Alessandra Tedeschi
Department of Hematology
Niguarda Hospital Milano

Alessandra Tedeschi COI

	Advisory Board	Speaker Bureau
Janssen	X	X
AbbVie	X	X
AstraZeneca	X	X
Beigene	X	X
Lilly	X	

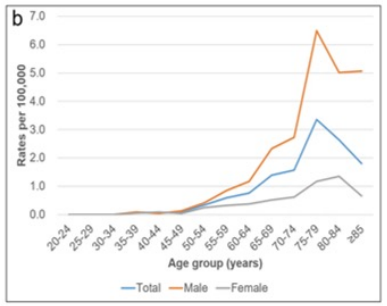
Treatment Decision in WM

Patient's factors:
- Age
- Comorbidities

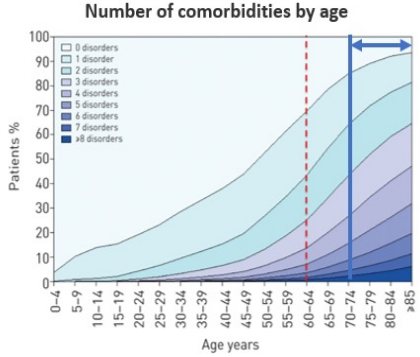
Disease factors:
- Hypervicosity
- Bulky Disease
- Disorders IgM related

TREATMENT DECISION

Incidence and prevalence of WM by age



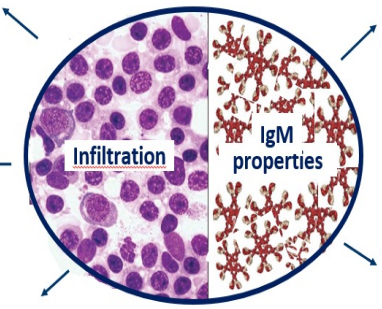
Number of comorbidities by age



-Hemoglobin <10 g/dL (60-75%)
-Platelet count < 100 000 mcL

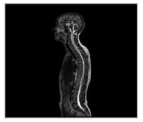
B symptoms
(Recurrent fever, night sweats, weight loss, fatigue)

Hyperviscosity Syndrome (10-15%) or IgM > 6000 mg/dL



Symptomatic:
Lympadenopathy/bulky
Hepatomegaly
Splenomegaly
Organ or tissue infiltration
(≤ 20% in first line)

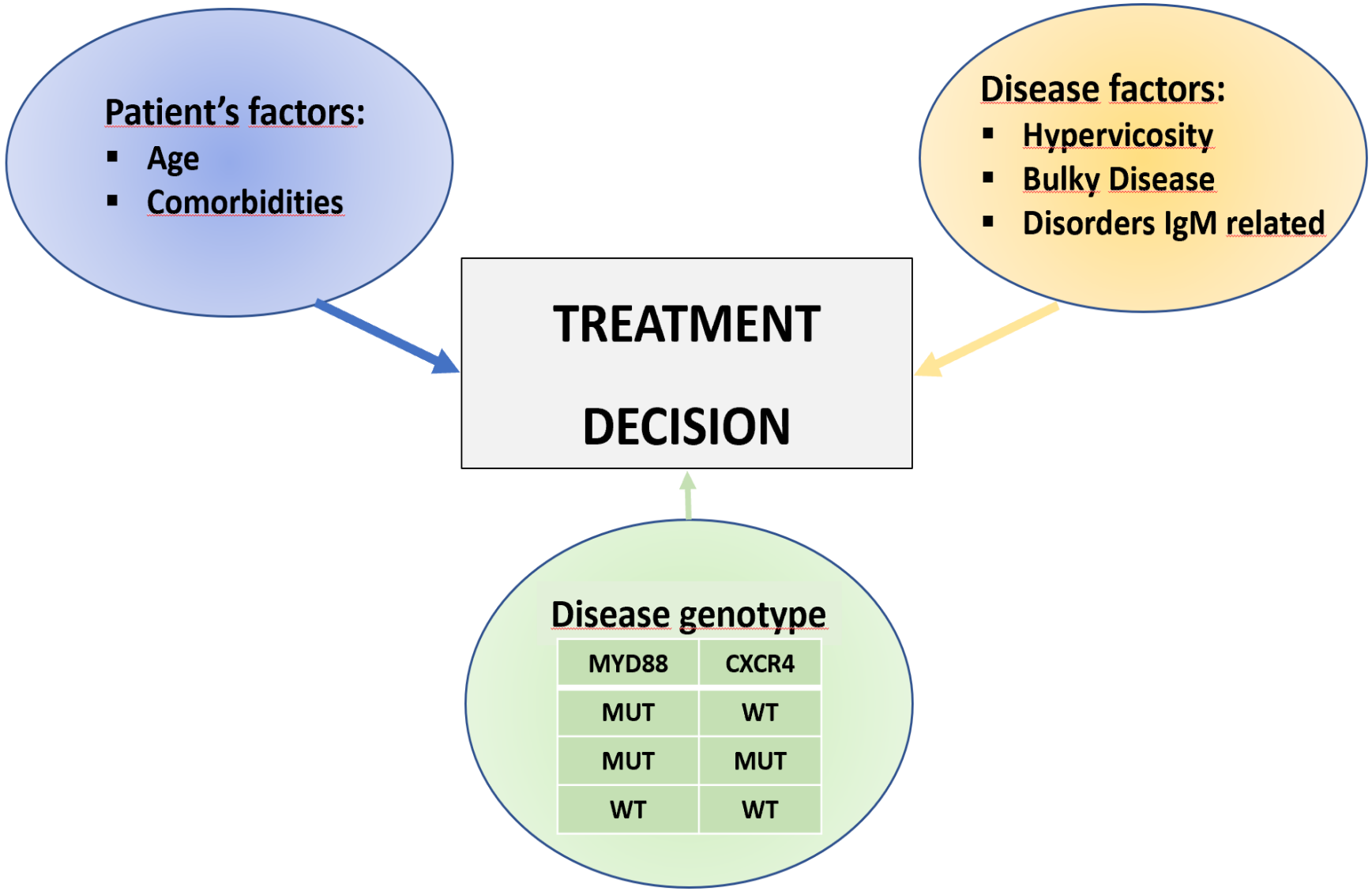
Symptomatic cryoglobulinemia (10%)
Cold agglutinin anemia (5%)
Immune hemolytic anemia
Immune thrombocytopenia
Nephropathy related to WM
Amyloidosis related to WM (10-15%)



Bing Neel Syndrome

Peripheral neuropathy (20-25%)

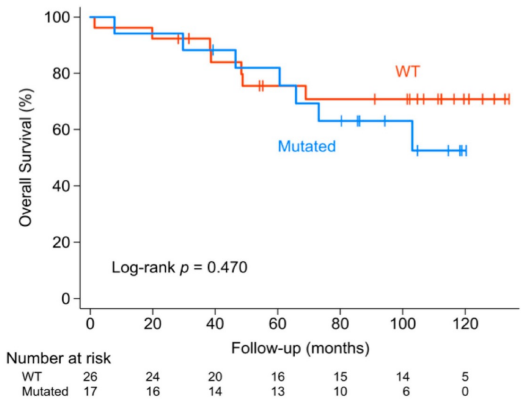
Treatment Decision in WM



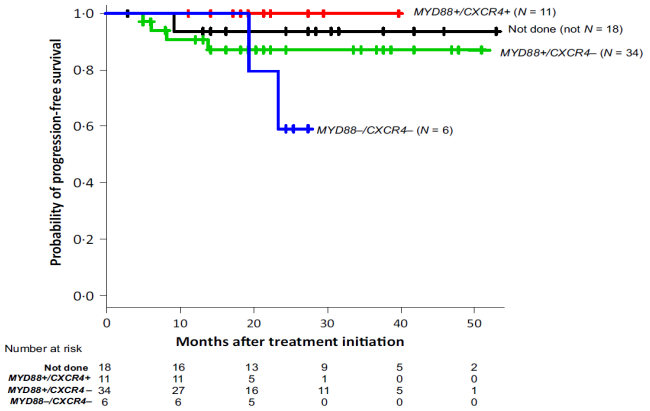
Role of genotype in WM treatment

Disease genotype	
MYD88	CXCR4
MUT	WT
MUT	MUT
WT	WT

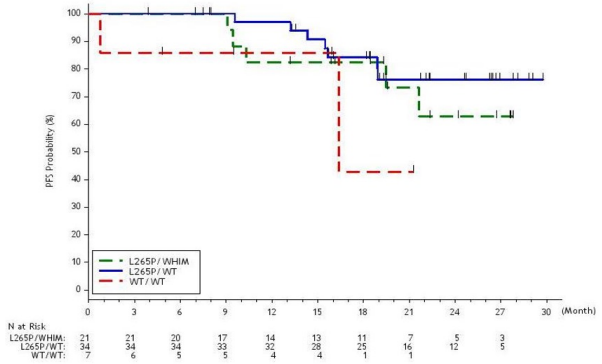
Bortezomib Rituximab First Line according to CXCR4 mut



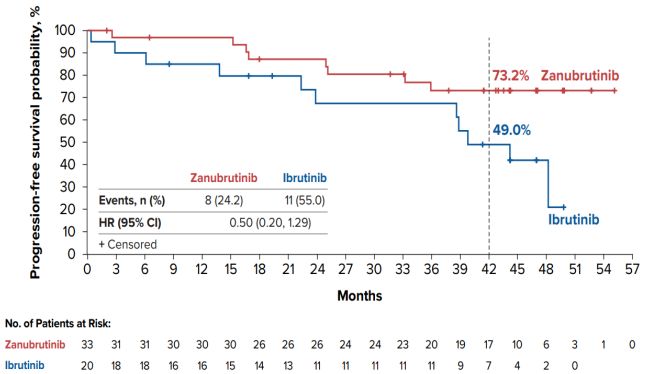
Bendamustine Rituximab First Line



Impact of genotype with Ibrutinib



Zanubrutinib vs Ibrutinib: PFS in CXCR4 mut



Zanubrutinib in MYD88 WT

MRR: 65%

At 42 months:

PFS: 53.8% (95% CI: 33.3, 70.6)

OS: 83.9% (95% CI: 62.6, 93.7)

First line treatment

Immuno-CHT

Benda Rituximab

DRC

(Bortezomib-Rituximab)

BTKi
Only for pts unsuitable for immuno-CHT

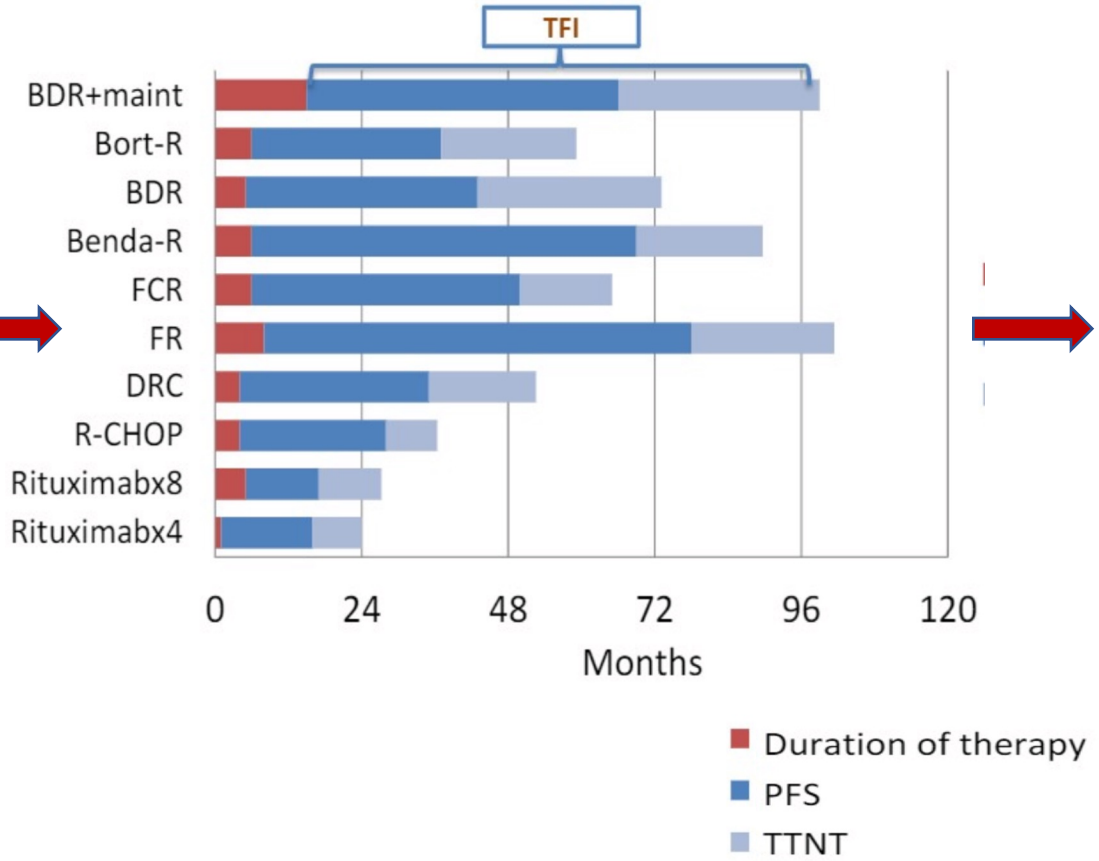
(Ibrutinib)°

Zanubrutinib

° not reimbursed in Italy

First Line fixed duration therapy in WM

Rituximab based therapy

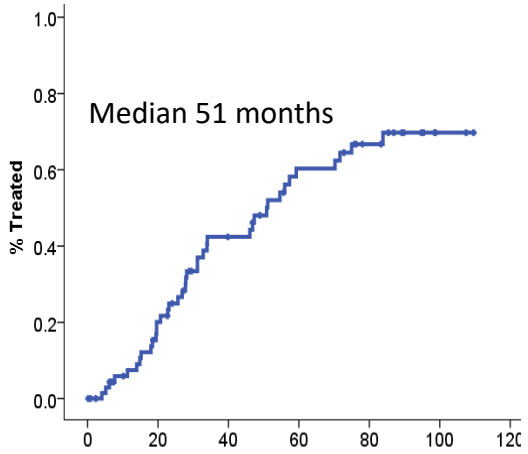


- ***Bendamustine Rituximab***
- ***Cyclophosphamide Rituximab DEX***

WM TREATMENT: first line

Rituximab Combination Treatment

DRC



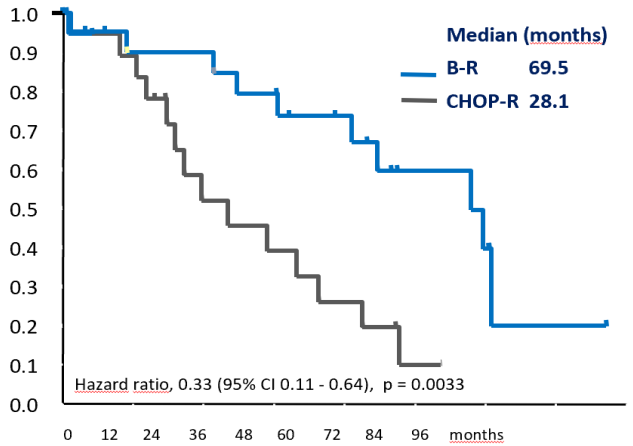
PROS:

- ✓ Minimal myelo/immuno-suppression
  89% pts completed 6 courses
- ✓ TTN 51 m

CONS:

- CR: 7%
- Median time to 50% IgM reduction: 4.1 m

Benda R



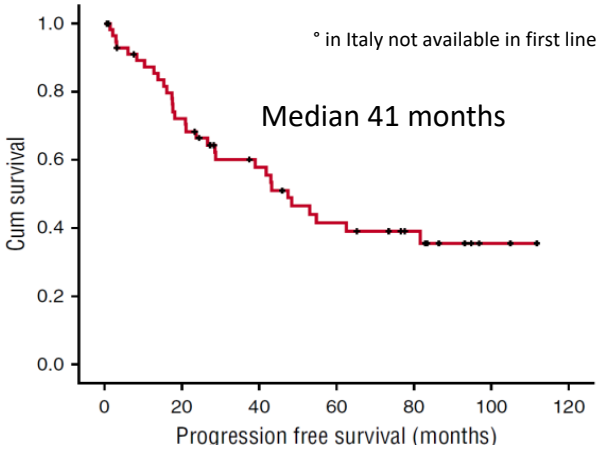
PROS:

- ✓ Rapidly effective/Prolonged PFS
- ✓ No impact from CXCR4 mut

CONS:

- Myelotoxicity/late infectious toxicities: dose reduction to 70 mg/sqm or 4 courses
- Secondary MDS/LAM (?): ~0-3%

Bortezomib°R



PROS:

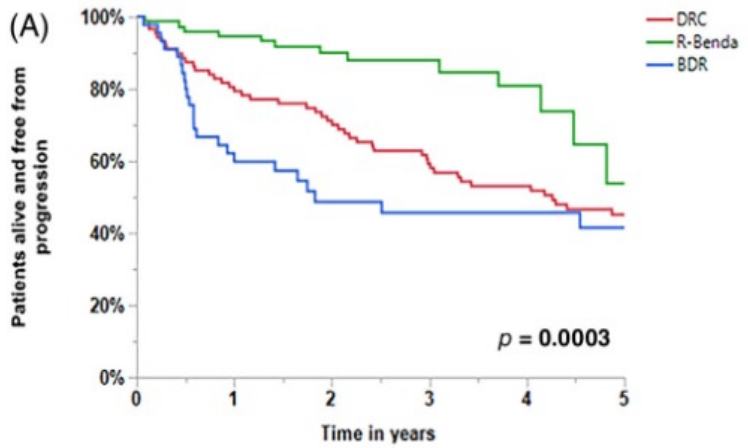
- ✓ Rapid IgM decrease
- ✓ Lower myelo/immuno-suppression

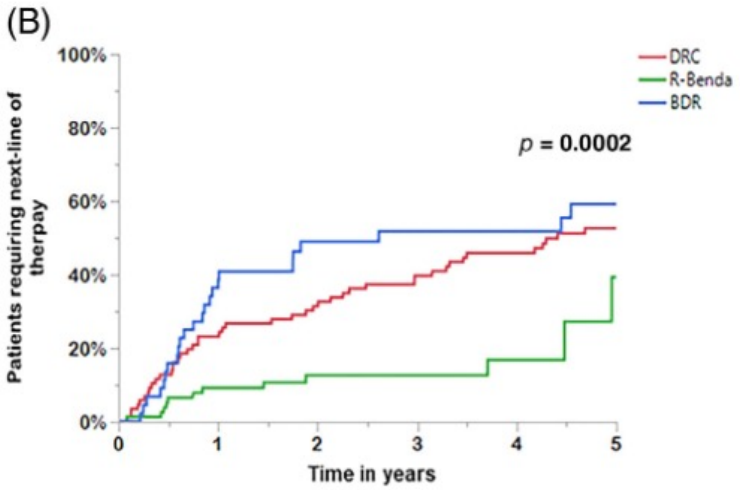
CONS:

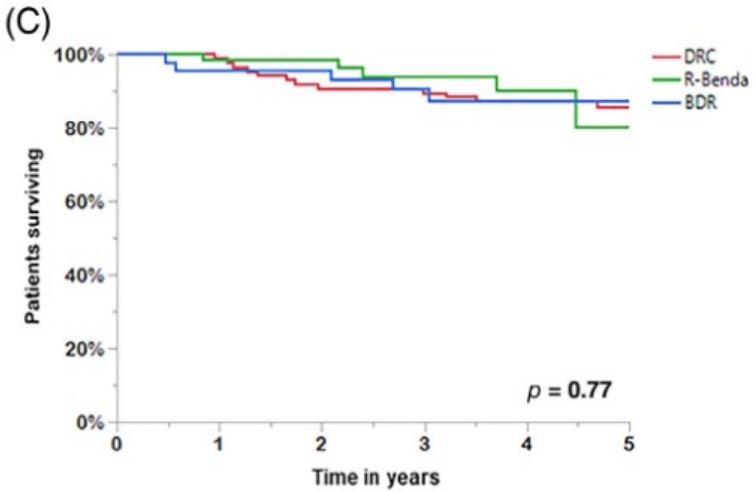
- High rate of Neuropathies

Assessment of fixed-duration therapies for TN WM

	MRR
R-Benda	96%
DRC	53%
BDR	68%







Abeykoon et al, 2021

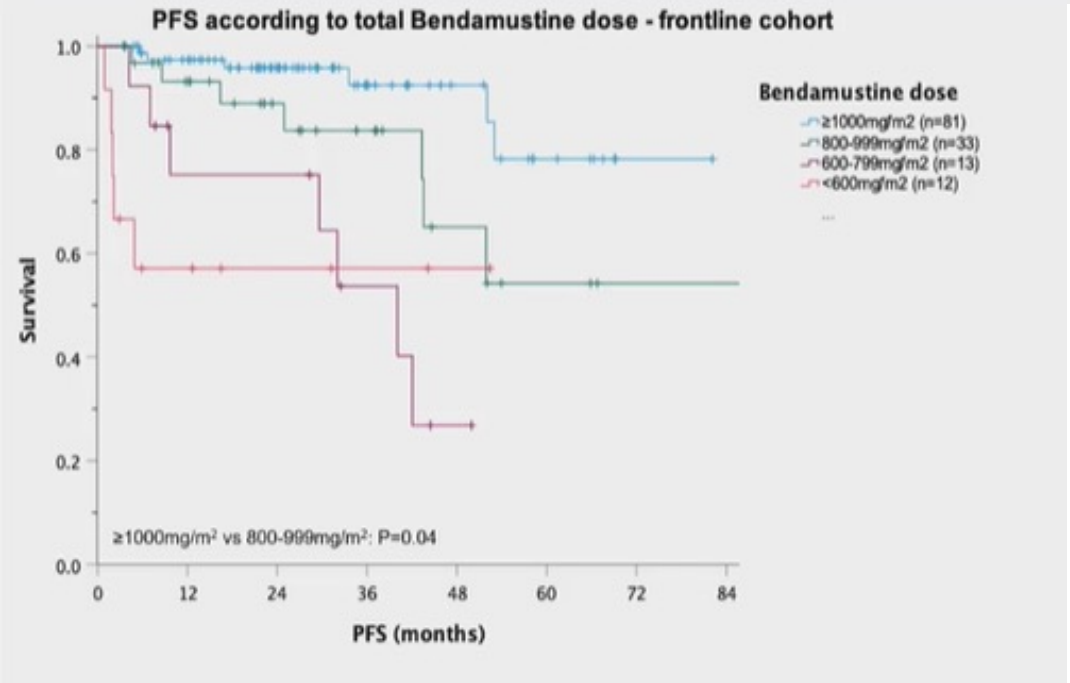
What if we reduce Benda dosage?

WM TREATMENT: first line

Bendamustine Rituximab

Outcomes according to Benda dosage

Dose category	Example dose schedule	E.g. total dose (mg/m²)
1. ≥1000 mg/m²	90 mg/m² for 6 cycles	1080 mg/m²
2. 800-999 mg/m²	70 mg/m² for 6 cycles	840 mg/m²
3. 600-799 mg/m²	90 mg/m² for 4 cycles	720 mg/m²
4. <600 mg/m²	70 mg/m² for 4 cycles	560 mg/m²

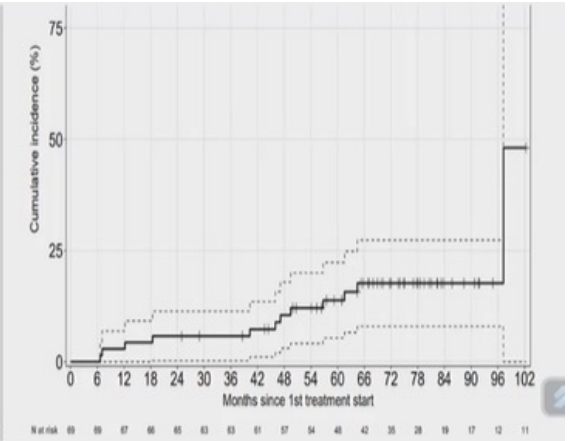


Late toxicities

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

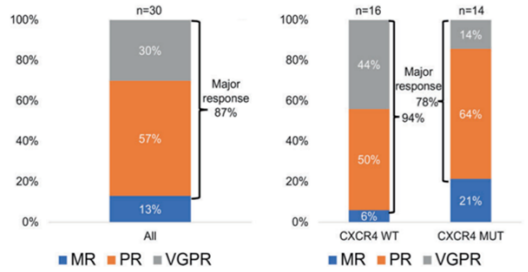
Arulogun S et al IWWM 2022
LeBlonde et al IWWM 2022

WM TREATMENT FIRST LINE TREATMENT

BTKi

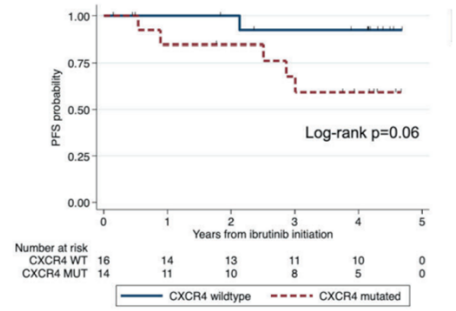
Ibrutinib° in MYD88^{mut}

median follow-up time of 50.1 m



Median time to Major Response: 1.9 m
Median longer for pts with:

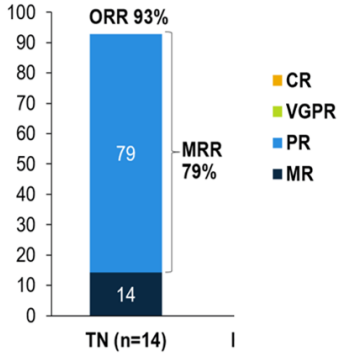
CXCR4^{mut}	7.3 m	*p = 0.02*
CXCR4^{wt}	1.8 m	

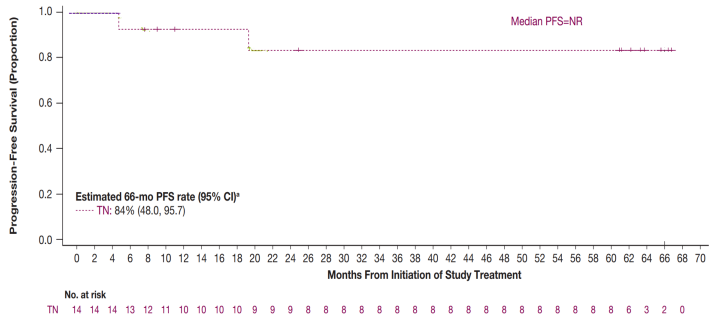


Castillo et al., 2021

° approved by EMA in unfit PTS not reimbursed in Italy

Acalabrutinib





Owen R et al., 2022

Aspen trial in MYD88^{mut}

median follow-up time of 19.4 m

	TN	
	Ibrutinib (n = 18)	**Zanubrutinib (n = 19)**
Best overall response, n (%)		
CR	0 (0)	0 (0)
VGPR	3 (17)	5 (26)
PR	9 (50)	9 (47)
MR	4 (22)	4 (21)
SD	1 (6)	0 (0)
PD	0 (0)	1 (5)
Not evaluable*	1 (1)	0 (0)
Response rates, % (95% CI)†		
VGPR or CR	17 (4-41)	26 (9-51)
P	NR	
MRR	67 (41-87)	74 (49-91)
ORR	89 (65-99)	95 (74-100)
Duration of CR/VGPR, mo		
Median (range)	NE (0+, 3+)	NE (0+, 22+)
18-Mo event-free rate, % (95% CI)§	NE (NE, NE)	100 (NE, NE)
Duration of major response, months		
Median (range)	NE (3+, 28+)	NE (0+, 25+)
18-Mo event-free rate, % (95% CI)§	00 (NE, NE)	80 (39-95)
PFS		
Median (range), mo	NE (0+, 31+)	NE (1, 31+)
18-Mo event-free rate, % (95% CI)§	94 (63-99)	78 (52-91)

Tam CS et al., 2020

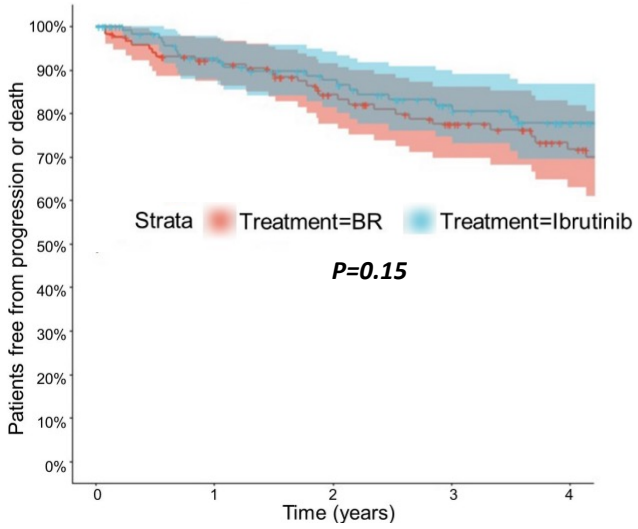
Multi-institutional, international study in Europe and the USA

Median follow-up: 4.2 years

1:1 age-matched analysis of 246 pts *MYD88^{mut}*
Ibrutinib (n=123) BR (n=123)
Significant higher responses with BR
Discontinuation due to AE: 13% BR and 33% ibrutinib

347 TN pts:
- **208 BR**
- **139 ibrutinib**

Progression-free survival



4-year OS: BR 95% (95% CI 91–99)
versus
Ibrutinib 86% (95% CI 80-93)
p=0.3

In a bivariate analysis adjusting for age and the treatment type only age emerged as a predictor for OS (HR 7.2, p=0.0001)

For patients with *MYD88* L265P mutation, selection between the two approaches should be dictated by:
- **Potential toxicities**
- **Patient comorbidities**
- **Patient/clinician preference (parenteral fixed duration vs. continuous oral)**
- **Access to therapies**

AE, adverse event; BR, bendamustine–rituximab; CI, confidence interval; HR, hazard ratio; MUT, mutant; OS, overall survival; PFS, progression-free survival; pts, patients; TN, treatment-naive; WM, Waldenström's macroglobulinemia.
Abeykoon JP et al. Abstract 7566 presented at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; Chicago, IL, USA, June 3–7, 2022.

May we improve DRC?

European Consortium Randomized trial

NCT01788020

DRC

Median 50.1 m (95% CI: 31.1; --)

Estimated PFS at 24 m: 72.8%

B-DRC: major R 79.1 %

grade ≥3 AEs DRC 47%

(p=0.32)

DRC Plus Bortezomib

Median PFS NR (95% CI: 33.5; --)

Estimated PFS at 24 m: 80.6%

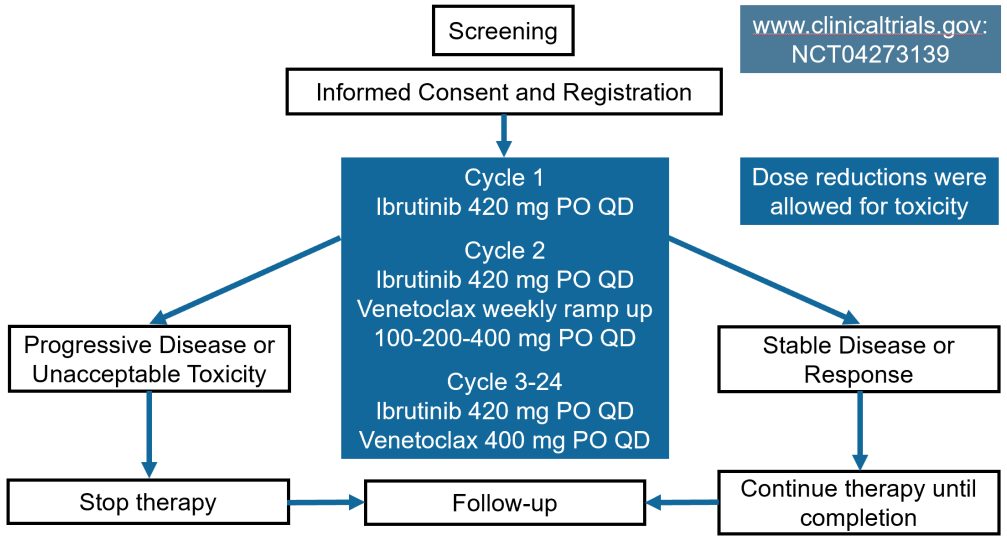
DRC: major R 68.9 %

grade ≥3 AEs B-DRC 48%

At this time point of analysis, adding Bortezomib to DRC did not induce significant differences in PFS compared to DRC alone

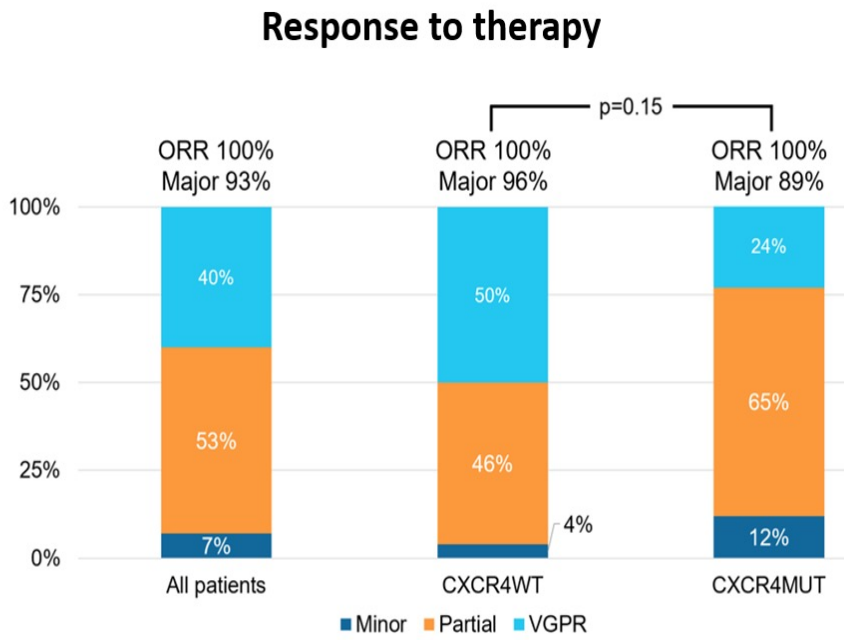
Fixed duration therapy in first line with target agents

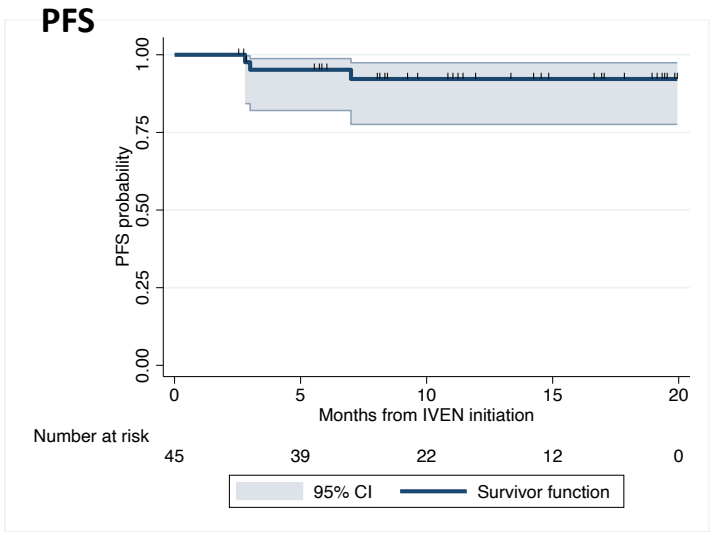
Venetoclax plus Ibrutinib



Median TTMR: **1.9 months**

Median TTMR: ***CXCR4*^{MUT}: 2.8 months**
***CXCR4*^{WT}: 1.9 months**





Castillo J et al., ASH 2022

Ibrutinib and venetoclax in previously untreated WM

Safety

Adverse events observed in ≥3 patients and of clinical importance

n=45

Adverse events	*Grade 2*	*Grade 3*	*Grade 4*	*Grade 5*	*Total*
Anemia	1	2			3
Atrial fibrillation	1	2	1		4
Diarrhea	8	1			9
Reflux	10				10
Mucositis	7	2			9
Nausea	5				5
Neutropenia	1	10	3		14
Hyperphosphatemia	8				8
Muscle/joint pain	14	2			16
Skin rash	6				6
Ventricular arrhythmia	1		1	2	4
Laboratory TLS		2			2

TLS: tumor lysis syndrome

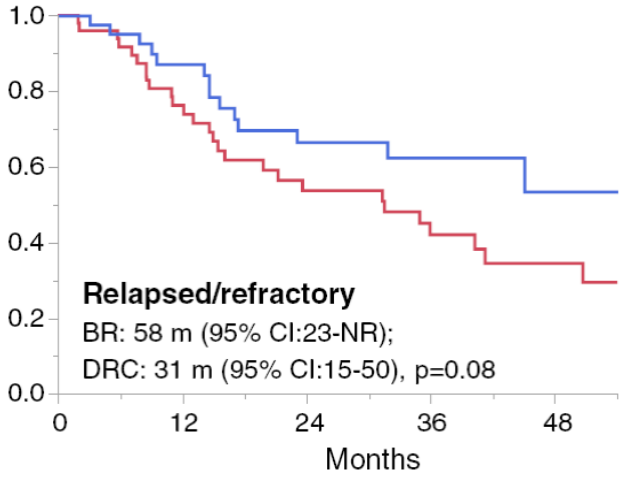
Castillo J et al., ASH 2022

Salvage treatment

Repeat or alternate immuno-CHT

DRC or Benda R

Benda R or DRC in RR WM

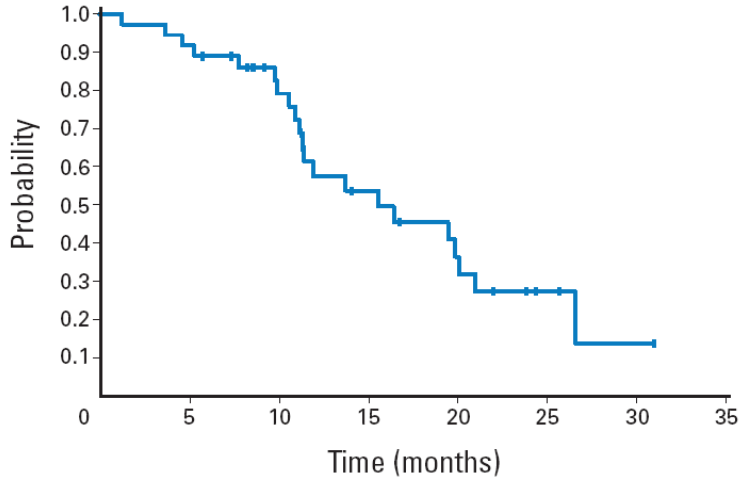


Inadequate treatment in first line!

	BR second line	DRC second line
Chlorambucil	7%	16%
Rituximab monotherapy	45%	68%
FAMP/2CdA monotherapy	6%	12%

Bortezomib-Rituximab

Bortezomib Rituximab



Paludo et al. Ann Hem 2018
Ghobrial et al. JCO 2010

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

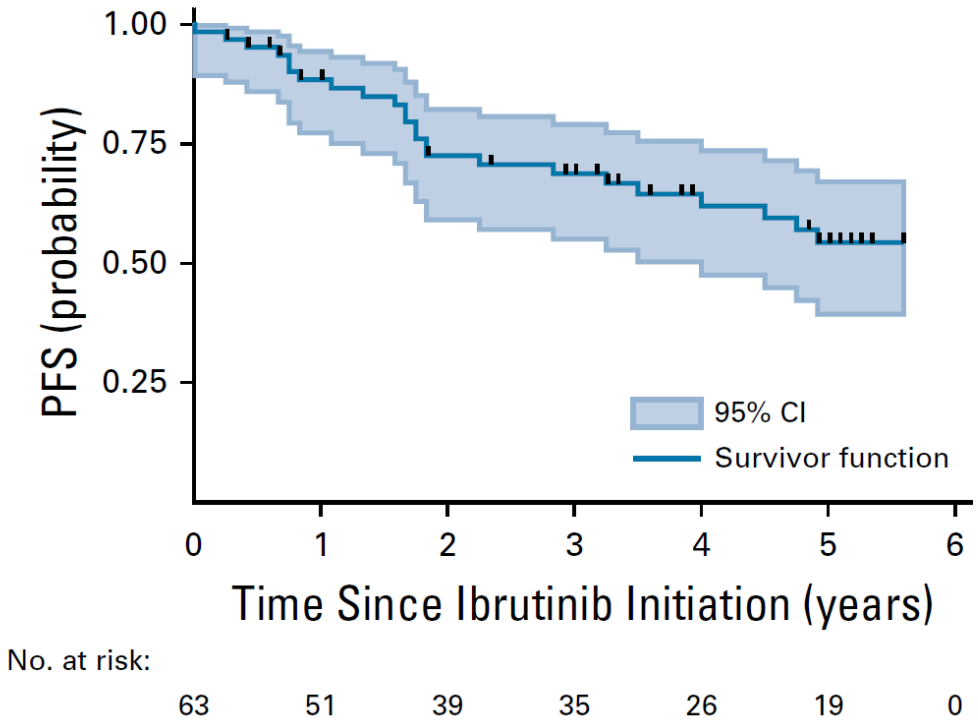
Symptomatic R/R ≥ 1 line of therapy

IBRUTINIB 420 mg

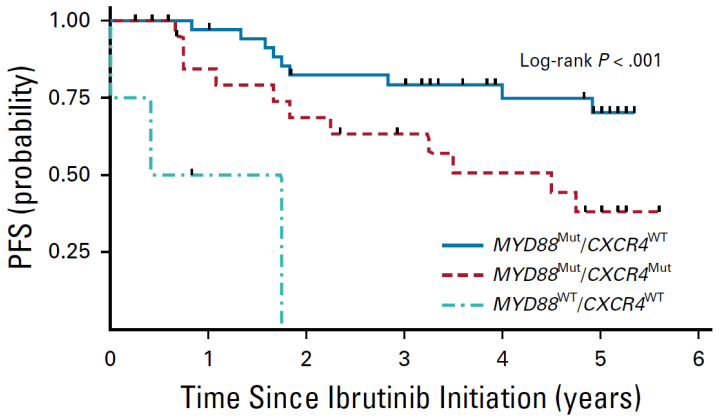
Continuous therapy

- **Median n° of prior therapies: 2 (1-9)**
- **40% pts refractory to most recent therapy**

Median study follow-up: 59 months
Progression Free Survival



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



No. at risk:

MYD88^{Mut}CXCR4^{WT}	36	34	26	25	18	14	0
MYD88^{Mut}CXCR4^{Mut}	22	16	13	10	8	5	0
MYD88^{Mut}CXCR4^{Mut}	4	1	0	0	0	0	0

Treon SP et al. J Clin Oncol 2021

Ibrutinib and Acalabrutinib studies in WM

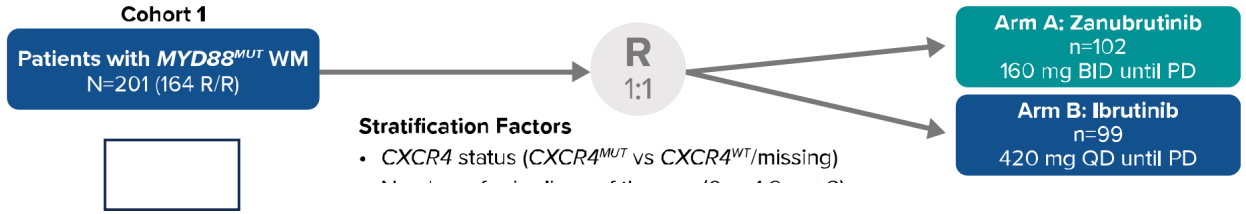
Study	N° pts	ORR	CR+GVPR	PR	Median FU time	PFS	PFS $CXCR4^{MUT}$ vs $CXCR4^{WT}$
Ibrutinib							
Treon et al 2015, 2021	63 RR	90.5%	30.2%	49.2%	59 m	Median PFS NR 5 year PFS rate, 54%	38% vs 70% (5 y)
Trotman et al, 2021 Refractory to Rituximab based tx	31 RR	87%	29%	48%	58 m	Median PFS 39 m 60 m PFS rate 40%	18 m vs NR (5 y)
Ibrutinib+Rituximab							
Buske et al, 2022	41 RR	93%	34%	42%	50 m	Median PFS NR 54 m PFS rate 70%	63% vs 72% (54 m) *Not significant*
Acalabrutinib°							
Owen et al, 2022	92 RR	95%	27%	57%	63.7 m	Median PFS: 67.5 m 66 m PFS rate 52%	Not done

AEs of Ibrutinib and Acalabrutinib

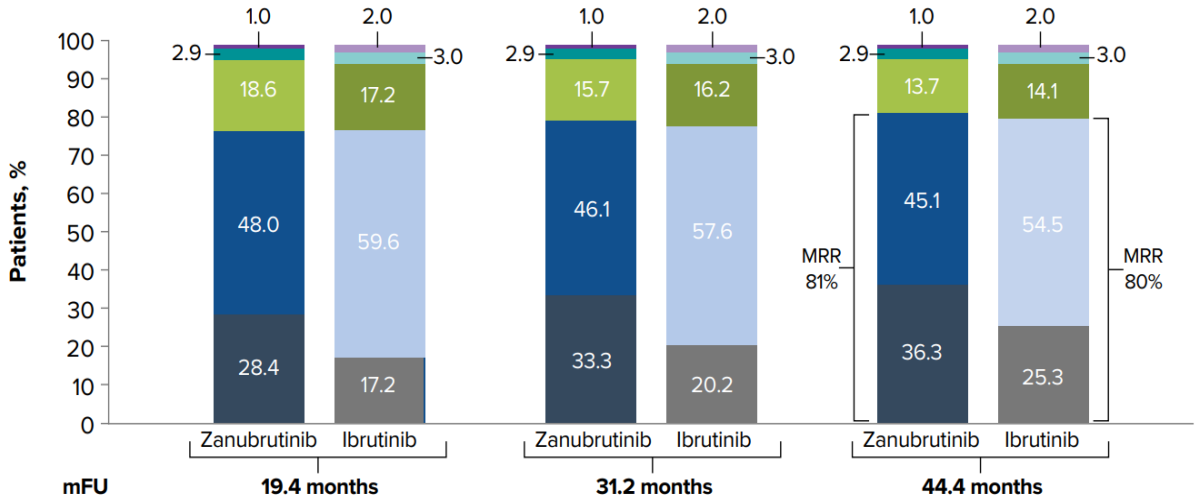
Ibrutinib monotherapy phase II study: Treon et al 2021	Ibrutinib plus R Innovate study: Buske et al 2022	Acalabrutinib Phase II study: Owen et al 2022
Median FU: 59 months	***Median FU: 50 months***	***Median FU: 60 months***
✓ *8% off-study due to AE* ✓ *19% dose reductions*	✓ *11% off-study due to AE* ✓ *23% dose reductions*	✓ *16% off-study due to AE*
Hematological AE Grade ≥ 3 • **Neutropenia: 15.9%** • **Thrombocytopenia: 11.1%**	**Hematological AE Grade ≥ 3** • **Neutropenia: 13%** • **Thrombocytopenia: 1%**	**Hematological AE Grade ≥ 3** **NA**
AE of interest with BTKi • **Atrial arrhythmia any grade 12.7%** • **Hypertension grade ≥ 2: 6%** • **Pneumonia grade ≥ 2: 8%**	**AE of clinical interest any grade** • **Atrial fibrillation 19%** • **Hypertension: 25%** • **Infections ≥ 3: 29%**	**AE of clinical interest any grade** • **Atrial fibrillation 12%** • **Hypertension: 8%** • **Infections ≥ 3: 33%**

	Study	N° pts	FU	Discontinuations due to AE	Dose reductions
Abeykoon et al, 2019	Retrospective	80 TN/RR	19 m	16%	18%
Frustaci et al, 2022	Retrospective	206 R/R	27 m	11%	19%

ASPEN study, Phase III randomized study: Ibrutinib versus Zanubrutinib



Responses by investigators



Median time to CR+VGPR:
shorter for zanubrutinib 6.7 m vs ibrutinib: 16.6 m

Primary objective significant superior CR+VGPR
According to IRC with zanubruitnib: not achieved

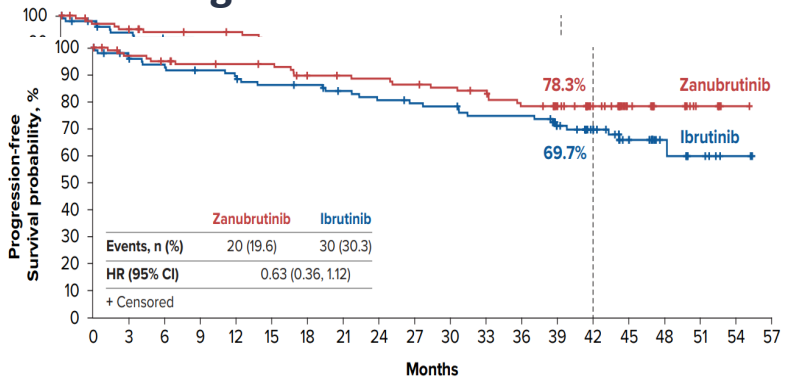
Responses by CXCR4

	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

Dimopoulous M et al., EHA 2022

ASPEN Phase III randomized study: Ibrutinib versus Zanubrutinib

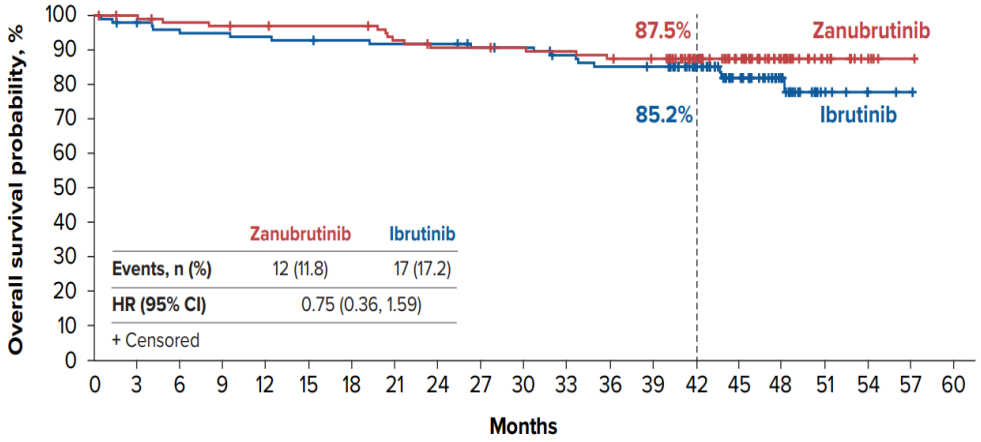
Progression Free Survival



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

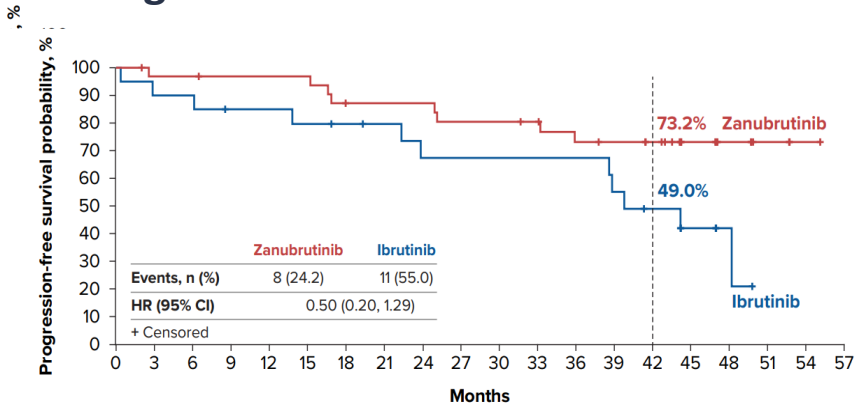
Overall Survival



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

Progression Free Survival in *CXCR4^{mut}*



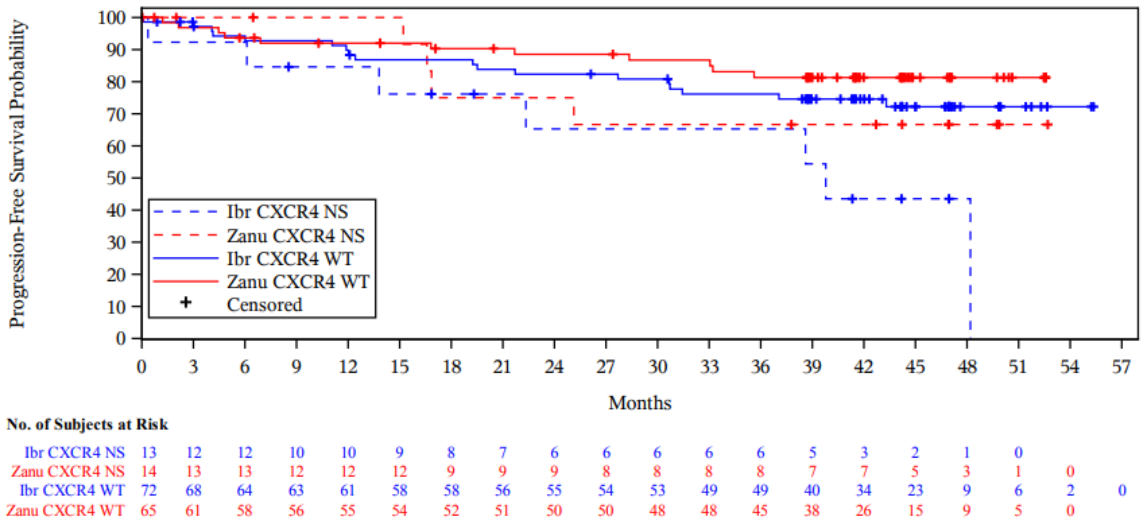
No. of Patients at Risk:

Zanubrutinib	33	31	31	30	30	30	26	26	26	24	24	23	20	19	17	10	6	3	1	0
Ibrutinib	20	18	18	16	16	15	14	13	11	11	11	11	11	9	7	4	2	0		

Dimopoulous M et al., EHA 2022

Zanubrutinib trends favorable for PFS versus ibrutinib in both $CXCR4^{NS}$ And $CXCR4^{FS}$

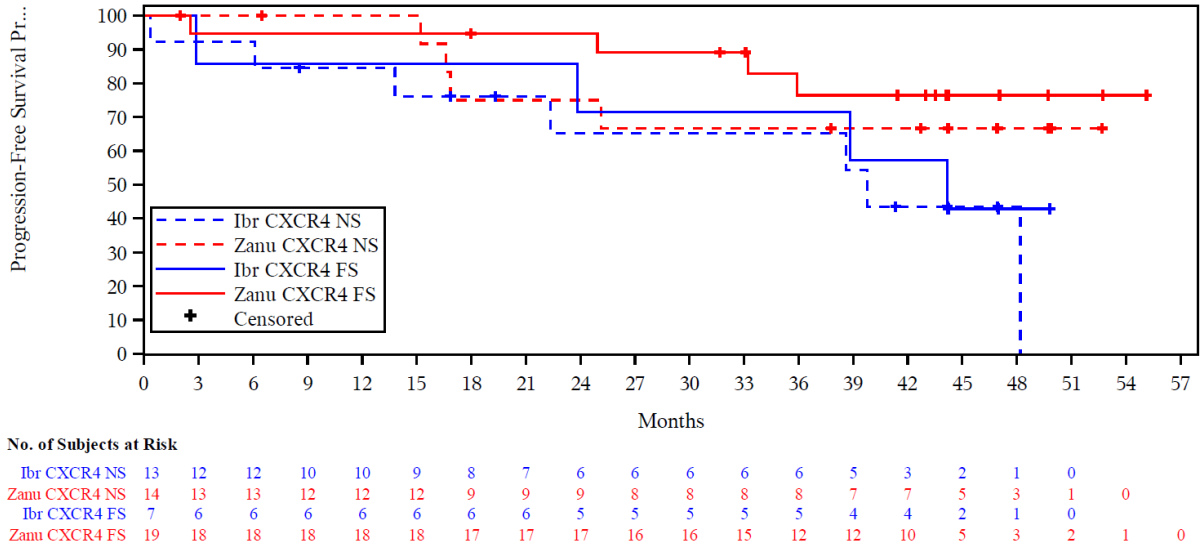
PFS in *CXCR4^{NS}* vs *CXCR4^{WT}*



No. of Subjects at Risk

Ibr CXCR4 NS	13	12	12	10	10	9	8	7	6	6	6	6	6	5	3	2	1	0	
Zanu CXCR4 NS	14	13	13	12	12	12	9	9	9	8	8	8	8	7	7	5	3	1	0
Ibr CXCR4 WT	72	68	64	63	61	58	58	56	55	54	53	49	49	40	34	23	9	6	2	0
Zanu CXCR4 WT	65	61	58	56	55	54	52	51	50	50	48	48	45	38	26	15	9	5	0	

PFS in *CXCR4^{NS}* vs *CXCR4^{FS}*



No. of Subjects at Risk

Ibr CXCR4 NS	13	12	12	10	10	9	8	7	6	6	6	6	6	5	3	2	1	0	
Zanu CXCR4 NS	14	13	13	12	12	12	9	9	9	8	8	8	8	7	7	5	3	1	0
Ibr CXCR4 FS	7	6	6	6	6	6	6	6	5	5	5	5	5	4	4	2	1	0	
Zanu CXCR4 FS	19	18	18	18	18	18	17	17	17	16	16	15	12	12	10	5	3	2	1	0

Mutation determined by NGS; NGS results were available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm.

Tam C et al., IWWM 2022

Zanubrutinib shows deeper and faster responses and favorable PFS versus ibrutinib in WM with *TP53*^{MUT}

Response	Patients with *MYD88*^{MUT} treated with ibrutinib		Patients with *MYD88*^{MUT} treated with zanubrutinib	
	TP53^{WT} (n=70)	*TP53*^{MUT} (n=22)	*TP53*^{WT} (n=72)	*TP53*^{MUT} (n=26)
VGPR or better, n (%)	21 (30.0)	**3 (13.6)**	27 (37.5)	**9 (34.6)**
MR, n (%)	60 (85.7)*	**14 (63.6)***	59 (81.9)	**21 (80.8)**
Median time to VGPR or better (min, max), months	11.4 (2.0, 49.9)	24.9 (5.6, 46.9)	6.5 (1.9, 42.0)	11.1 (3.0, 26.0)
Median time to MR (min, max), months	2.9 (0.9, 49.8)	3.0 (1.0, 13.8)	2.8 (0.9, 49.8)	2.8 (1.0, 5.6)
PFS				
Events, n (%)[b]	18 (25.7%)	11 (50.0%)	10 (13.8%)	9 (34.6%)
Event-free rate at 42 months, %	72.1	57.9	84.6	62.0
P value[c]	-	**0.027**	-	0.120

Data cutoff: October 31, 2021.
Bold text indicates >10% difference between MUT and WT. **Bold red** text highlights P value < 0.05.
**P* value <0.05, based on a logistic regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and TERT (WT, MUT) statuses as covariates. WT is the reference group.
[a]Mutation determined by NGS and available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b]Includes the number of progressive disease or death.
[c]Estimated using a Cox regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and *TERT* (WT, MUT) mutational status as covariates. WT is the reference group.
MR, major response; MUT, mutant; PFS, progression-free survival; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; *TERT*, telomerase reverse transcriptase gene; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WT, wild type.

Tam C et al., IWWM 2022

ASPEN Phase III randomized study: Ibrutinib versus Zanubrutinib

Patients disposition

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

Long term toxicity

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/ 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)

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]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 sepsis.

Dimopoulous M et al., EHA 2022

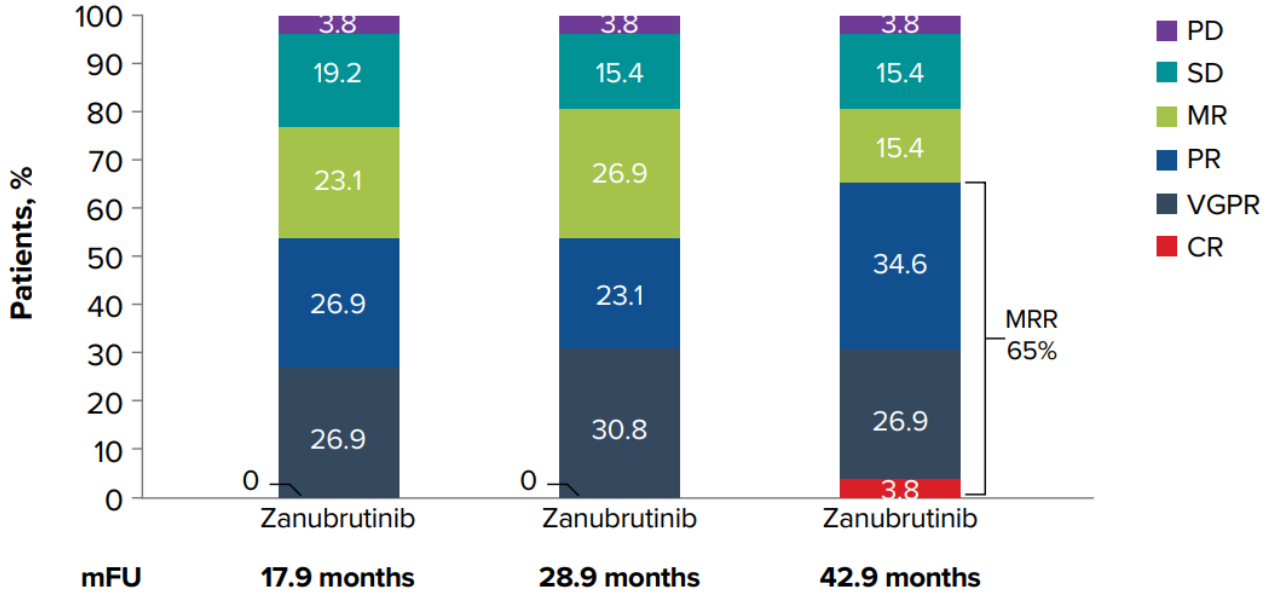
ASPEN study: Cohort 2 *MYD88^{WT}* (Zanubrutinib monotherapy)

Patients with *MYD88^{WT}* WM
N=28 (23 R/R)

→

Arm C: Zanubrutinib
N=28
160 mg BID until PD

Responses Overtime



At 42 months:

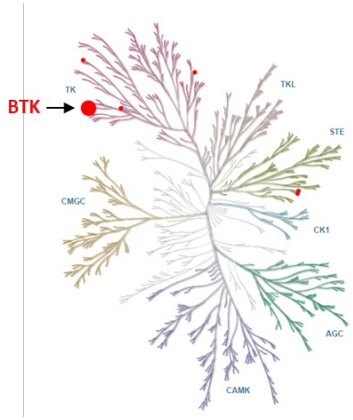
PFS: **53.8% (95% CI: 33.3, 70.6)**

OS: **83.9% (95% CI: 62.6, 93.7)**

Dimopoulous M et al., EHA 2022

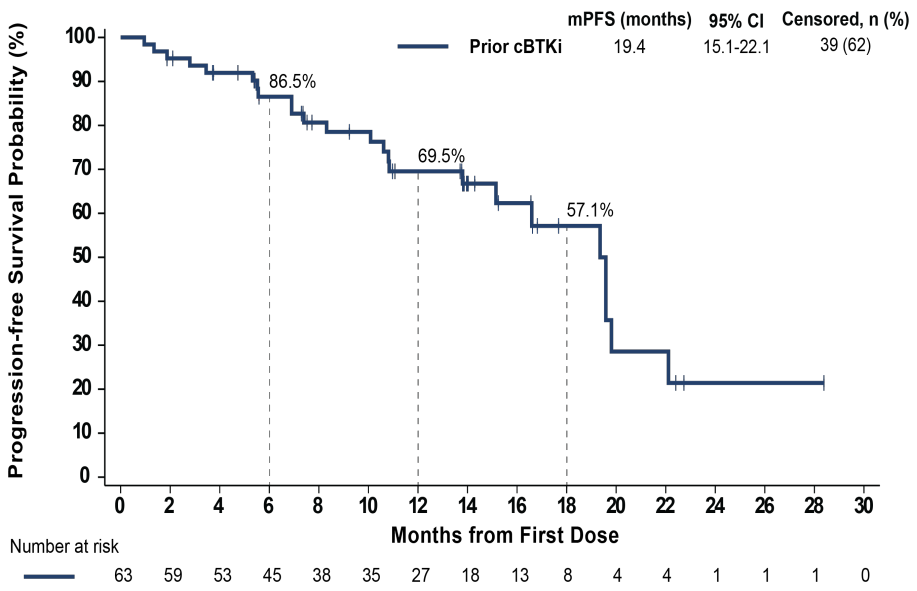
What comes next in WM?

Pirtobrutinib: non covalent BTKi

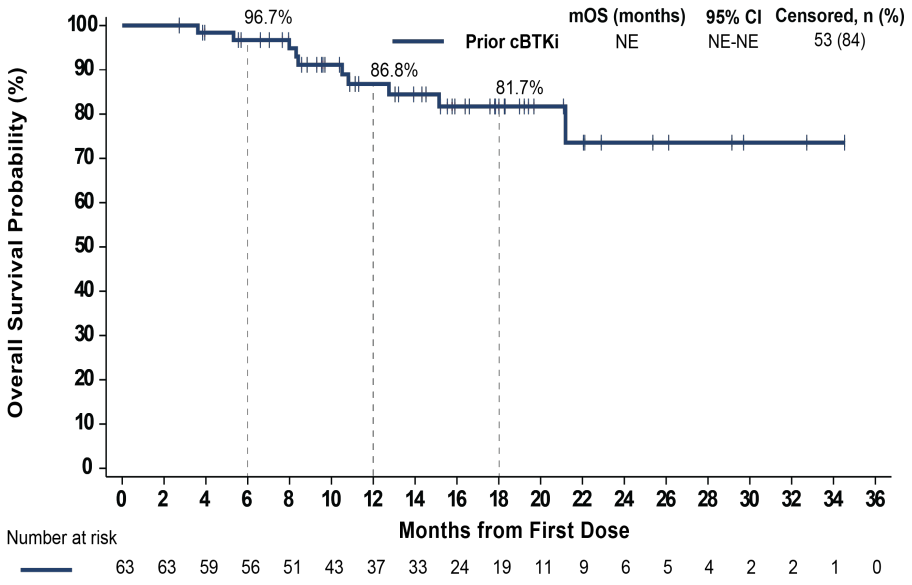


Highly Selective for BTK[1,2]

Progression-Free Survival



Overall Survival



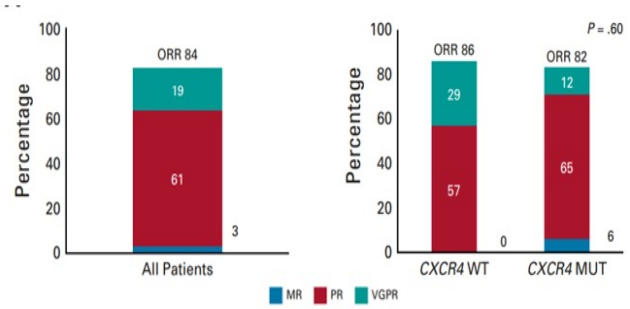
- The median follow-up for PFS and OS in patients who received prior cBTKi was 14 and 16 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

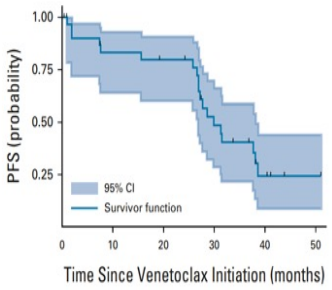
Palomba et al, IWWM 2022

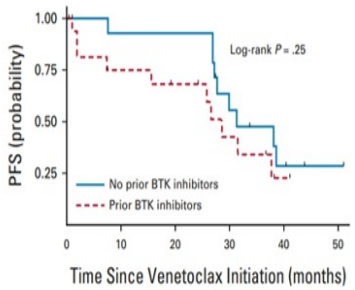
Effective salvage treatments (currently not in development)

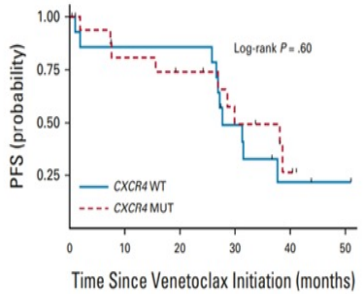
Venetoclax as salvage therapy

32 pts
Median prior Tx: 2 (1-10)
Prior BTKi: 66%
MYD88^{MUT}: 100%
CXCR4^{MUT}: 53%









Castillo et al 2021

Next generation Proteasome inhibitors salvage therapy

Induction:
8 cycles q28 days

> SD

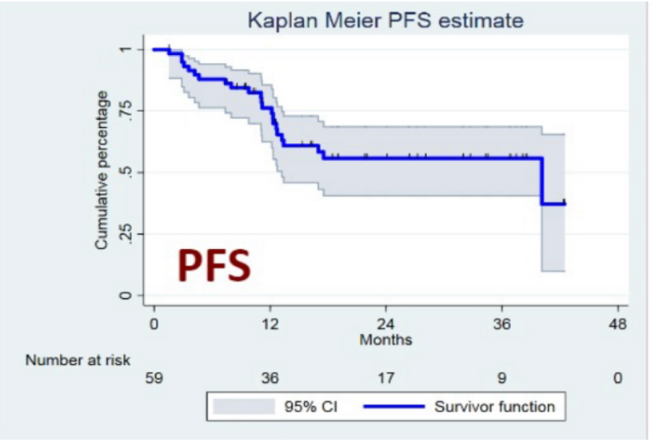
Maintenance:
2 years q3months

- Ixazomib citrate 4 mg d1,8,15
- Rituximab 1400 mg sc d1
  cycle 3-8 (1st dose iv)
- Dexamethasone 20 mg d1,8,15,22

- Rituximab 1400 mg sc d1

59 pts
Mdian prior tx: 2

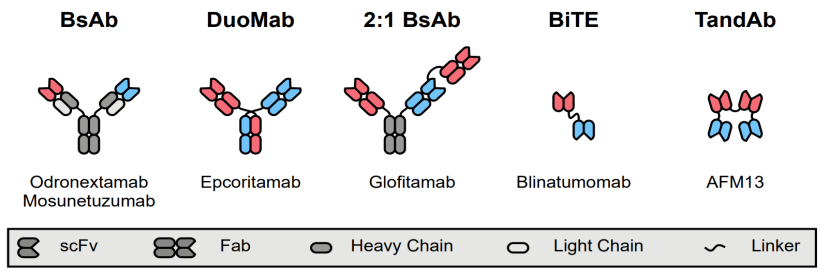
ORR: 85%
VGPR: 15%
PR 46%



Kersten et al, 2019

Near Future treatments

Bispecific Ab



- ✓ Active in high grade and low grade lymhomas heavly pretreated
- ✓ Few pts with WM inlcuded in studies

Ansell S. IWWM 2022

Car-T

- ✓ No approved CAR-T for WM treatment

- ✓ anti-WM activity in second-generation anti-CD19 CAR T cells -
  - 3 pts treated:
    - treatment was welltolerated only g 1–2 toxicities
    - responses were seen in all three patients

Palomba et al, 2021

- ✓ CD20 CAR-T (MB-106) (third generation targeted CAR)

2 pts treated:

- responses were seen in all patients

FDA has granted orphan drug designation to MB-106, for the treatment of patient with WM

Shadman M. IWWM 2022

CONCLUSIONS

- **TN patients:**
  - **Immuno-chemotherapy remains treatment of choice**
  - **Zanubrutinib in pts unsuitable for immuno-CHT (consider genotype)**
- **R/R patients:**
  - **BTKi treatment of choice:**
    - **consider genotype (better outcomes with zanubruitnib in high risk pts)**
    - **patients comorbidities (better tollerability with zanubruitnib)**
- **IBRUTINIB/ZANUBRUTINIB refractory pts:**
  - **pirtobrutinib**
- **UNMET NEED:**
  - **salvage after BTKi failures**

Car-T protocol ongoing (ZUMA 25)