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Waldenstrom's Macroglobulinemia – Approach to Diagnosis and Treatment

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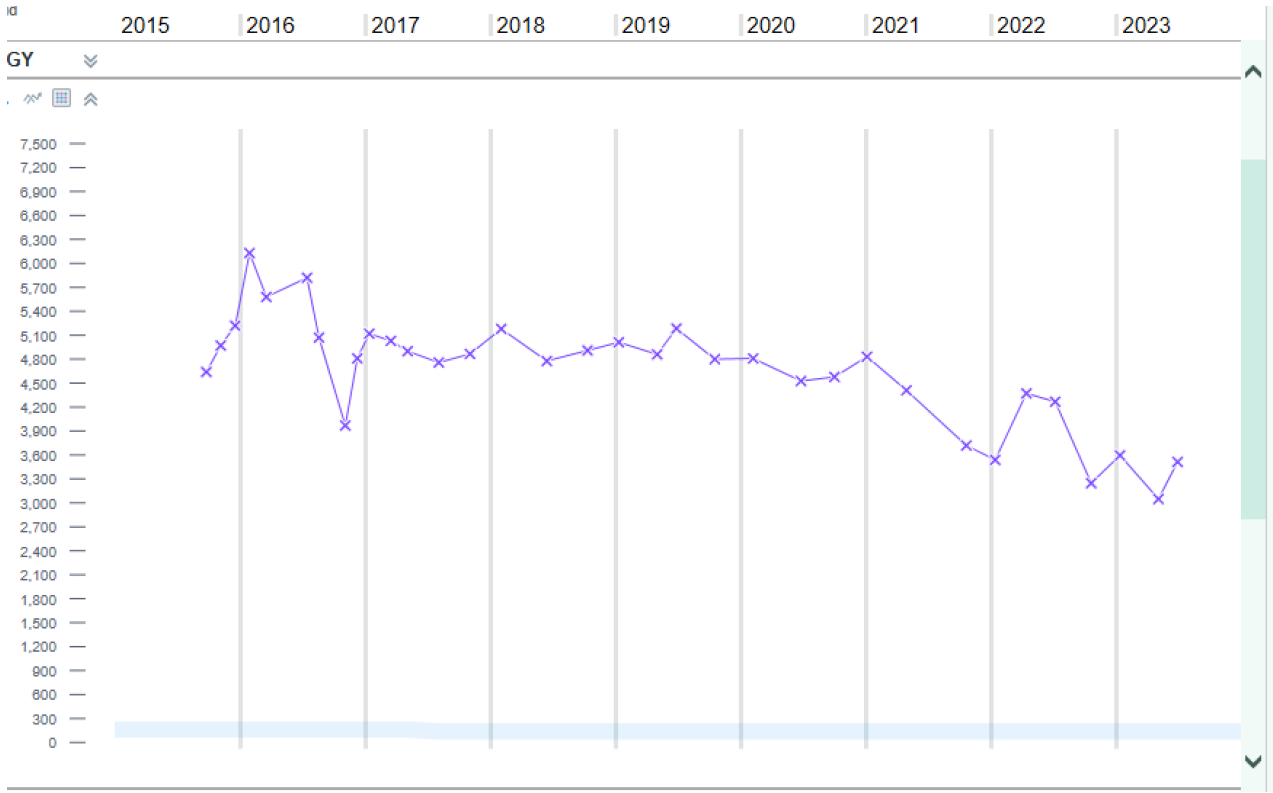
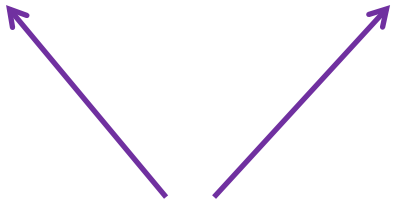
Case 1

- 69 y/o gentleman diagnosed with mild symptoms of peripheral neuropathy 2012.
- Labs from 07/28/2014 showed an IgM of 5130 mg/dL, M-spike of 3.6 g/dL, free kappa light chain of 149 , lambda light chain 3.6 mg/L. Free kappa lambda ratio of 41.3. Underwent a 24-hour urine for protein estimation on 08/04/2014, showing 126 mg of protein over 24 hours. Urine protein electrophoresis showed faint bands with no detectable protein. Beta 2 microglobulin was 2.44. Albumin 3.9, LDH WNL
- Underwent a skeletal survey on 08/01/2014, showing possible lytic lesion within the C4 and C5. MRI showed multilevel degenerative disk disease, prominent in C5-C6 region, at least moderate spinal stenosis at the C5-C6 level, but no lytic lesions were seen.
- Bone marrow biopsy from 09/15/2014 showing 15% lymphoplasmatoid; plasma cells were 0.2% of the cellularity, raising suspicion suggesting lymphoplasmacytic lymphoma, MYD88, CXCR4 mutation status unavailable



Spectrum of IgM disorders

IgM MGUS	Smoldering WM	Symptomatic WM
<3 g/dl serum IgM	≥3 g/dl serum IgM	Any size IgM
AND	OR	AND
<10% marrow involvement	≥10% marrow involvement	≥10% marrow involvement
AND	AND	AND
no end-organ damage*	no end-organ damage*	end-organ damage*



Observation

Start Treatment

Rajkumar et al, 2006

*Resulting from underlying WM

Revised IPSS-WM

Table 1

	Points
Age <65	0
Age 66–75	1
Age >75	2
B2 microglobulin >4 mg/L	1
LDH >250 IU/L	1
Serum albumin <3.5 g/dL	1

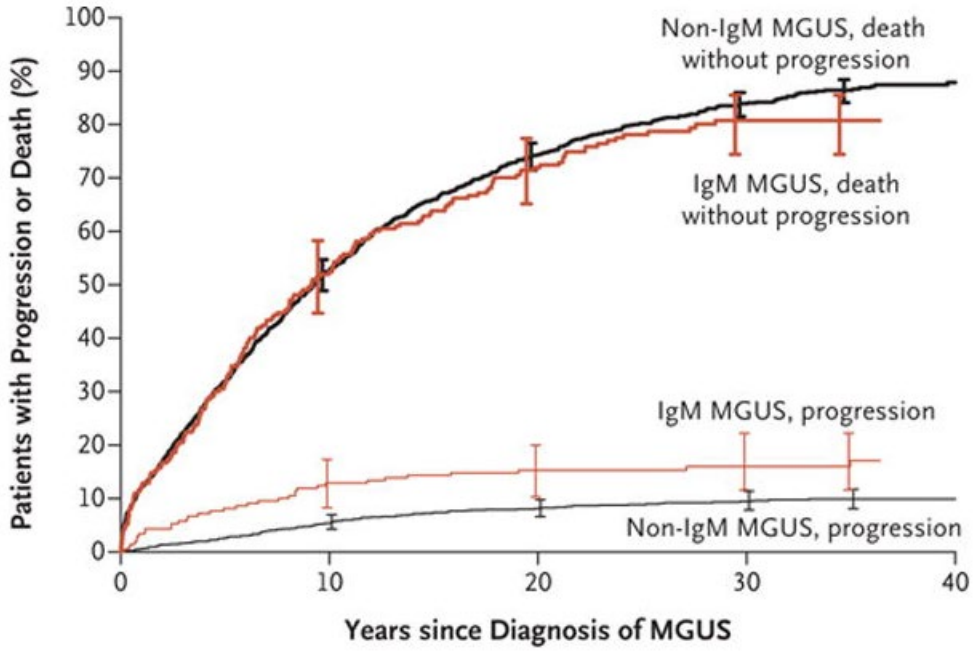
Table 2

Score*	Stage	3-yr WM-related death rate	10-yr OS rate
0	Very Low	0%	84%
1	Low	10%	59%
2	Intermediate	14%	37%
3	High	38%	19%
4–5	Very High	48%	9%

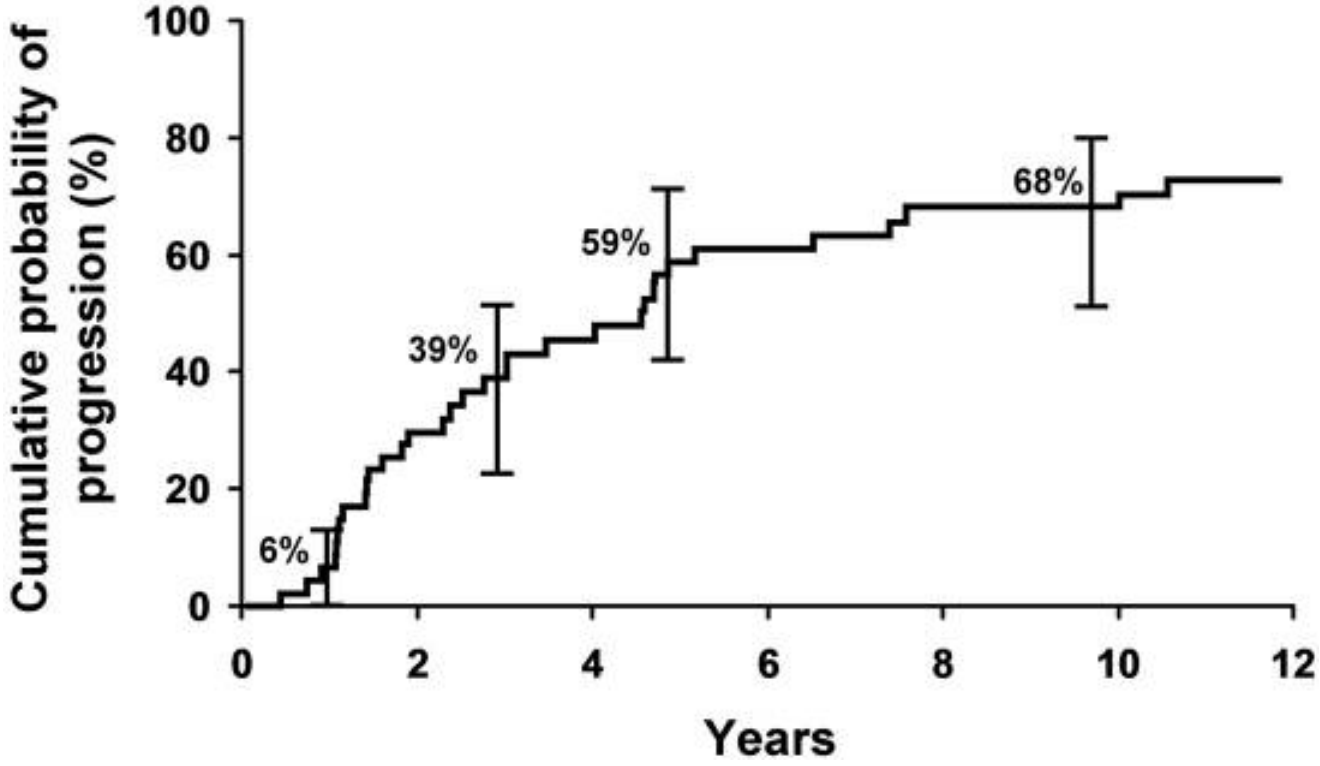
*Sum of total points in table 1

Long-Term Follow-up of MGUS and Smoldering WM

MGUS



Smoldering WM



Risk of progression =

- 2% per year in 1st 10 years after diagnosis
- 1% per year thereafter

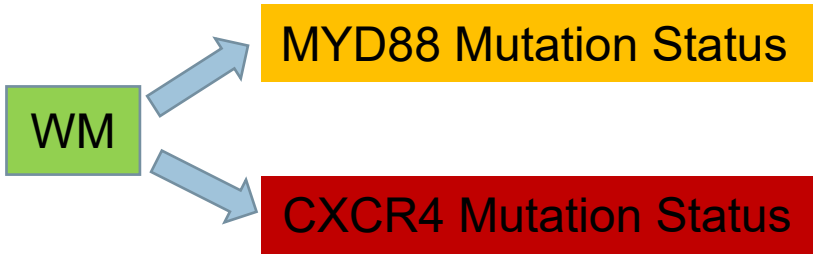
Kyle et al. Blood 2012; 119(19): 4462–6 Kyle et al NEJM 2018; 378:241-9

Labs to perform

- CBC
- CP-COMP
- SPEP
- SIFx
- UPEP
- UIFx
- B2 microglobulin
- LDH
- Quantitative immunoglobulins
- Serum viscosity

- Bone marrow biopsy – MYDD88 L265P, CXCR4 mutation
- PET/CT
- Neuropathy panel
- Anemia panel
- Coags
- Hepatitis panel

WM Genotyping



- MYD88 L265P variant is the most prevalent mutation in patients with WM (93-97%)
- MYD88 L265P disease typically presents at
  - younger age
  - with a higher % bone marrow infiltration
  - Superior 10-year OS (90% vs 73%, p <0.001)
  - Lower rate of transformation to DLBCL

- 30% of patients who have MYD88 mutation harbor somatic mutations in the C-terminal domain of CXCR4.
- *CXCR4* WHIM mutations (usually nonsense or frameshift)
  - lower incidence of adenopathy
  - convey resistance to ibrutinib
  - does not influence length of survival
- TP53 mutations are rare, but more commonly associated with $MYD88^{L265P}$ $CXCR4^{WHIM}$ WM than $MYD88^{L265P}$ $CXCR4^{WT}$

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Kapoor P, Treon SP, Blood, 2020

Reasons to Treat WM

History

- Fever > 101 F
- Drenching Night Sweats
- Weight Loss
- Severe Neuropathy
- Severe Fatigue

Physical

- Fundoscopic exam
- Lymphadenopathy
- Organomegaly
- Neuropathy

Other Diseases/Signs

- Amyloidosis
- Kidney Impairment
- Cryoglobulinemia
- Transformation

Monoclonal Protein

- IgM by Densitometry
- No Certain Level

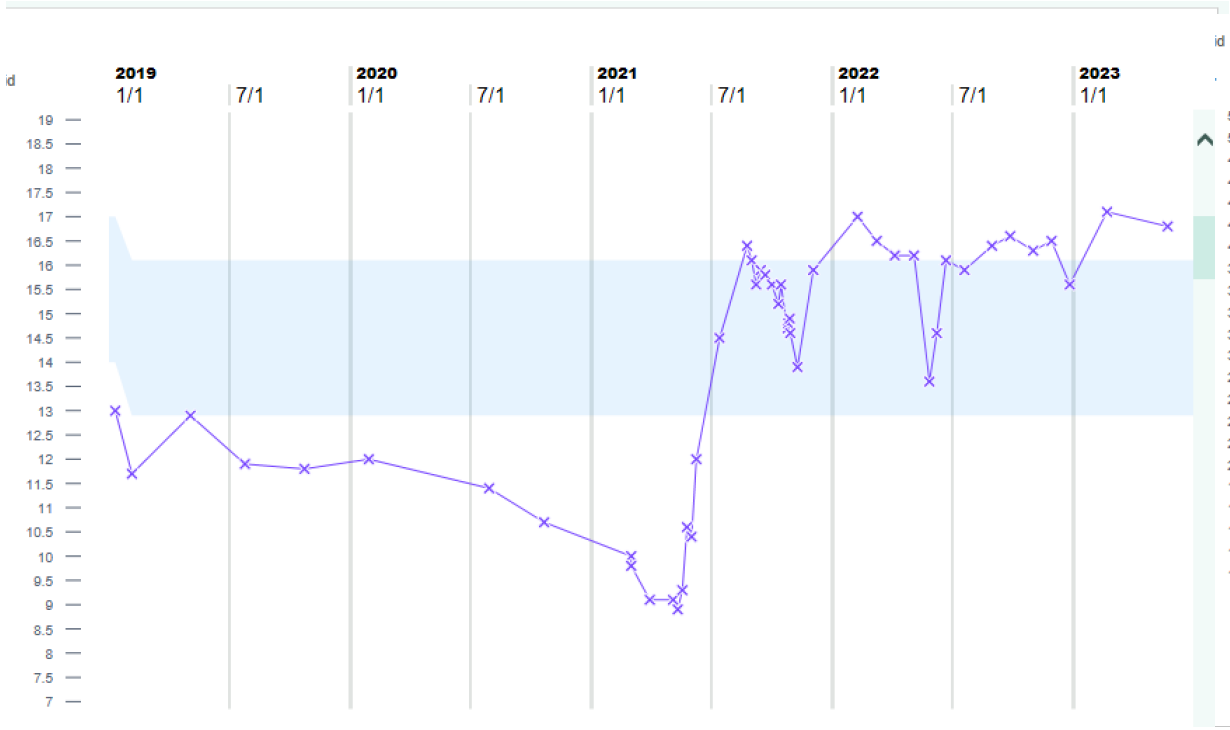
Rising

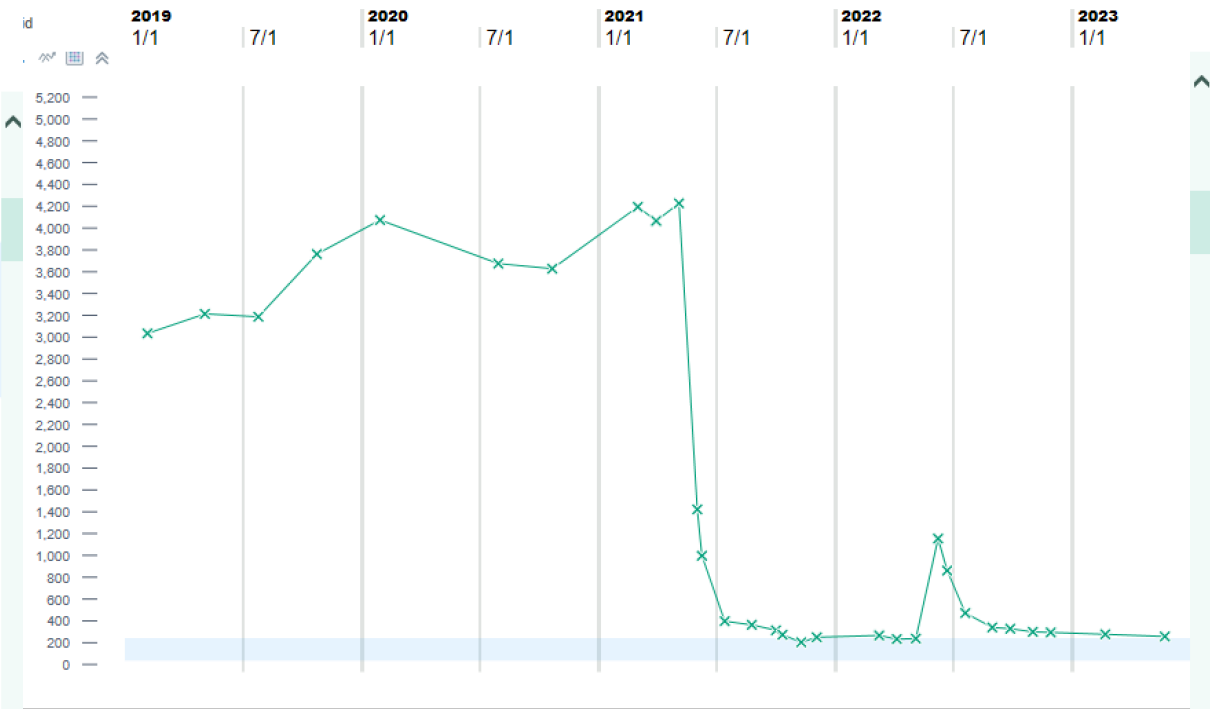
Other Tests

- Hemoglobin $\leq$ 10g/dL
- Platelets < 100 x 10^9/L due to WM
- Bulky lymph nodes/liver/spleen
- Hyperviscosity with signs (~>4 cp)

Pratt et al. 2022 Br J Haemat

Symptomatic WM – treatment effect





National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023 Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

PRIMARY THERAPY FOR WM/LPL[a] (Order of regimens is alphabetical and does not indicate preference)	
Preferred Regimens	
• Bendamustine/rituximab	• Zanubrutinib (category 1)
• Bortezomib/dexamethasone/rituximab[b]	
• Ibrutinib ± rituximab (category 1)	
Other Recommended Regimens	
• Bendamustine	• Rituximab
• Carfilzomib/rituximab/dexamethasone	• Rituximab/cyclophosphamide/dexamethasone
• Ixazomib/rituximab/dexamethasone	• Rituximab/cyclophosphamide/prednisone

Fixed duration

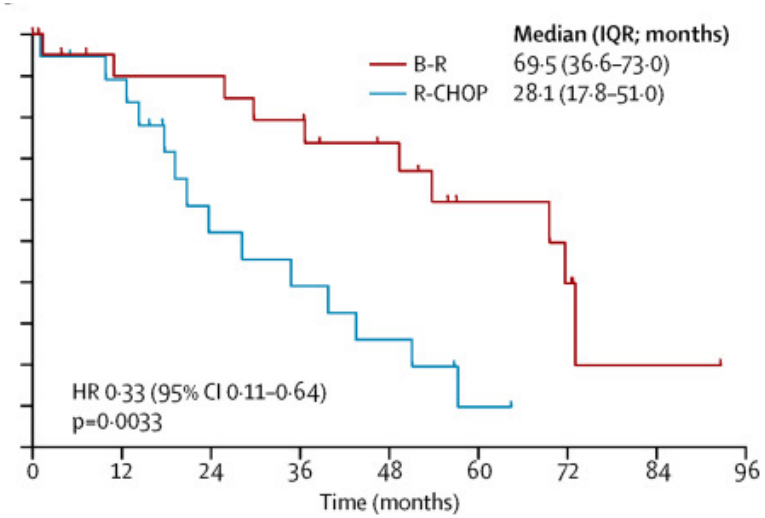
- Bendamustine + Rituximab +/- Dexamethasone
- Cyclophosphamide + Rituximab +/- Dexamethasone
- Bortezomib + Rituximab +/- Dexamethasone
- Carfilzomib + Rituximab +/- Dexamethasone
- Ixazomib + Rituximab +/- Dexamethasone

Indefinite duration

- Ibrutinib +/- Rituximab
- Zanubrutinib

Chemoimmunotherapy

Regimen	Major Response Rate	PFS (mos)	When to use?
R-Bendamustine	90-96%	65-69	Rapid response needed; Pts with LAD/organomegaly
R-CHOP	91%	28	
R-Cyclophosphamide-Dex	74-87%	34-35	Well tolerated. Med time to response 4.1 mos.
R-2CdA or R-Fludara +/- Cy	75-95%	36-62	



Considerations

- Risk of 2ndary MDS/leukemia
- Cytopenias (low blood counts)
- Stem cell toxicity (Nucleoside Analogs)
- Activity appears unaffected by MYD88 mutation status
  - R-Benda and R-Cy-Dex

Laribi et al. 2019 Br J Haem 186(1): 146-9. Rummel et al. Blood (2019) 134 (Supplement_1): 343. Kastritis et al. 2015 Blood 126 (11) 1392-4. Paludo et al. 2017 Br J Haem 179(1): 98-105

Proteasome Inhibitor Based Therapies

Regimen	Major Response Rate	PFS (mos)	Considerations
R-Bortezomib-Dex	68%	42	PN > than Car or Ixa, better sc and weekly
R-Carfilzomib-Dex*	68%	46	HTN, Heart and Kidney impairment; PN < 5%
R-Ixazomib-Dex**	77%	NR @ 36 mos.	Improved convenience

* Response not impacted by $MYD88^{L265P}$ or $CXCR4^{WHIM}$ mutation status.

** Response not impacted by $CXCR4^{WHIM}$ mutation status. (all pts had $MYD88^{L265P}$ WM)

Considerations

- No 2nd malignancy risk
- No Stem cell toxicity
- BDR – median time to response 4-8 weeks

Dimopoulos et al. Blood 2013 Treon et al. Blood 2014 Castillo et al Clin Cancer Res 2018

Phase III Trial of DRC vs. bortezomib-DRC

Regimen	Major Response Rate (VGPR/CR at EOT)	24-month PFS (p=0.32)	Time to 1st response (mos)
R-Cy-Dex	69.9% (9.6)	72.8%	5.5
R-CyBorD	80.6% (17.2)*	80.6%	3

* VGPR/CR 32.6% at best response

Regimen	≥ Grade 3 AEs(all)	≥ Grade 3 Sensory Neuropathy
R-Cy-Dex	49%	0 pts
R-CyBorD	49.5%	2 pts

Buske et al. JCO e-pub 2/2023 DOI: 10.1200/JCO.22.01805

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Fixed duration

- Bendamustine + Rituximab +/- Dexamethasone
- Cyclophosphamide + Rituximab +/- Dexamethasone
- Bortezomib + Rituximab +/- Dexamethasone
- Carfilzomib + Rituximab +/- Dexamethasone
- Ixazomib + Rituximab +/- Dexamethasone

Indefinite duration

- Ibrutinib +/- Rituximab
- Zanubrutinib

Clinical Responses to Ibrutinib

Median of 9 (range 1-18) Cycles

	(N= 63)	(%)
VGPR	10	15.9
PR	36	57
MR	11	17.5

Response criteria adapted from 3rd International Workshop on WM (Treon et al, BJH 2011)

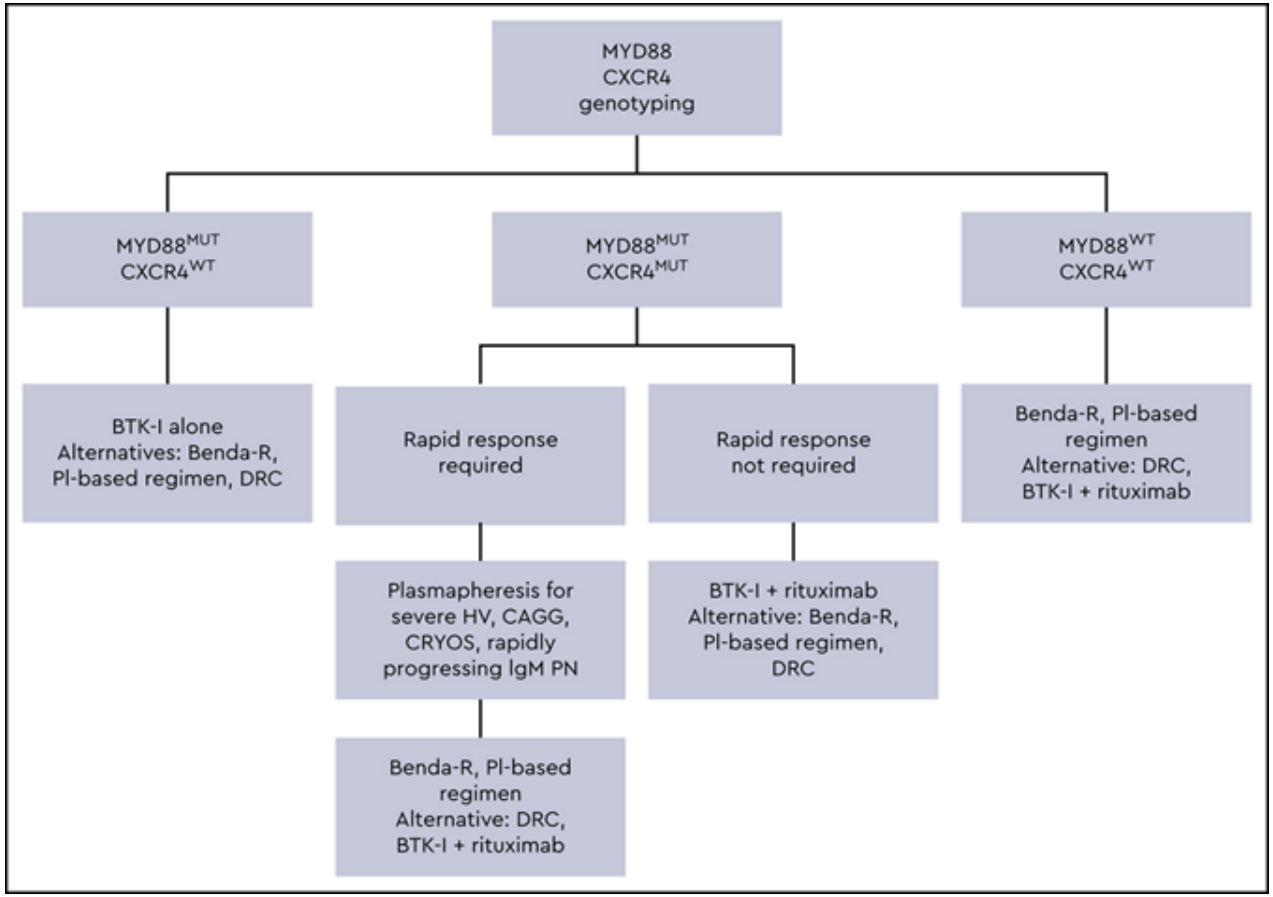
ORR: 90.5% Major RR (≥ PR): 73%

Treon et al, NEJM 2015

Rate of Response to Ibrutinib in Patients with Waldenström's Macroglobulinemia, According to Mutation Status.

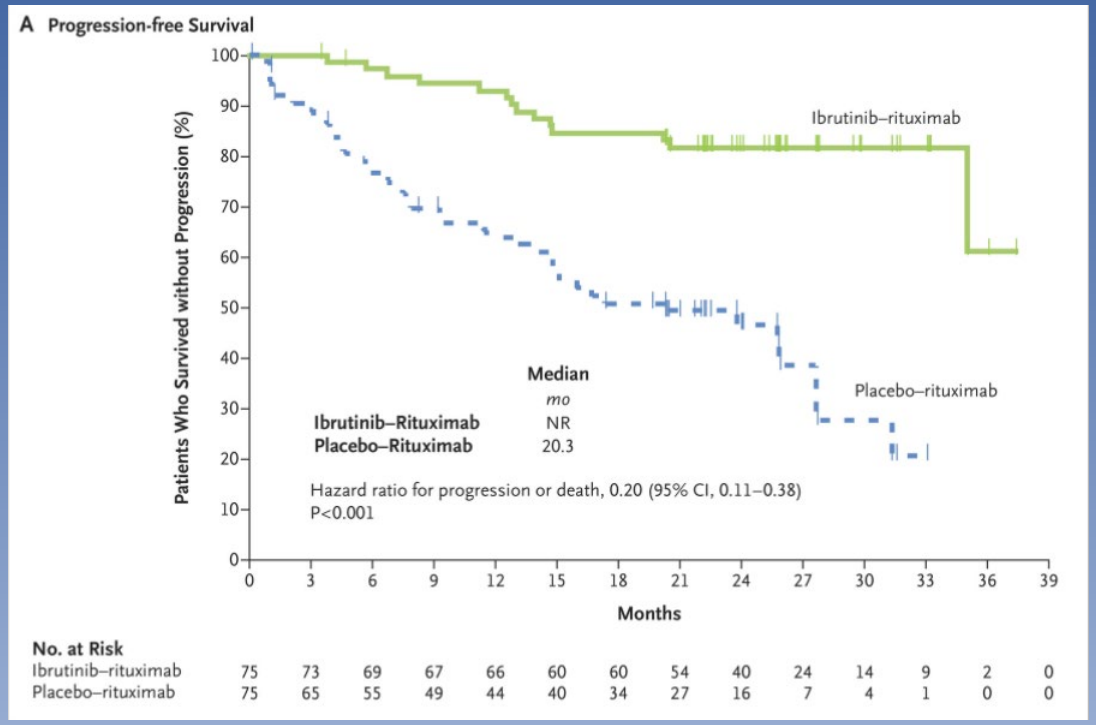
Table 1. Rate of Response to Ibrutinib in Patients with Waldenström's Macroglobulinemia, According to Mutation Status.*

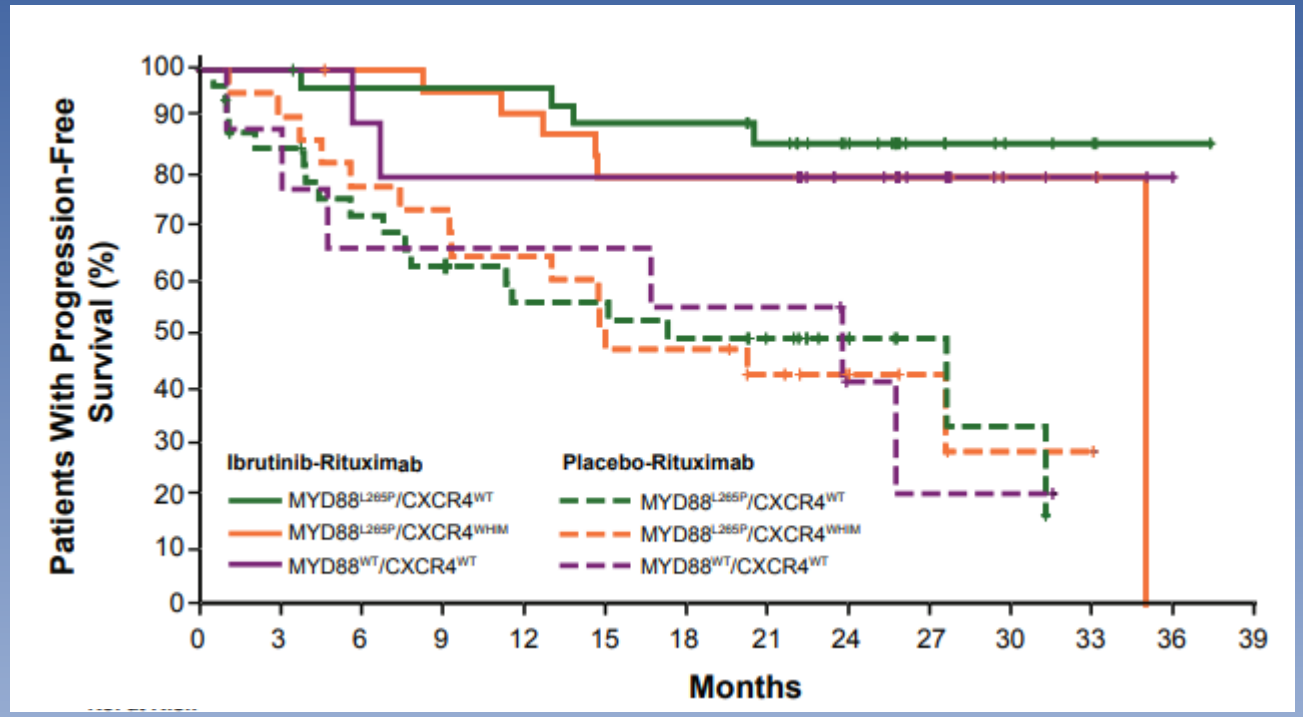
Response Rate	Mutated *MYD88* and Wild-Type *CXCR4* (N=36)	Mutated *MYD88* and *CXCR4* WHIM (N=21)	Wild-Type *MYD88* and *CXCR4* (N=5)	P Value†
		percent		
Overall	100	85.7	60	0.005
Major	91.7	61.9	0	<0.001



Treon SP et al. N Engl J Med 2015;373:584-586, Jorge J. Castillo,Steven P. Treon, Management of Waldenström macroglobulinemia in 2020, Hematology Am Soc Hematol Educ Program, 2020

iNNOVATE:
Ibrutinib-Rituximab vs. Placebo-Rituximab





30 month PFS:
- 82% for I-R vs 28% for placebo-R
- HR 0.20; P<0.001

30mos PFS	Ibrutinib-R	Placebo-R
MYD88 L265P/*CXCR4* WT	86%	33%
MYD88 L265P/*CXCR4* WHIM	80%	29%
MYD88 WT/*CXCR4* WT	80%	21%

iNNOVATE:
Ibrutinib-Rituximab vs. Placebo-Rituximab

Table 2. Adverse Events and Duration of Treatment.

Variable	Ibrutinib–Rituximab (N=75)	Placebo–Rituximab (N=75)
Median duration of treatment (range) — mo	25.8 (1.0–37.2)	15.5 (0.4–34.3)
Most common adverse events of any grade — no. of patients (%)*		
Infusion-related reaction	32 (43)	44 (59)
Diarrhea	21 (28)	11 (15)
Arthralgia	18 (24)	8 (11)
Nausea	16 (21)	9 (12)
Anemia	14 (19)	22 (29)
Asthenia	12 (16)	19 (25)
Fatigue	10 (13)	20 (27)
Headache	10 (13)	17 (23)
IgM flare	6 (8)	35 (47)
Adverse event of grade ≥3 — no. of patients (%)†	45 (60)	46 (61)
Hypertension	10 (13)	3 (4)
Atrial fibrillation	9 (12)	1 (1)
Anemia	8 (11)	13 (17)
Neutropenia	7 (9)	2 (3)
Pneumonia	7 (9)	2 (3)
Hyponatremia	4 (5)	2 (3)
Infusion-related reaction	1 (1)	12 (16)
Thrombocytopenia	0	4 (5)
Serious adverse event — no. of patients (%)‡	32 (43)	25 (33)
Pneumonia	6 (8)	2 (3)
Atrial fibrillation	5 (7)	1 (1)
Respiratory tract infection	3 (4)	0
Anemia	2 (3)	0
Congestive cardiac failure	2 (3)	0
Fall	2 (3)	0
Gastroenteritis	2 (3)	0
Myocardial ischemia	2 (3)	0
Arthralgia	2 (3)	0

* Listed are adverse events of any grade that occurred in at least 20% of the patients in either treatment group and for which the frequency differed between treatment groups by at least 5 percentage points. Data regarding major hemorrhage (which occurred in 4% of the patients in each group) are not listed because the incidence did not meet the criteria for reporting here.
† Listed are adverse events of grade 3 or higher that occurred in at least 5% of the patients in either treatment group.
‡ Listed are serious adverse events that occurred in at least 2% of the patients in either treatment group.

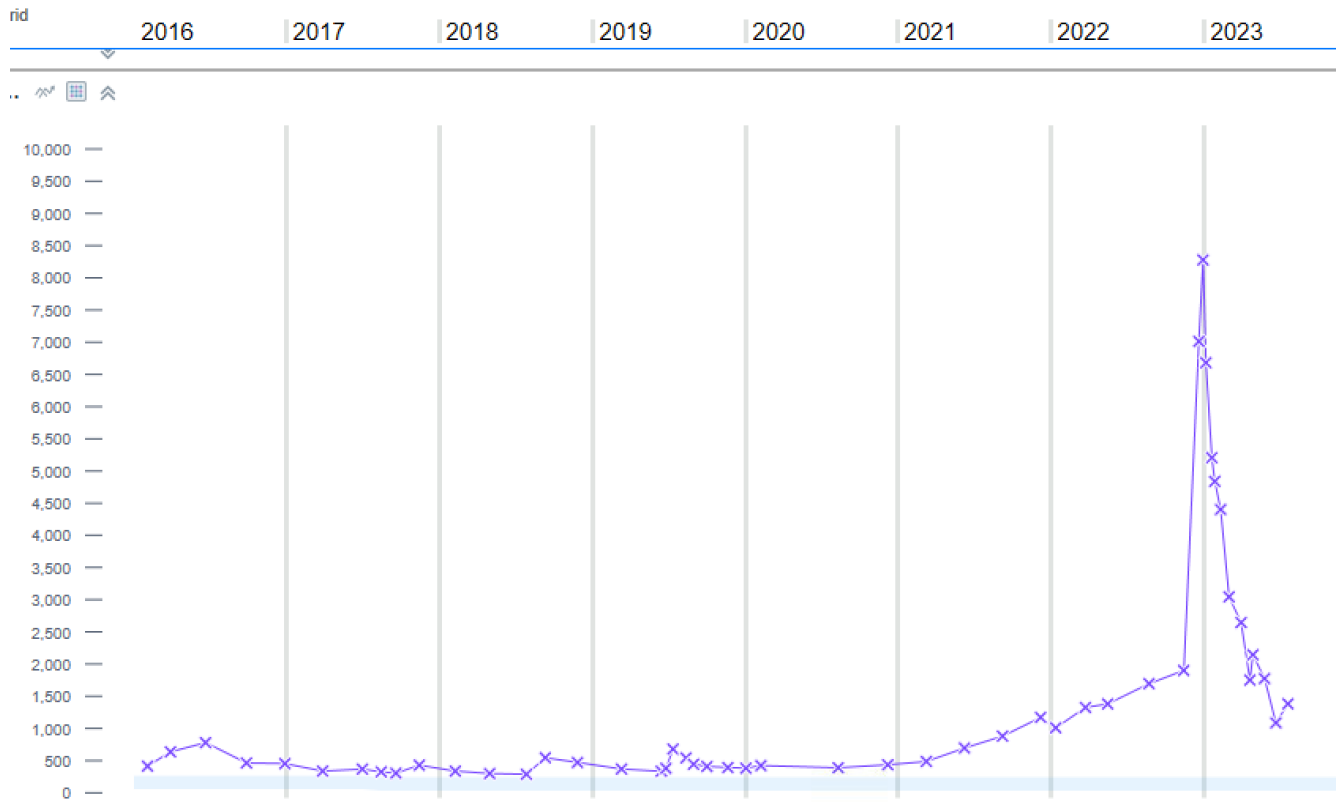
* Bleeding events (51% vs 21%)

Considerations:

- Stop taking ibrutinib 3 to 7 days before the surgery or procedure.
- Talk with your doctor about any other blood thinners/antiplatelet therapies you may be taking
- Stopping therapy is associated with rapid disease relapse/progression

Practical Considerations - Ibrutinib

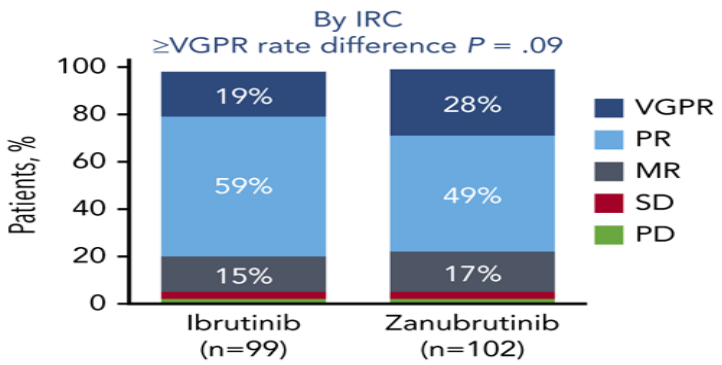
- Check MYD88 mutation status prior to initiating ibrutinib monotherapy.
- Recommend pharmacy consult prior to initiation due to CYP3A interacting meds
- Bleeding risk, 3% major
  - Avoid in combination with warfarin if possible
  - Instruct not to take with NSAIDs, Fish oil, Seville oranges, grapefruit and starfruit
  - Need to stop 3 days prior to minor surgery and 7 days prior to major surgery
- 10% risk of atrial fibrillation
- 20% risk of hypertension
- Approved as primary therapy in WM by the FDA, Health Canada, and the EMA.
- Should not be stopped unless toxicity or progression is suspected.

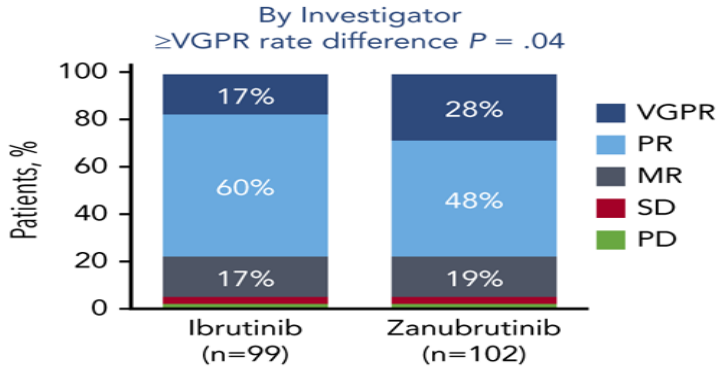


The ASPEN study

ASPEN: Zanubrutinib vs ibrutinib in patients with *MYD88*^{L265P} Waldenström macroglobulinemia

Best Overall Responses



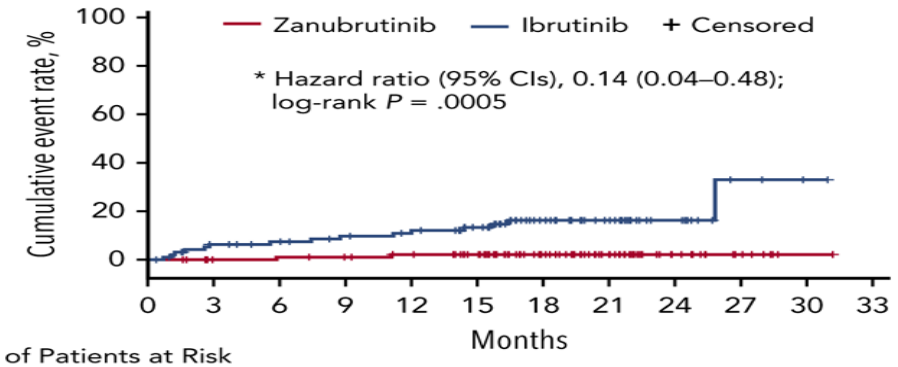


AE Categories, n (%) (Pooled Terms)	All Grades	
	Ibrutinib (n=98)	Zanubrutinib (n=101)
Atrial fibrillation/flutter*	15 (15.3)	2 (2.0)
Diarrhea (PT)	31 (31.6)	21 (20.8)
Hemorrhage	58 (59.2)	49 (48.5)
Major hemorrhage	9 (9.2)	6 (5.9)
Hypertension	17 (17.3)	11 (10.9)
Neutropenia*	13 (13.3)	30 (29.7)
Infection	66 (67.3)	67 (66.3)

*Descriptive 2-sided $P < .05$

Data cutoff 31Aug2019

Time-to-event analysis of atrial fibrillation/flutter events



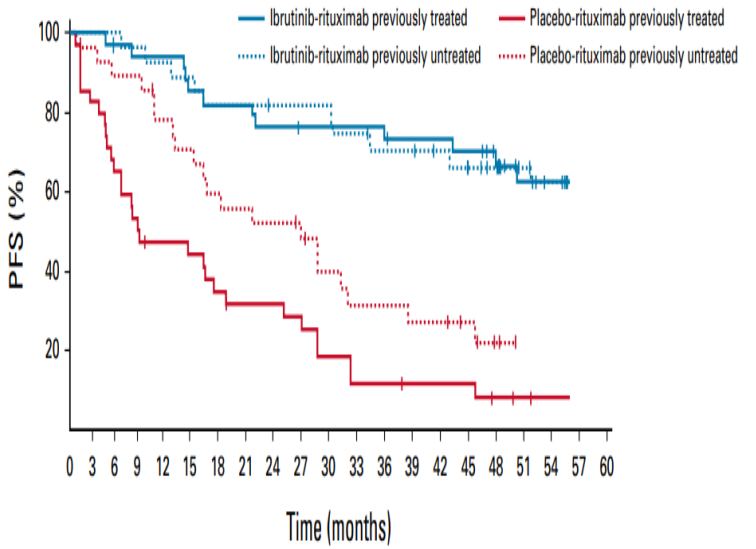
No. of Patients at Risk

Zanubrutinib	101	95	94	92	89	81	57	34	15	7	1	0
Ibrutinib	98	87	83	78	74	66	46	28	13	3	1	0

Tam C. et al. Blood 2020

BTK Inhibitors for WM

Study	N TN/Total	Population	ORR (%)	MRR (%)	PR (%)	VGPR+ (%)	PFS (%)
Ibrutinib	63	RR	91	79	49	30	5y 54
Ibrutinib	30	TN	100	87	57	30	4y 76
iNNOVATE Ibrutinib+ Rituximab Placebo + Rituximab	150 34/41 34/41	TN/RR	91/93 53/37	76/76 41/22	50/42 32/20	27/34 9/2	4y 70/71 32/20
Acalabrutinib	106 14 92	TN RR	93 95	78 84	71 57	7 23	5.5y 84 (TN) 52 (RR)
Zanubrutinib AU-003	77	TN+RR	100	83	37	44	2-yr 81
Zanubrutinib AU-003	24	TN	100	87	54	33	2-yr 91
ASPEN Cohort 1($MYD88^{mut}$) Zanubrutinib Ibrutinib	 102 99	TN/RR	 95 94	 81 67/80	 45 55	 28 36 19 22	1y 3.5y 90 78 87 70
Zanubrutinib	19	TN	94	73	53	26	1.5y 78
Ibrutinib	18	TN	89	67	50	17	1.5y 94
ASPEN Cohort 2 Zanubrutinib ($MYD88^{WT}$)	26	TN/RR	81	65	35	31	1.5 3.5y 68 NA
Tirabrutinib	27	TN/RR	96	89	78	11	NR
Ibrutinib-venetoclax	45	TN	100	93	53	40	1y 92%



AEs,[a] n (%)	All grades Ibrutinib (n=98)	All grades Zanubrutinib (n=101)	Grade ≥3 Ibrutinib (n=98)	Grade ≥3 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/ nonskin 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)

Treon SP et al. *J Clin Oncol*. 2021;39(6):565-575. Castillo JJ et al. *Leukemia*. 2022;36(2):532-539. Buske C et al. *J Clin Oncol*. 2022;40(1):52-62. Trotman J et al. *Clin Cancer Res*. 2021;27(21):5793-5800. Owen et al. *HemaSphere*. 2022. Trotman J et al. *Blood*. 2020;136 (18): 2027-2037. Tam et al. *J Clin Oncol*. 2022. Sekaguchi et al. *Cancer Sci*. 2020. Zhou et al. ASH 2021. Mato AR et al. *Lancet*. 2021;397(10277):892-901. Palumba L et al. ASH 2022. Abstract 229. Castillo JJ et al. ASH 2022. Abstract 231.

Bendamustine Rituximab versus Ibrutinib as Primary Therapy for Waldenström Macroglobulinemia: An International Collaborative Study

Jithma P. Abeykoon[1], Shaji Kumar[1], Jorge J. Castillo[2], Shirley D'sa[3], Efstathios Kastritis[4], Eric Durot[5], Encarl Uppal[3], Morel Pierre[6], Jonas Paludo[1], Reema Tawfiq[1], Shayna R Sarosiek[7], Olabisi Ogunbiyi[8], Pascale Cornillet-Lefebvre[9], Robert A. Kyle[1], Alain Delmer[10], Morie A. Gertz[1], Meletios A Dimopoulos[11], Steve P. Treon[2], Stephen M. Ansell[1], and Prashant Kapoor[1]

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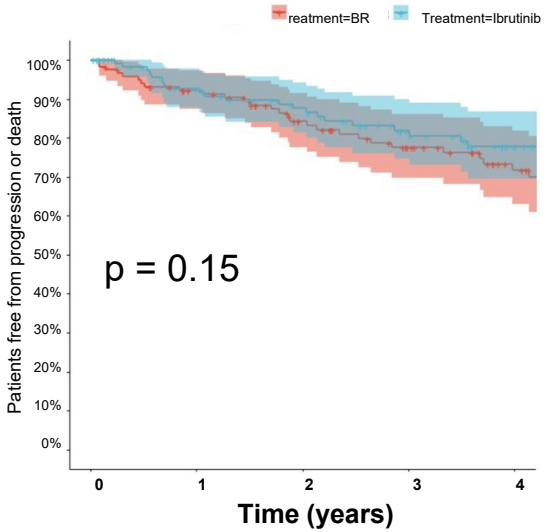
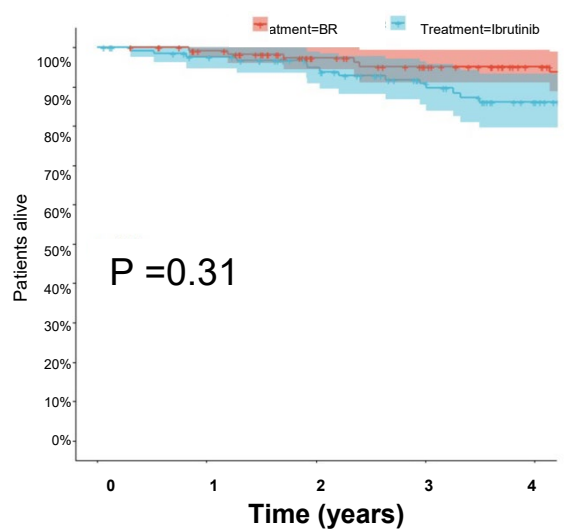
Variable	BR	Ibrutinib	p-value
Follow-up, median, 95%CI, y	4.5 (3.7-4.9)	4.5 (4-4.7)	0.7
Age, median, range, y	68 (40-86)	68 (39-86)	0.9
IPSS, %			
Low	11	17	0.63
Intermediate	33	33	
High	56	48	
Cycles, median (range)	6 (1-6) >4 cycles, 77%	42 (0.3-98)	
Overall response rate %	94	94	0.91
Major response rate, %	92	83	0.05
Complete response, %	20	2	**<0.001**
≥VGPR, %	50	33	**0.009**
4-year PFS, % (95%CI)	72 (63-82)	78 (70-87)	0.15
4-year OS, % (95%CI)	95 (91-99)	86 (80-93)	0.31

Progression-free survival



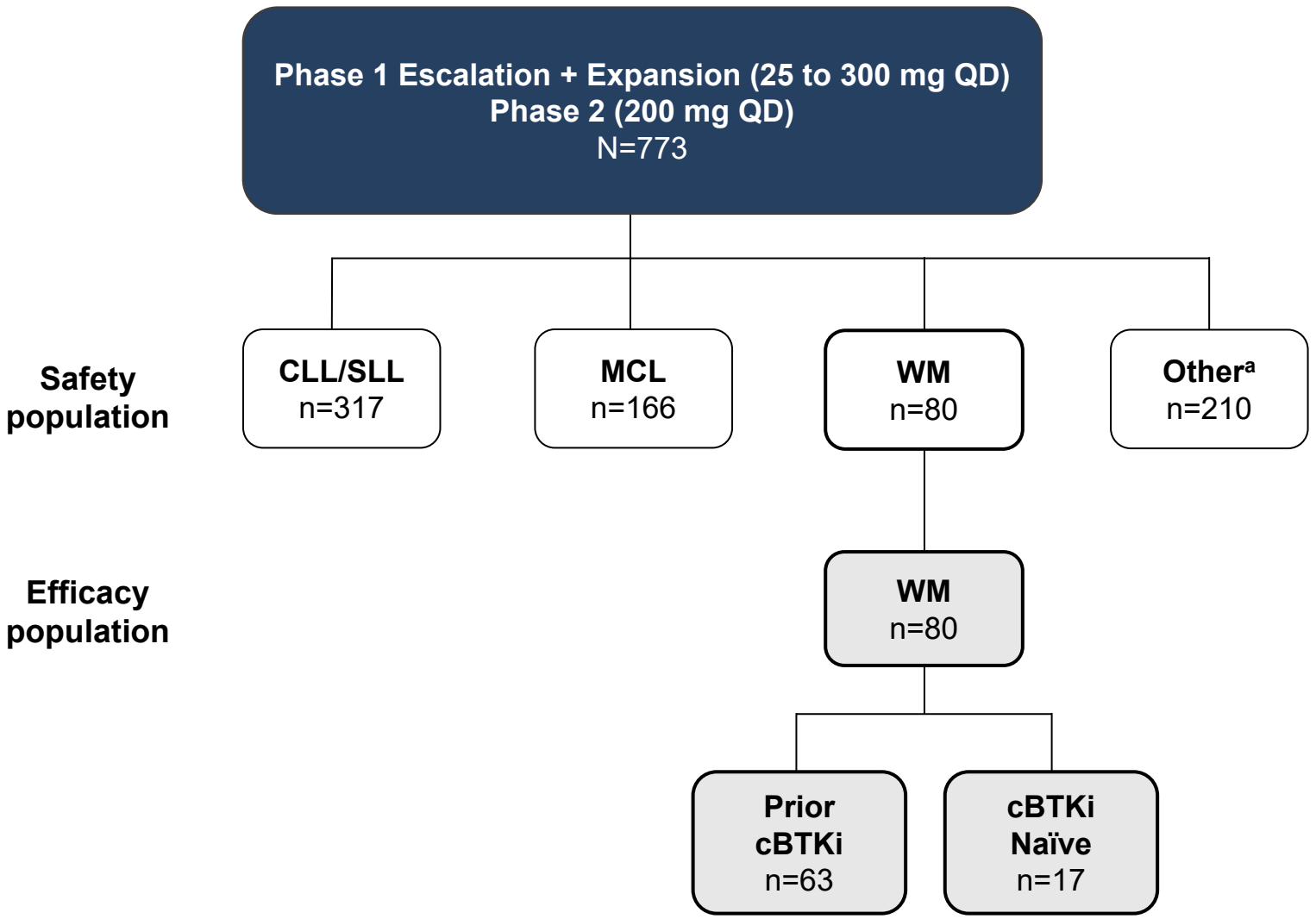
Overall survival



- Analysis of age-matched patients who received either BR or Ibrutinib (N=246)
- MYD88 WT patients excluded
- Median Follow-Up: 4.2 years

Abeykoon et al. Abstract 7566, ASCO 2022

Phase 1/2 BRUIN Study: Design, Eligibility and Enrollment



Phase 1 3+3 design

- 28-day cycles
- Intra-patient dose escalation allowed
- Cohort expansion permitted at doses deemed safe

Eligibility

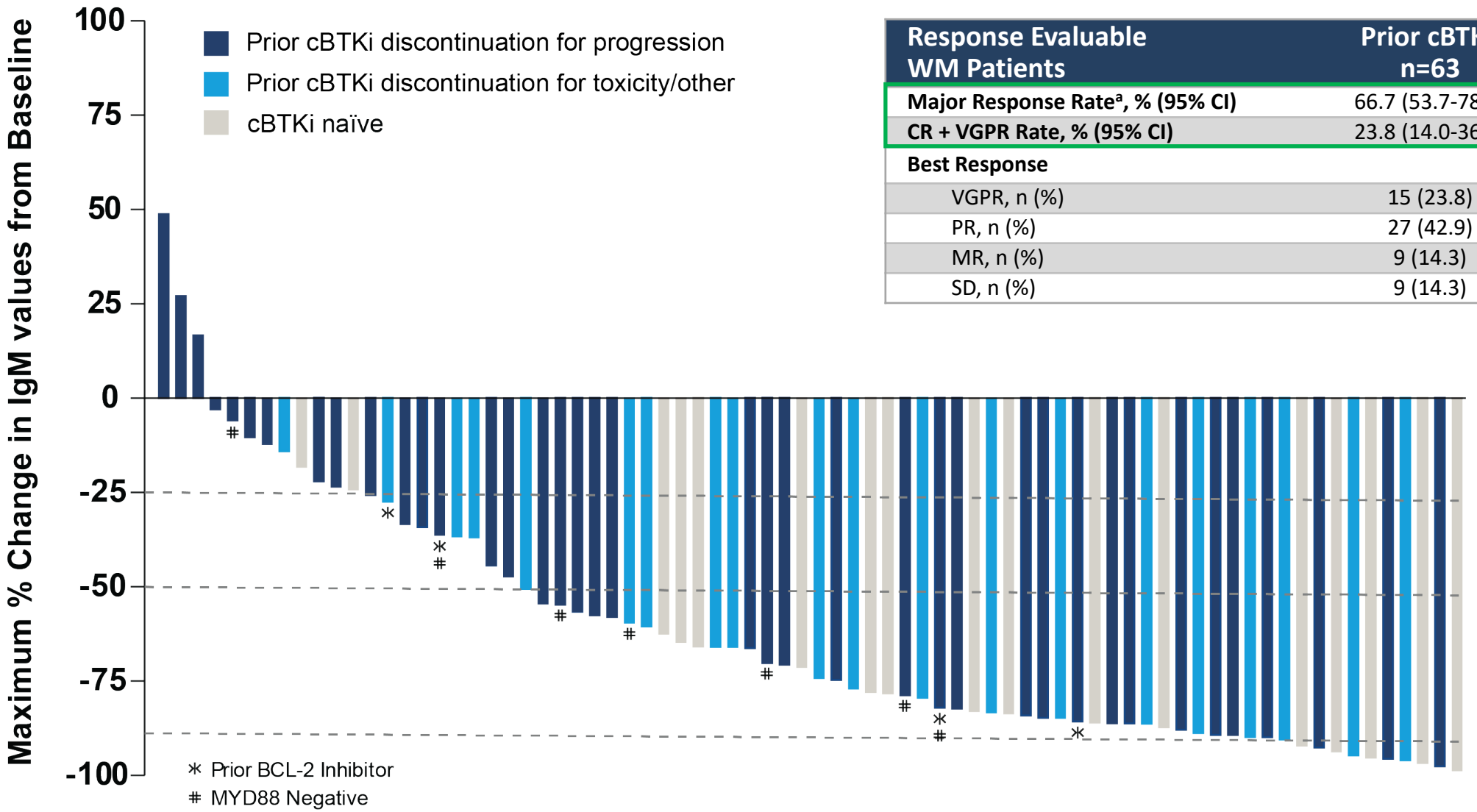
- Age ≥18
- ECOG 0-2
- Active disease and in need of treatment
- Previously treated

Key endpoints

- Safety/tolerability
- Determine MTD and recommended Phase 2 dose
- Pharmacokinetics
- Efficacy according to ORR and DoR (IWWM6/Modified IWWM6) as assessed by Investigator

Palomba ML et al. Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

Pirtobrutinib Efficacy in WM Patients

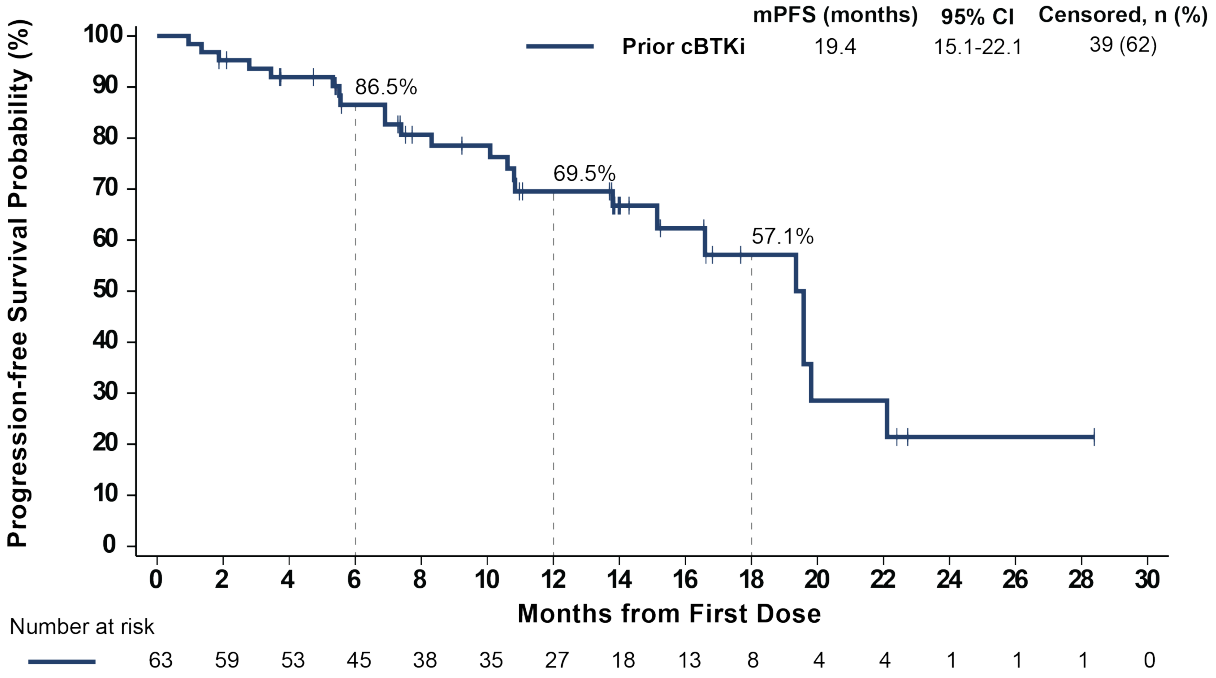


Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD, n (%)	9 (14.3)	2 (11.8)

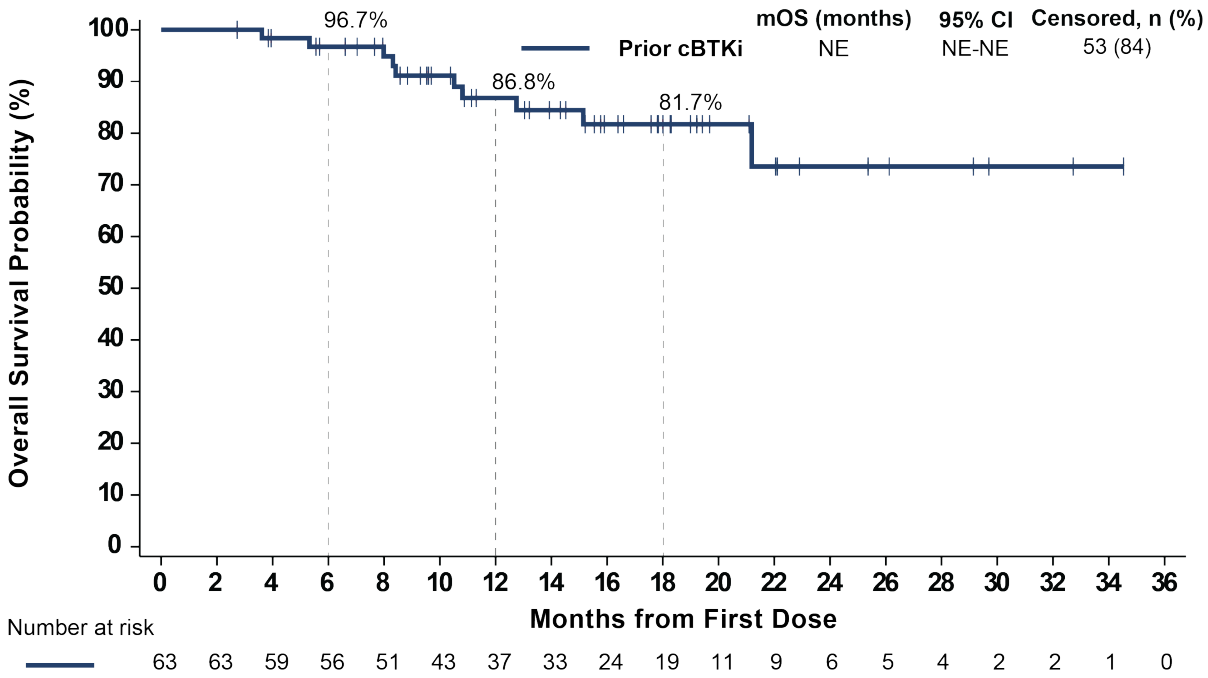
Palomba ML et al. Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed / Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study

Progression-Free Survival and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



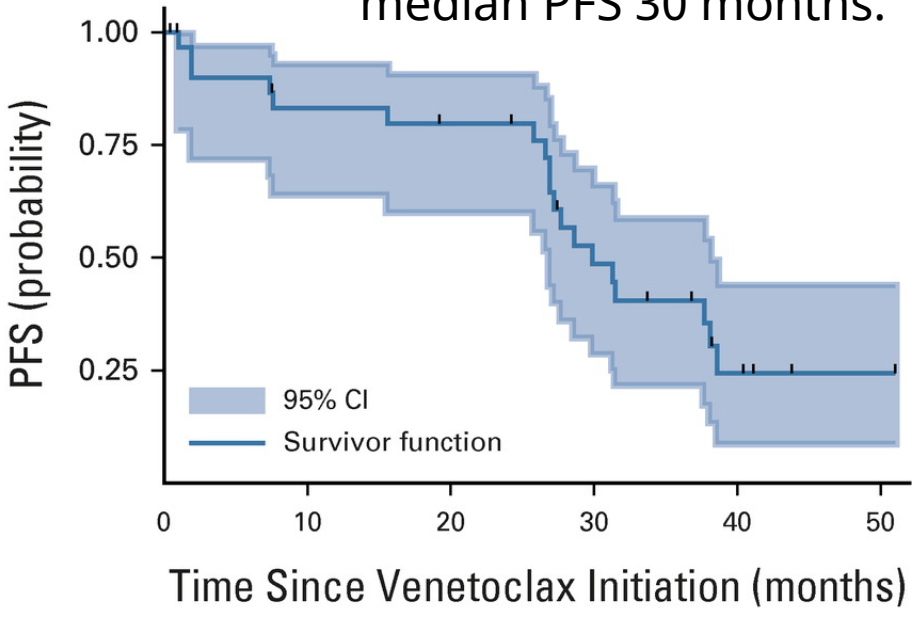
- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

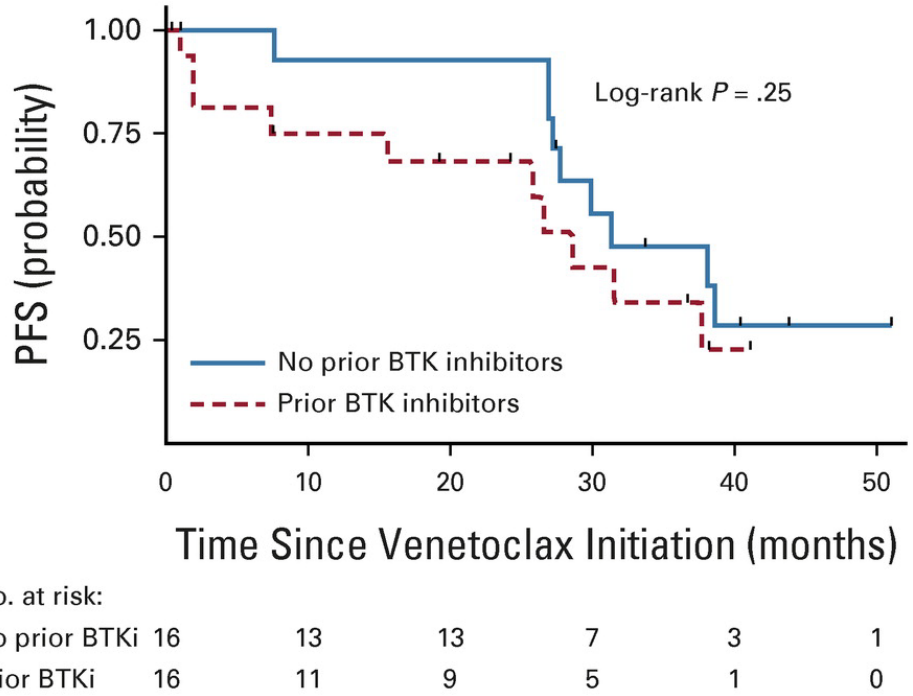
Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

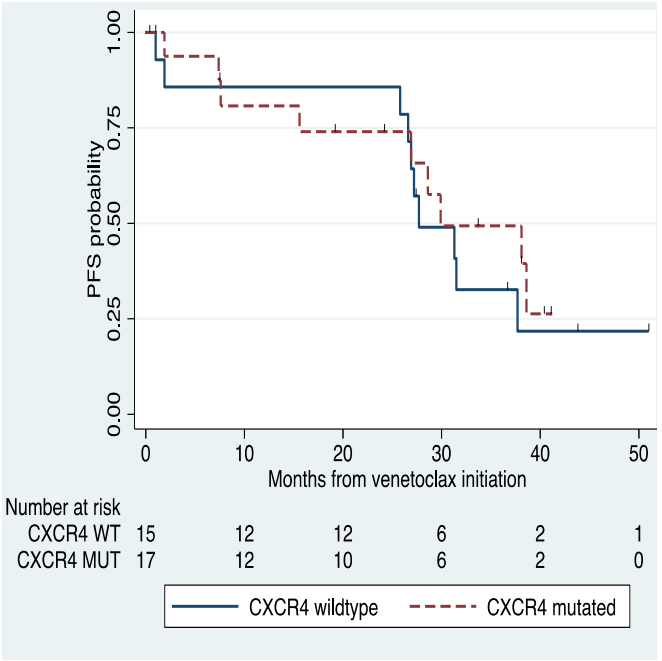
VENETOCLAX

Study	N	Patient Population	ORR (%)	MRR (%)	PR (%)	VGPR (%)	PFS (%)
Phase 1 Venetoclax	4	RR	100	100	100	0	NA
Phase 2 Venetoclax	32	RR	84	81	61	19	2-yr 80

median PFS 30 months.







CXCR4 mutations did not affect response or PFS

Davids, M. S. *et al. J Clin Oncol* **35**, 826-833, 2017
Castillo J. et al. JCO (January 01, 2022)

Autologous SCT

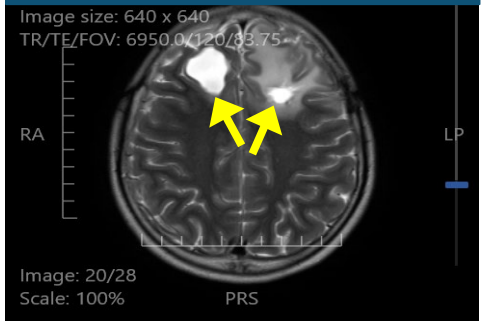
- No RCT data to suggest OS benefit.
- EBMT study:158 patients, median time from diagnosis to ASCT 20 months, **93% chemo-sensitive**
- 70% of patients achieved ≥VGPR.
- PFS at 5-year 40% and 5-years OS 70%, **influenced by number of lines of therapy and chemo-refractoriness at ASCT**.
- In young patients, stem cell mobilization is recommended after first line of therapy (deeper response, less treatment exposure).

CLR 131 Phospholipid Drug Conjugate (PDC)

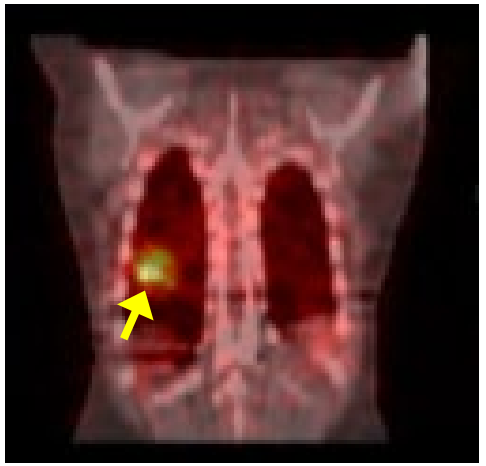
Validated Delivery Platform

- Tumor cells utilize lipids at significantly greater quantities than normal tissue
  - Energy source (b-oxidation)
  - Cell membrane production
  - Signaling molecules
- CLR-131 exploits cancer cells' needs for lipids to provide targeted delivery
  - Bind to specialized regions on tumor cell surface and internalized
  - Delivers 20-40% of infused drug to tumor
- CLR 131: targeted delivery of I-131 (validated therapeutic isotope)
  - Kills tumor cells by creating double stranded breaks in the DNA

PET and SPECT Scans post IV dosing



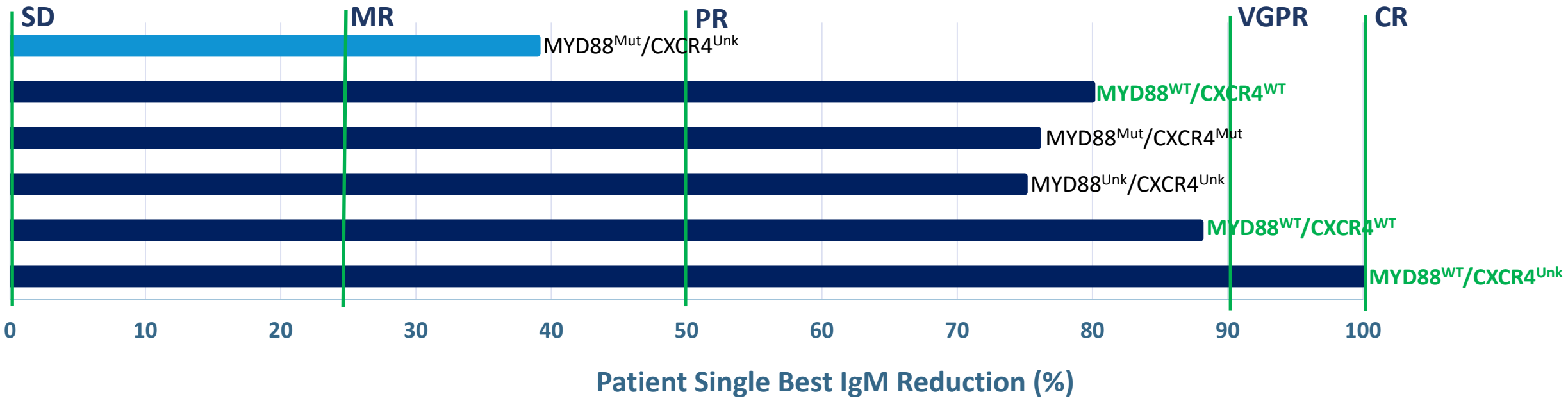
Crossing the BBB Metastatic Ependymoma



SPECT scan NSCLC

CLR 131 Phase 2 WM Best Response by Patient

Demonstrates Activity in All Patients Subtypes



- CLR 131 Responses
  - 100% Overall Response Rate (ORR)
  - 83.3% Major Response Rate (MRR)
  - 100% MRR in MYD88WT patients
  - 16.7% Complete Response Rate (CR)

Summarize: Always check for mutations status

Newly diagnosed:

- **Bendamustine-Rituximab (BR)**
- **Ibrutinib-Rituximab**
- **Zanubrutinib**

First relapse

-Relapse on a covalent BTK inhibitor- (ibrutinib, zanubrutinib, acalabrutinib, orelabrutinib or tirabrutinib) based regimen - **Bendamustine-Rituximab (BR)**

-Off therapy, post BR/ other chemoimmunotherapy or covalent BTK inhibitor-naïve

- **Bendamustine-Rituximab (BR)**
- **Ibrutinib-Rituximab**
- **Zanubrutinib**

Salvage therapies

- **Venetoclax**
- **Pirtobrutinib**
- **Proteasome inhibitor combinations**
- **ASCT in select patients**
- **Repeat previously used fixed duration therapy**

Questions

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EMORY WINSHIP CANCER INSTITUTE