (6): 666–670; Martinelli J Clin Oncol 2005 Mar 20;23(9):1979-83; Mazzoni Eur J Haematol 2025 Jan;114(1):70-78

Largest randomized phase III trial in MZL (IELSG-19): R-chl is superior to chl AND to rituximab in monotherapy

MZL patients with no prior systemic therapy (n=454)

- Chl 6mg/m2 plus R weekly x 4, then monthly x 4(n=152)
- R weekly x 4, then monthly x 4 (n=151)
- Chl 6mg/m2 (n=151)



No. at risk:

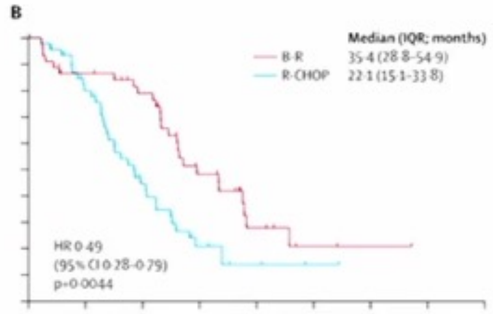
Arm A	131	89	70	53	42	16	0
Arm B	132	110	94	77	59	23	0
Arm C	138	90	71	31	2	0	0

5 years PFS: 72% vs 59% vs 56%

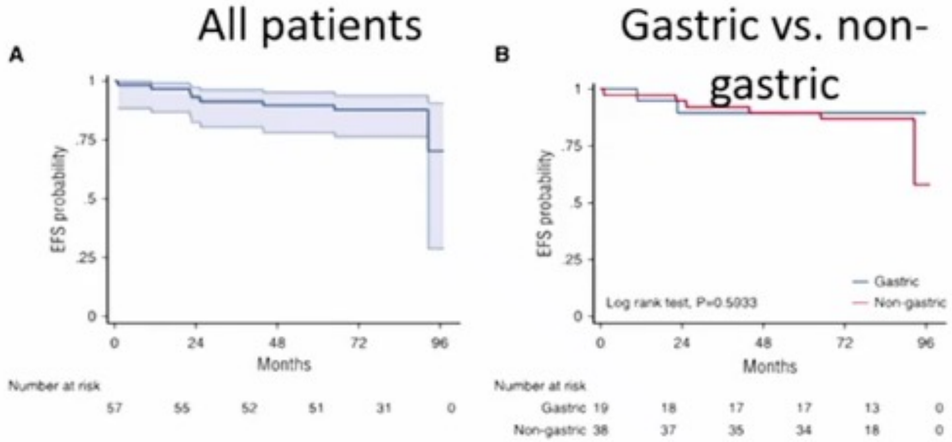
Zucca JCO 2017

Bendamustine plus rituximab in TN MZL

PFS



StIL Trial:
N=37 BR
N=30 R-CHOP
***difference is not statistically significant



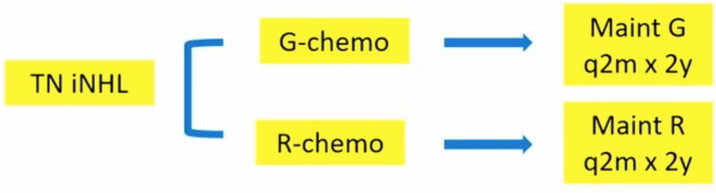
MALT 2008-01
N=57 evaluable MZL

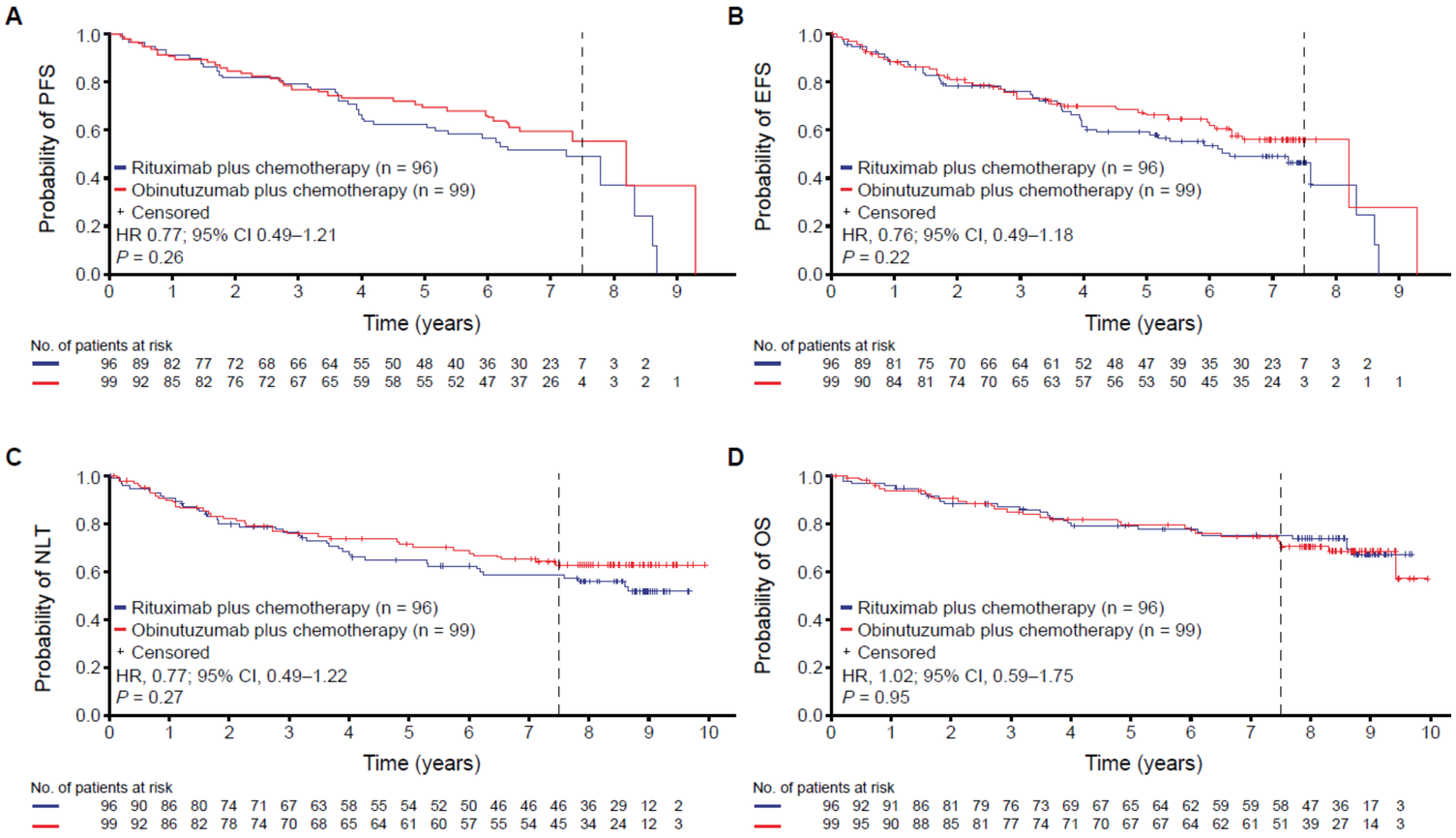
BR x 3 → IF CR→ BR x 1 more; IF PR→ BR x 3 more

OS >96% at 7y

Rummel Lancet 2013; Salar Blood 2018

Obinotuzumab in MZL: Gallium subset analysis consistent with FL data





Townsend W. Hemasphere 2023

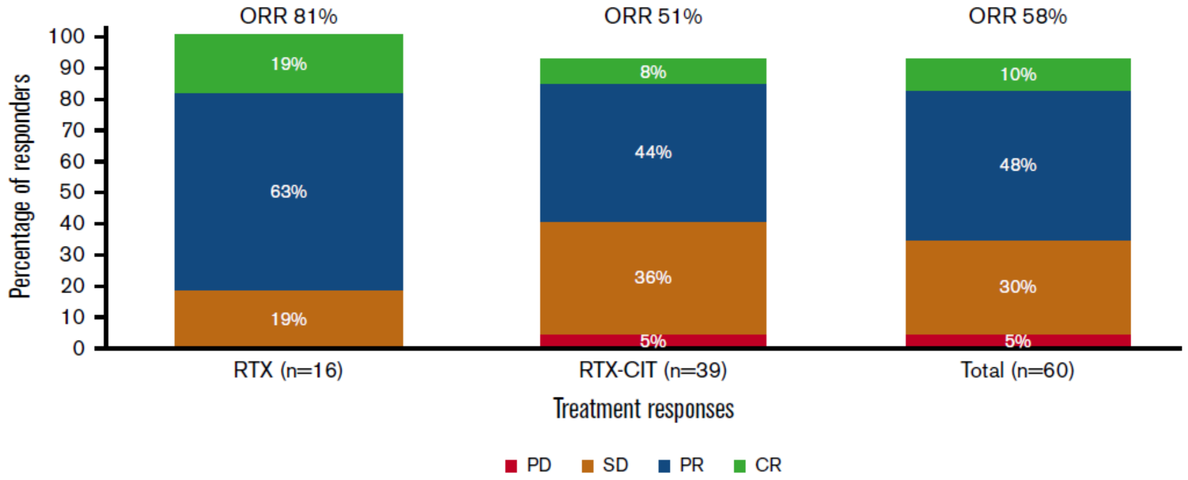
Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis

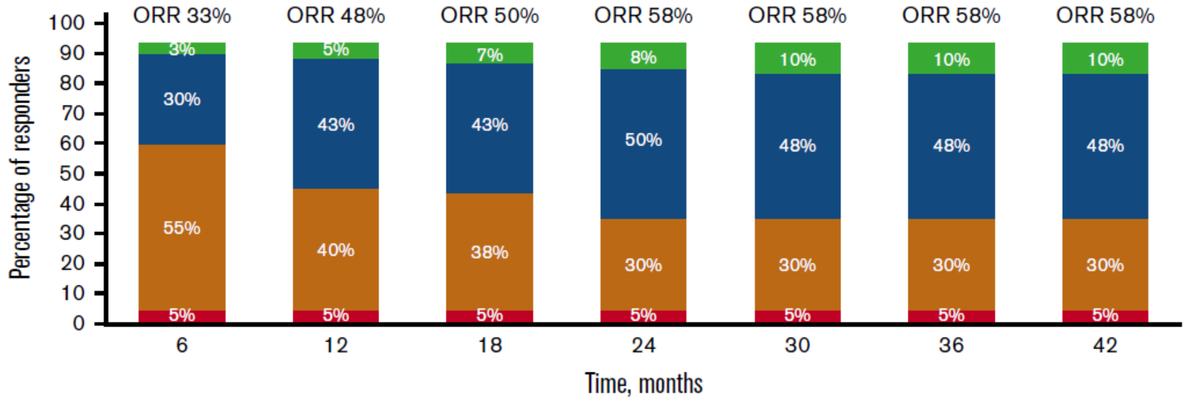
Characteristic	Prior line of therapy			Total (N = 63)
	RTX (n = 17)	RTX-CIT (n = 40)	Other* (n = 6)	
Median age (range), y	66.0 (30-86)	64.5 (41-90)	82.0 (57-92)	66.0 (30-92)
Age ≥65 y, n (%)	11 (65)	20 (50)	5 (83)	36 (57)
Bulky disease status, n (%)				
Not bulky (≤6 cm)	12 (71)	27 (68)	4 (67)	43 (68)
Bulky (>6 cm)	3 (18)	10 (25)	1 (17)	14 (22)
NA, spleen only	2 (12)	3 (8)	1 (17)	6 (10)
Bone marrow involvement, n (%)	8 (47)	13 (33)	0	21 (33)
Baseline cytopenias, n (%)				
Any cytopenia	10 (59)	15 (38)	2 (33)	27 (43)
Hemoglobin ≤11 g/dL	10 (59)	15 (38)	2 (33)	27 (43)
Platelets ≤100 × 10^9/L	1 (6)	5 (13)	0	6 (10)
ANC ≤1.5 × 10^9/L	1 (6)	0	0	1 (2)
LDH ≥350 U/L, n (%)	1 (6)	10 (25)	1 (17)	12 (19)
Creatinine clearance <60 mL/min, n (%)	1 (6)	4 (10)	4 (67)	9 (14)
Median number of prior systemic therapies (range)	1.0 (1-4)	2.0 (1-9)	2.5 (2-5)	2.0 (1-9)
1, n (%)	14 (82)	9 (23)	0	23 (37)
2, n (%)	2 (12)	13 (33)	3 (50)	18 (29)
≥3, n (%)	1 (6)	18 (45)	3 (50)	22 (35)
Patients refractory† to their last prior therapy at enrollment, n (%)	8 (57)	4 (10)	2 (33)	14 (22)
Distribution of MZL subtype, n (%)‡				
Extranodal	9 (53)	21 (53)	2 (33)	32 (51)
Nodal	1 (6)	13 (33)	3 (50)	17 (27)
Splenic	7 (41)	6 (15)	1 (17)	14 (22)

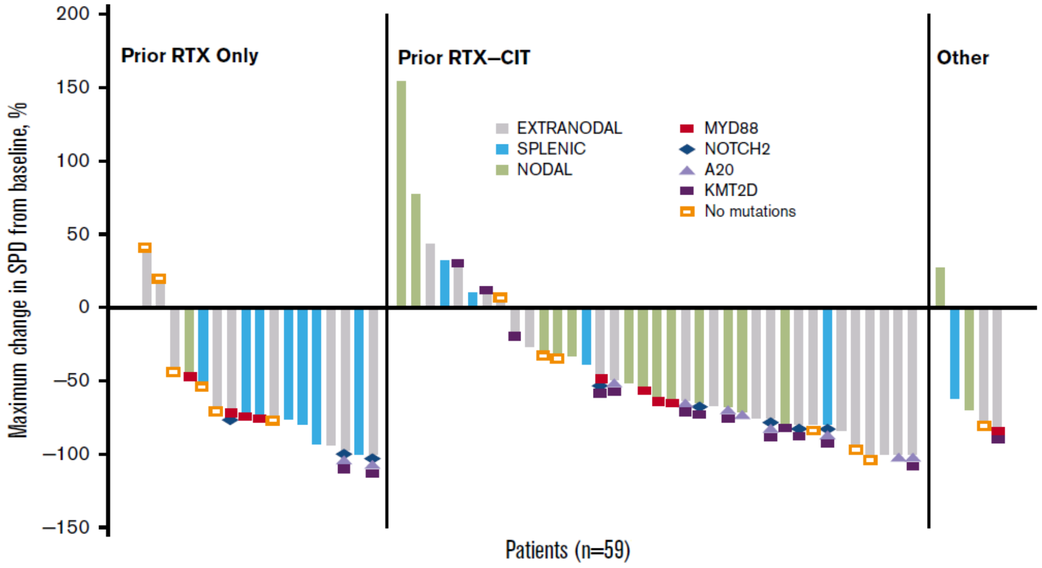
ANC, absolute neutrophil count; LDH, lactate dehydrogenase; NA, not applicable.
*Patients in the "Other" category had prior treatment with both single-agent RTX and chemotherapy or investigational therapies.
†Defined as documented failure to achieve at least PR.
‡Percentages may not total 100 because of rounding.

Noy A. *Blood Adv*, 2020; 4: 5773-5784

Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis







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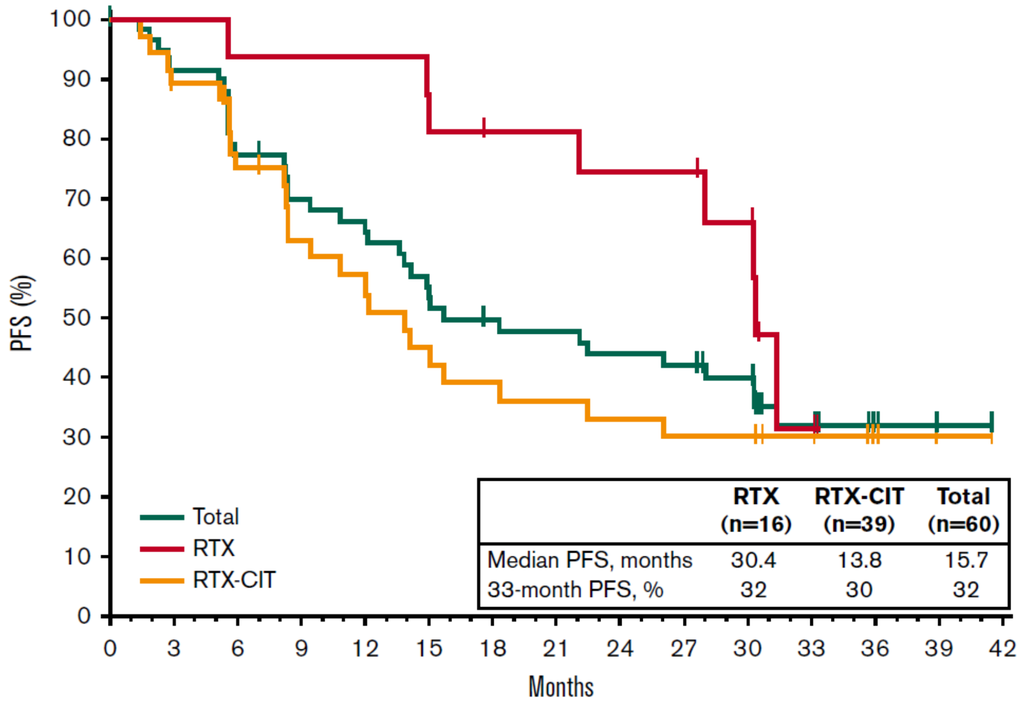
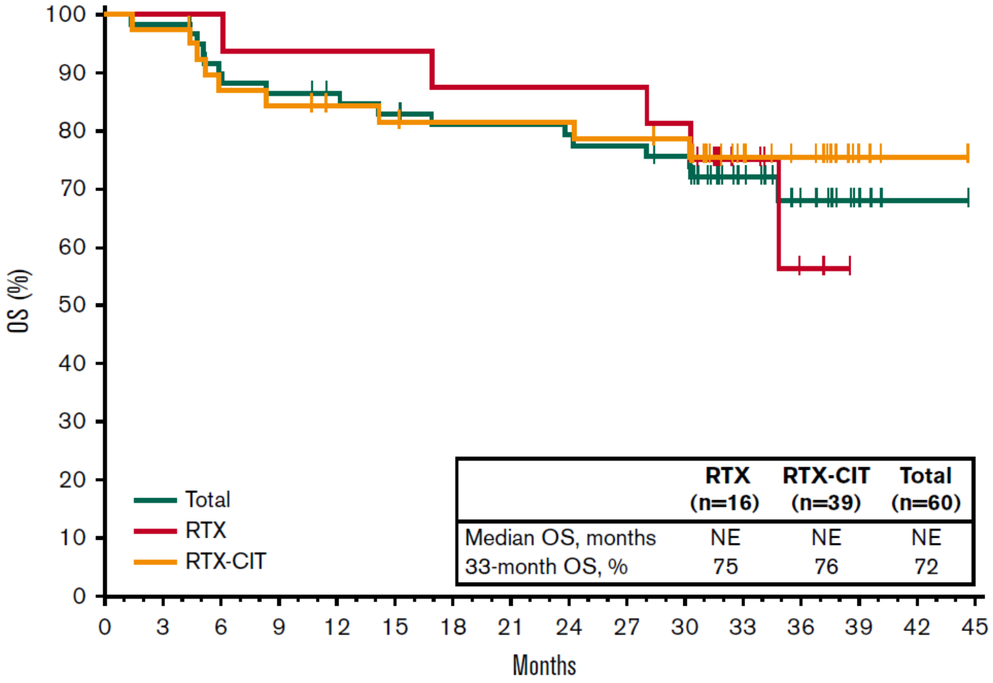
Durable ibrutinib responses in relapsed/refractory marginal zone lymphoma: long-term follow-up and biomarker analysis



	RTX (n=16)	RTX-CIT (n=39)	Total (n=60)
Median PFS, months	30.4	13.8	15.7
33-month PFS, %	32	30	32



	RTX (n=16)	RTX-CIT (n=39)	Total (n=60)
Median OS, months	NE	NE	NE
33-month OS, %	75	76	72

Noy A. *Blood Adv*, 2020; 4: 5773-5784

Phase 2 Study of Zanubrutinib in R/R MZL

MAGNOLIA

Phase 2

Study identifier: BGB-3111-214, NCT03846427

Primary endpoint: ORR assessed by IRC according to Lugano classification 2014[2]
Key secondary endpoints: ORR by PI, PFS, OS, DOR, safety

Key eligibility criteria

- R/R MZL patients who received at least one prior line of CD20-directed regimen

Treatment

Zanubrutinib 160 mg BID (N=68)

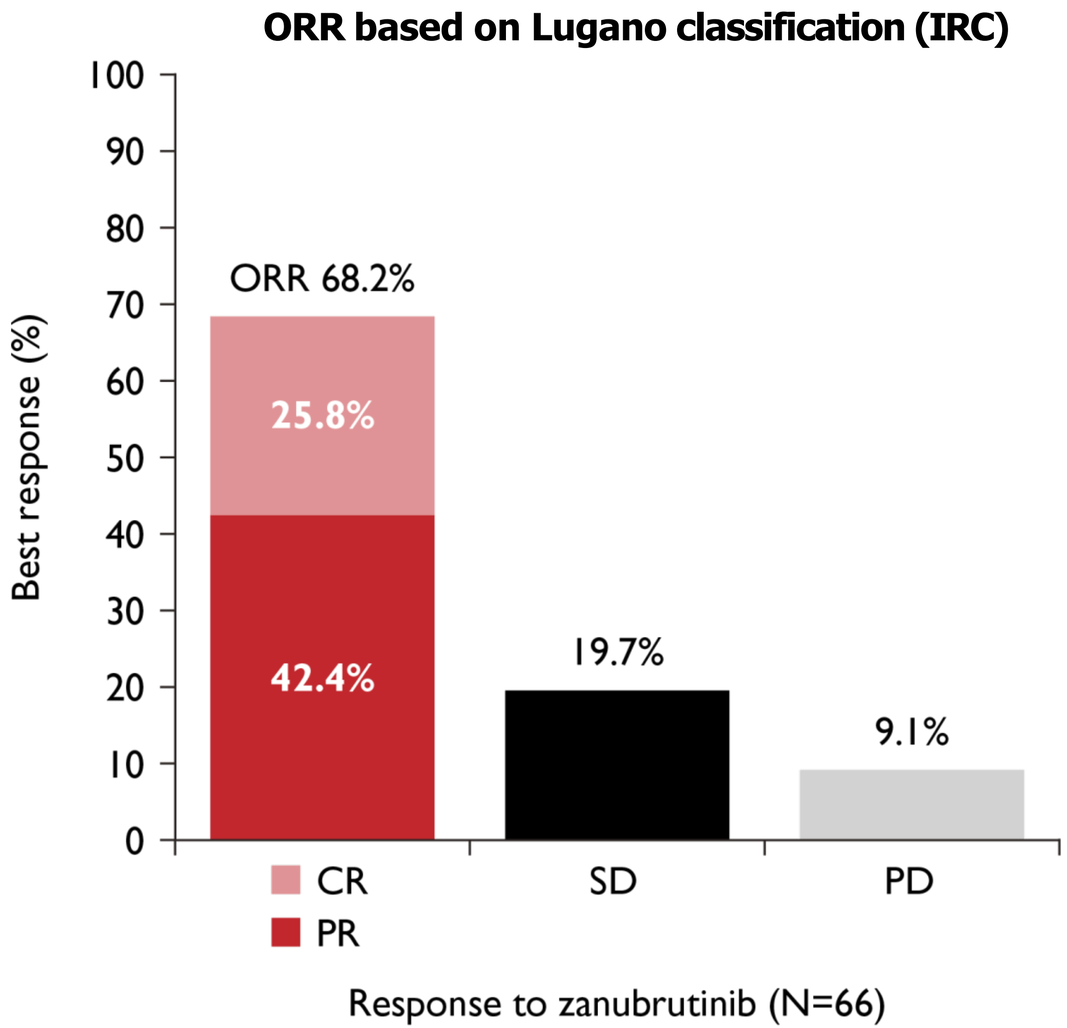
Treatment until disease progression, unacceptable toxicity, withdrawal of consent or end of study

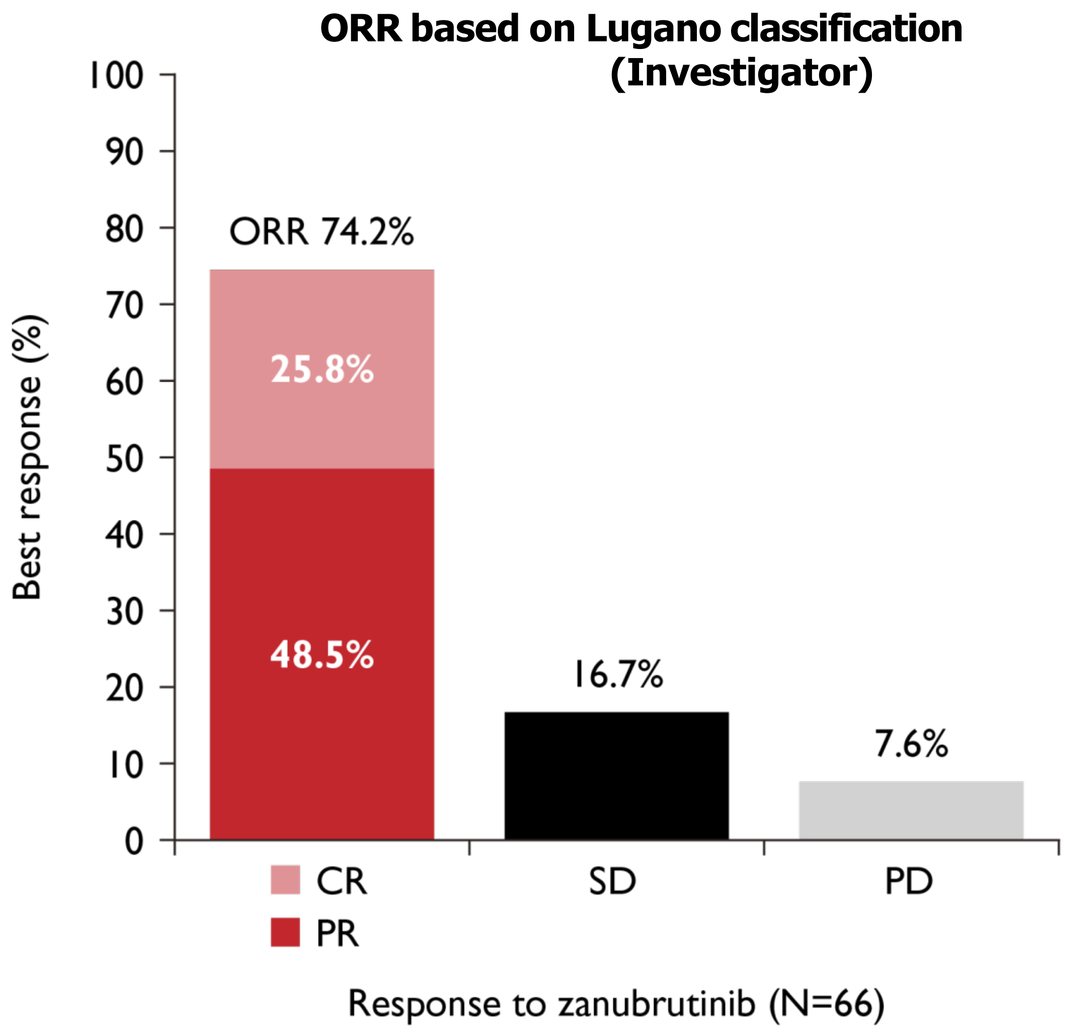
- Tumor response by investigator assessment will be presented herein
  - Response is based on the Lugano classification for non-Hodgkin lymphoma[2]
  - Blinded response assessment by independent review committee is ongoing

BID=twice a day, CD=cluster of differentiation, 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. Opat S et al. ASH 2020. Abstract 339. 2. Cheson BD et al. *J Clin Oncol*. 2014;32:3059–3067..

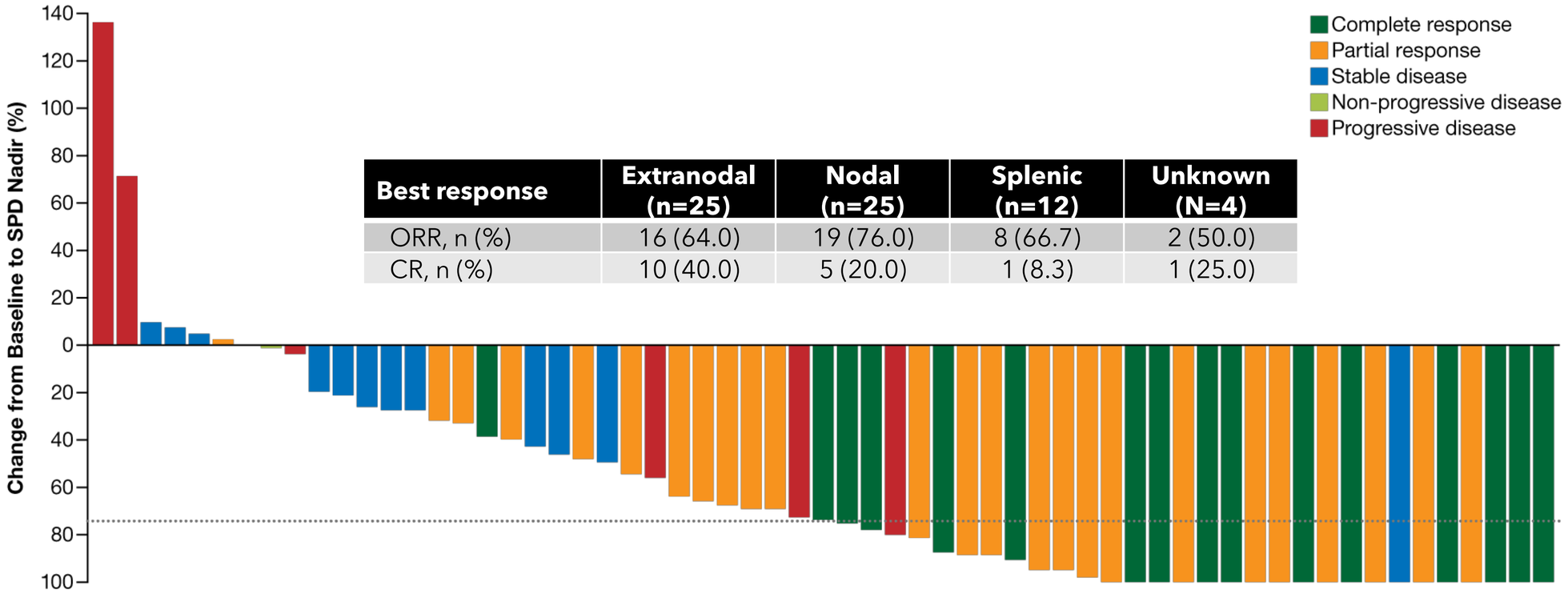
Overall Response by IRC and Investigator Assessment





1. Opat S et al. Clin Cancer Res 2021.

Change in Target Lesion SPD by IRC



Best response	Extranodal (n=25)	Nodal (n=25)	Splenic (n=12)	Unknown (N=4)
ORR, n (%)	16 (64.0)	19 (76.0)	8 (66.7)	2 (50.0)
CR, n (%)	10 (40.0)	5 (20.0)	1 (8.3)	1 (25.0)

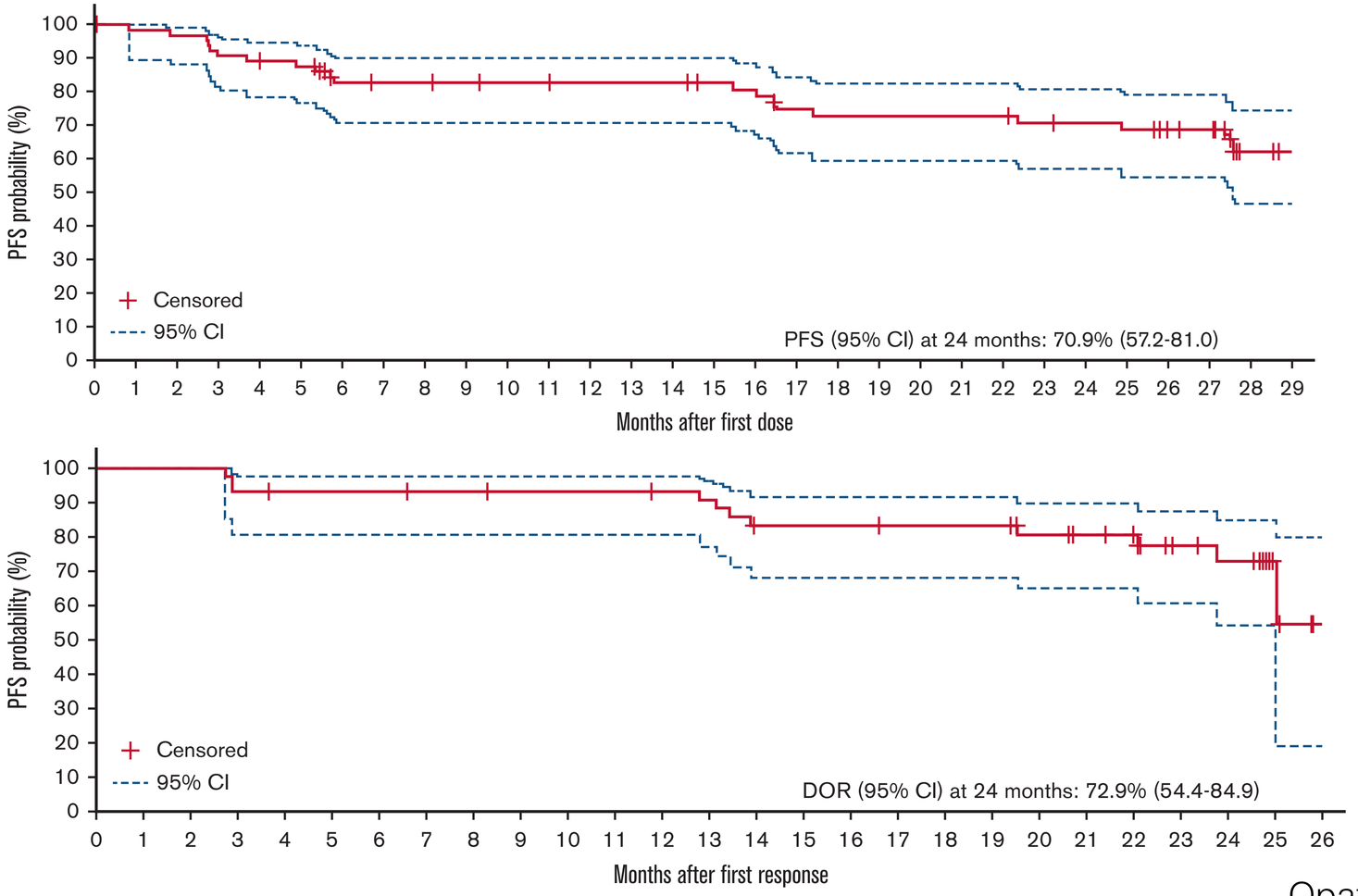
Data cutoff: 18 January 2021

Only patients with non-missing BOR and SPD percentage change were included (n=61). Dashed lines = median reduction in SPD (-74%).

BOR=best overall response, CR=complete response, IRC=independent review committee, MZL=marginal zone lymphoma, PD=progressive disease, PR=partial response, SD=stable disease, SPD=sum of products of perpendicular diameters

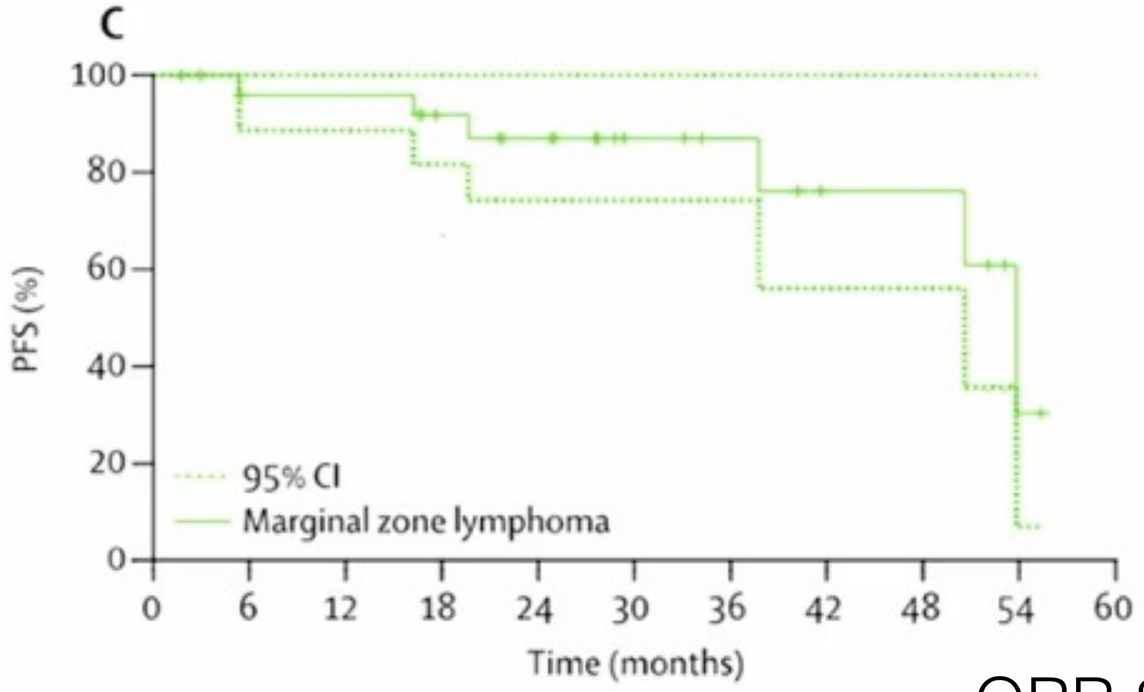
Opat S et al. *Clin Cancer Res* (2021) 27 (23): 6323–6332. This study is registered at ClinicalTrials.gov (NCT03846427)

PFS and Duration of Responses by IRC



Opat S. Blood Advances 2023

Phase II Rituximab+Lenalidomide



	Follicular lymphom (n=50)	Marginal zone lymphoma (n=30)	Small lymphocytic lymphoma (n=30)
Age (years; median, range)	56 (35-84	59 (36-77)	59 (34-76)
Sex, female	22 (44%)	18 (60%)	12 (40%)
Stage			
III	23 (46%)	9 (30%)	0
IV	27 (54%)	21 (70%)	30 (100%)
High tumour burden (as per GELF)	27 (54%)	13 (43%)	14 (47%)

ORR:89%
CR:67%
Median PFS 53.8 months
3-year PFS 87%

Fowler N. Lancet Oncol 2014

R/R Marginal Zone Lymphoma

- BTKi
- Car-T
- Emerging Agents: Loncastuximab/bispecific antibodies

Grazie per l'attenzione!