Società Italiana di Ematologia

FORMAZIONE SIE

I linfomi: un nome con almeno 40 sfaccettature!

25 giugno 2026

Bologna
Royal Hotel
Carlton

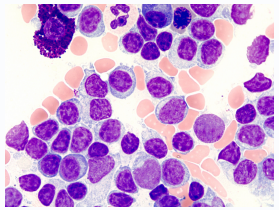
Macroglobulinemia di Waldenstrom

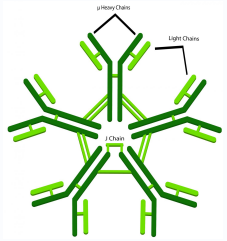
Anna Maria Frustaci

Disclosures of Anna Maria Frustaci

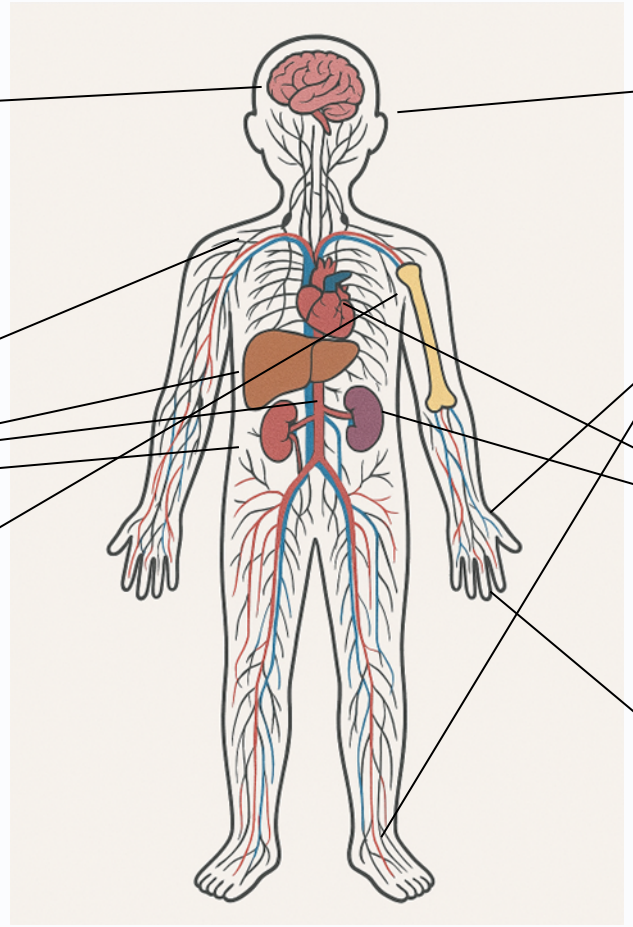
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						X	X
BeOne						X	X
AbbVie						X	X
AstraZeneca						X	X
Eli-Lilly						X	X

Lymphoma-related treatment criteria



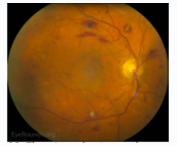


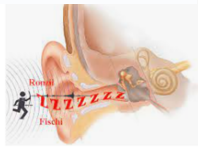
Paraprotein-related treatment criteria



Bing Neel syndrome

Hyperviscosity (*NB: IgM>6000 mg/dl*)

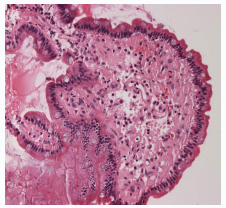




Symptomatic/bulky:
Lympadenopathy
Hepatomegaly
Splenomegaly
Organ or tissue infiltration

Peripheral neuropathy

Amyloidosis



Anemia (*Hb <10 g/dl*)
Thrombocytopenia (*Plts <100.000/mmc*)

Symptomatic cryoglobulinemia
Cold agglutinin anemia
Immune hemolytic anemia
Immune thrombocytopenia

How WM differs from other lymphomas

- Clinical severity is **not directly correlated** with tumor burden

  e.g. Hyperviscosity, Neuropathy, Cytopenia

- Treatment may be a **medical emergency**

  e.g. Hyperviscosity syndrome

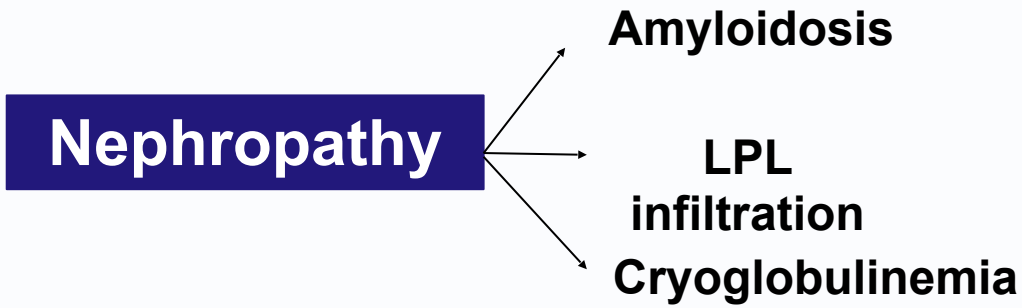
- Some specific symptoms need to be promptly treated as they may become **irreversible** once established

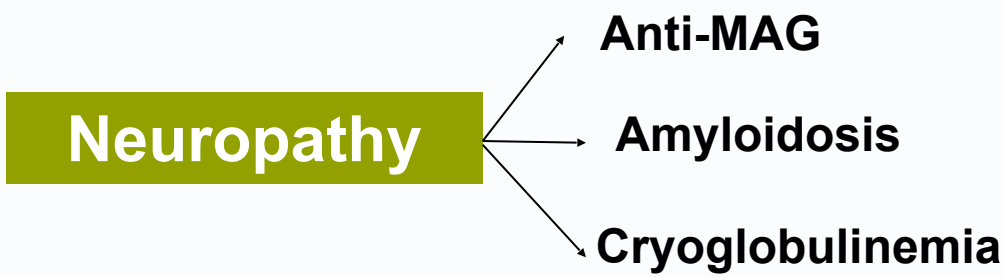
  e.g. Neuropathy, Amyloidosis

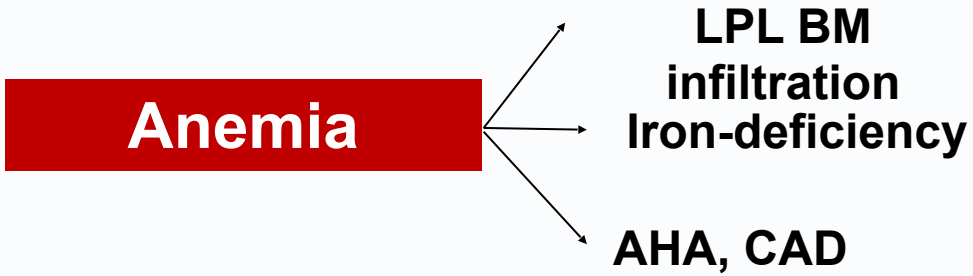
- Each clinical manifestation may arise from **distinct pathogenic mechanisms,** requiring **tailored treatments**

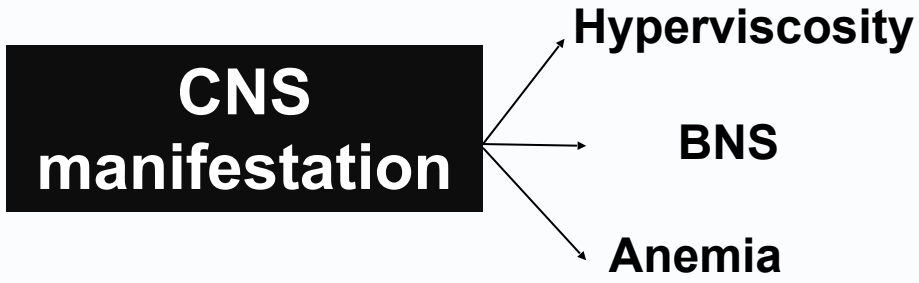
  e.g. Nephropathy, Anemia, Neuropathy

From Symptom to Strategy: It’s Not One-Size-Fits-All

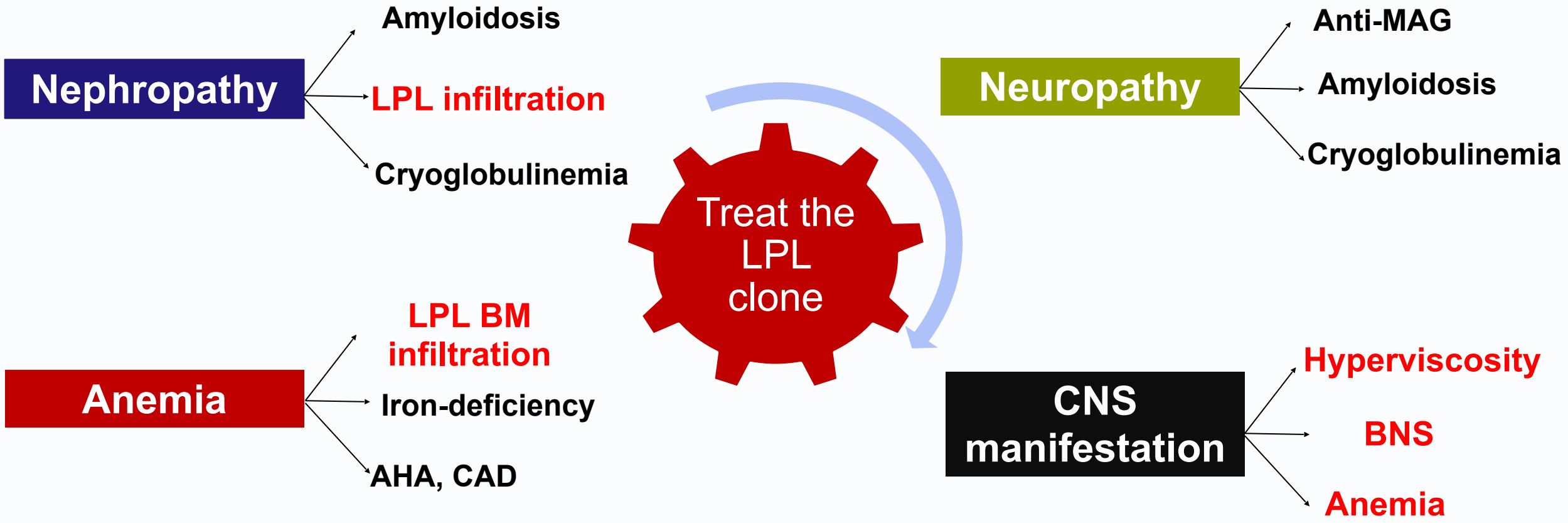








From Symptom to Strategy: It’s Not One-Size-Fits-All



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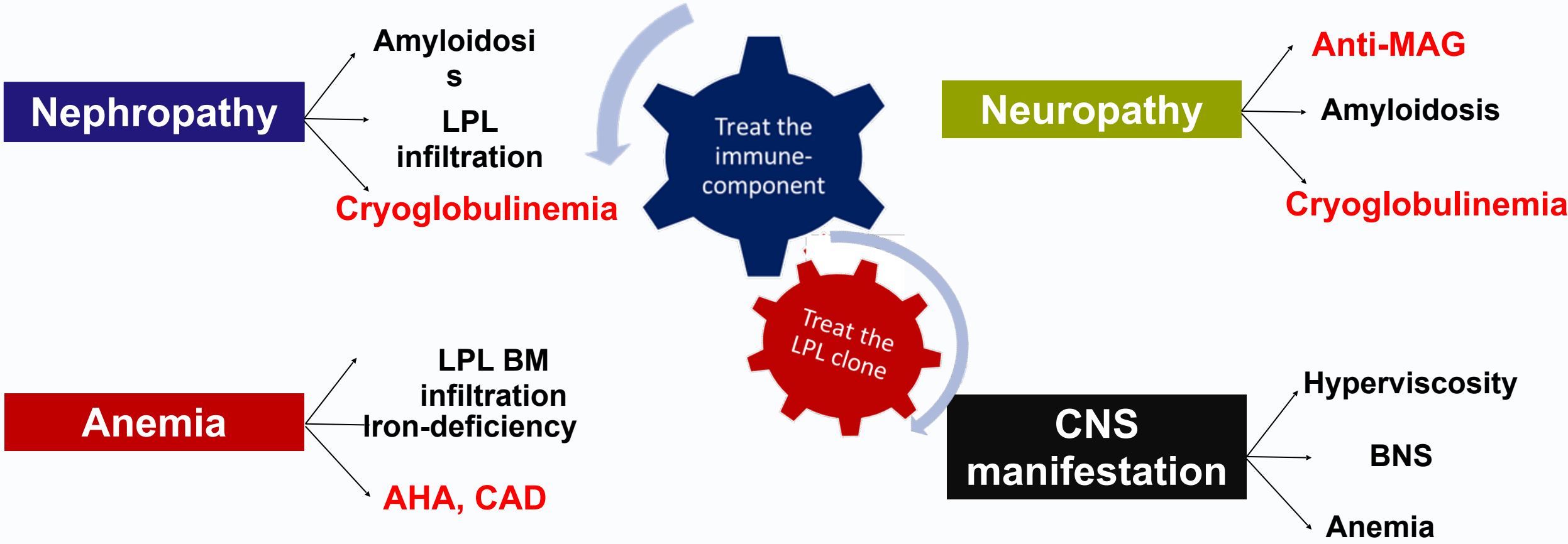
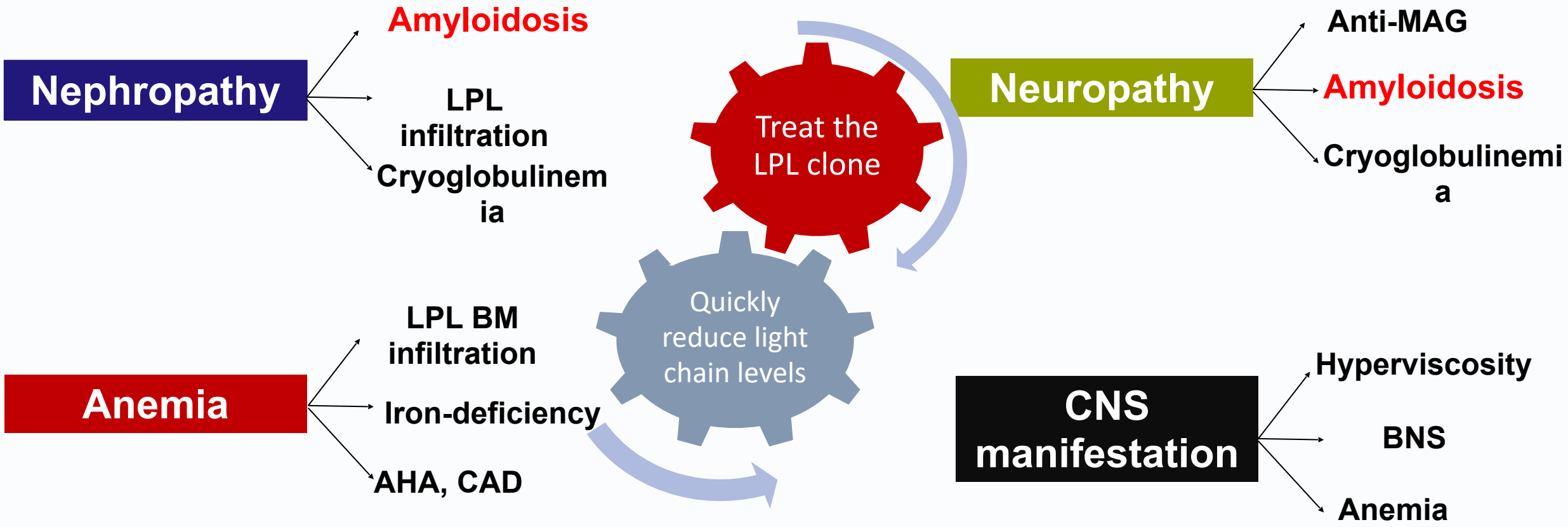


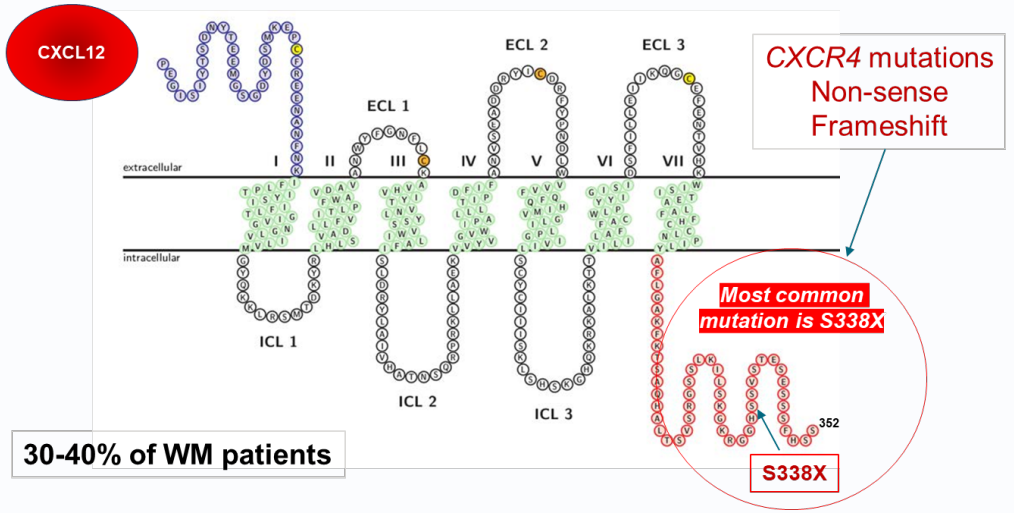
From Symptom to Strategy: It’s Not One-Size-Fits-All



MYD88 and CXCR4 mutational status in WM

MYD88 L265P mutation in lymphoid B malignancies	
WM	90-100%
IgM-MGUS	41-56%
SMZL	7-13%
MALT	9%
CLL	3-10%
ABC-DLBCL	29%

Treon, 2012; Landgren, 2014



1) Kahler A and Sticht H. AIMS Biophysics. 2016;3(2):211-231; 2) Hunter ZR et al. Blood. 2014;123(11):1637–1646; 3) Poulain S et al. Clin Cancer Res. 2016;22(6):1480-8.

Three prognostic groups:

- ***MYD88^{MUT} / CXCR4^{WT}***
- ***MYD88^{MUT} / CXCR4^{MUT}***
- ***MYD88^{WT} / CXCR4^{WT}***

CHALLANGE #1

cBTKi may be less active in *MYD88 WT* and *CXCR4 mut* cases

Chemoimmunotherapy in 1° line

Chemoimmunotherapy

DRC (*Dexamethasone, Rituximab, Cyclophosphamide*)

BR (*Bendamustine + Rituximab*)

BTKi

Zanubrutinib*

Ibrutinib

*only for pts not eligible to CIT

***Personal opinion*:**

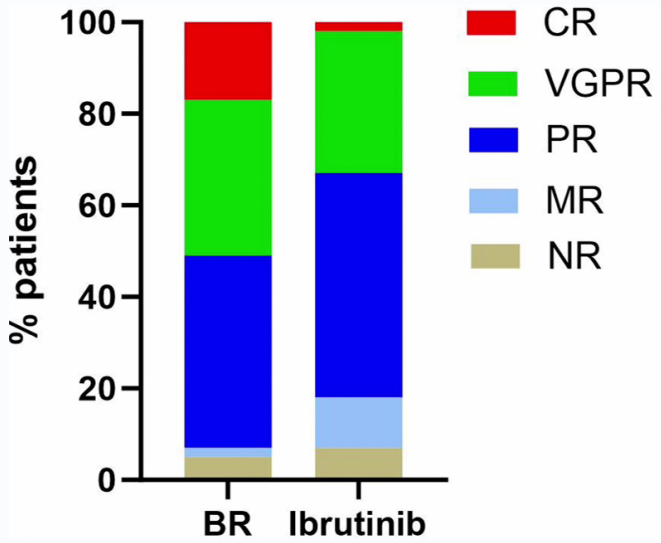
Until new approvals, I usually prefer CIT in 1° line based on:

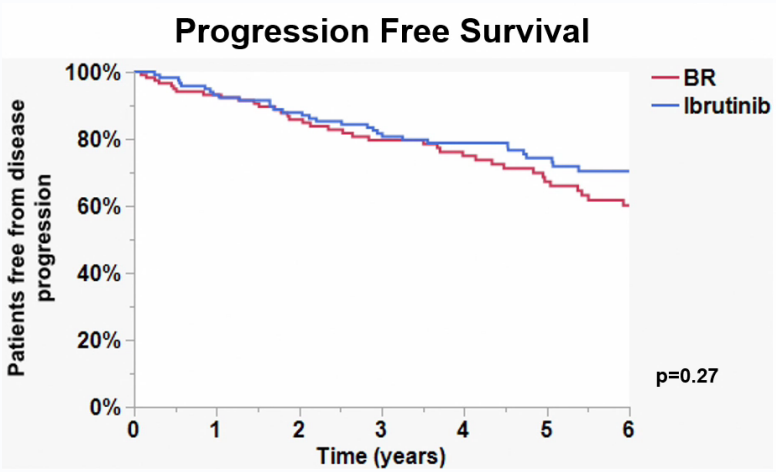
- ❑ FD with long-term TTNT
- ❑ Sequencing

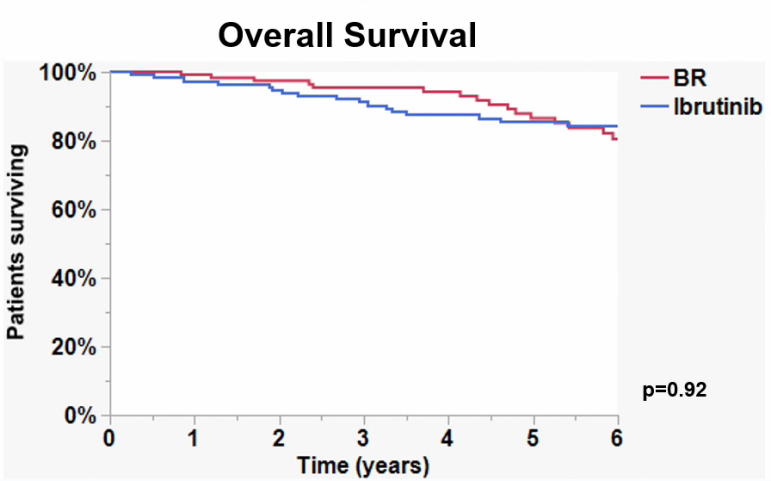
***Preferred use of upfront cBTKi in*:**

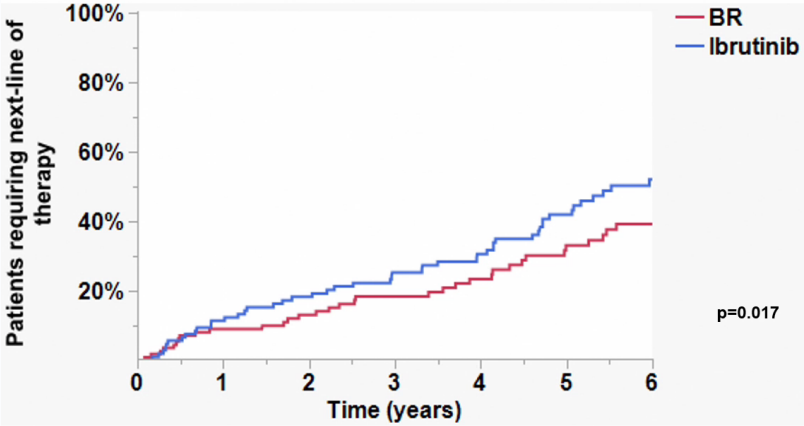
- ❑ Unfit + need of rapid disease control
- ❑ Bing Neel syndrome
- ❑ *TP53* aberrant patients

Age-matched analysis of BR vs ibrutinib in first line









TTNT:

Ibru: 5.5 yrs

BR: NR

p= .017

Tx discontinuation due to Aes or PD:

BR: 23%

Ibr: 41%

Abeykoon, IwWM 2024

Single agent ibrutinib in R/R WM

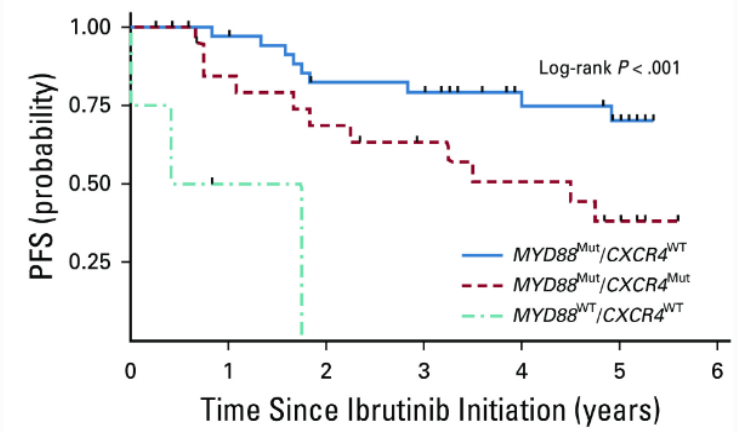
Median study follow-up: 59 months

	All	MYD88^{Mut} CXCR4^{WT}	MYD88^{Mut} CXCR4^{Mut}	MYD88^{WT} CXCR4^{WT}	*p*
No. Of pts	63	36	22	4	
ORR	90.5%	100%	86.4%	50%	<.0100
MRR	79.4%	97.2%	68.2%	0	<.0001
m time to MR (≥PR)	1.8 mo	1.8 mo	**4.7 mo**	NA	.0200

Median study follow-up: 58 months

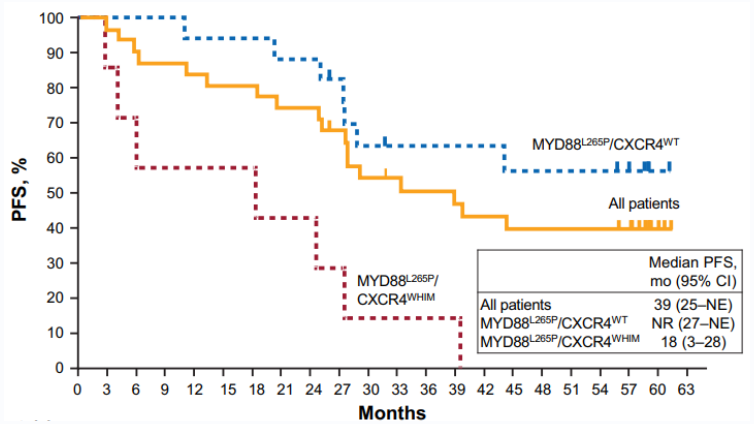
	All	MYD88^{Mut} CXCR4^{WT}	MYD88^{Mut} CXCR4^{Mut}	MYD88^{WT} CXCR4^{WT}
No. Of pts	31	17	7	1
ORR	87%	86%	88%	0
MRR	77%	88%	71%	0
m time to MR (≥PR)	1.9 mo	1 mo	**3.6 mo**	NA

5 yrs mPFS:
74 vs 38% (CXCR4 WT vs mut)



Treon et al JCO 2021

5 yrs mPFS:
NR vs 18 mo (CXCR4 WT vs mut)



Trotman, CICR 2021

ASPEN Study Design: Zanubrutinib vs Ibrutinib in MYD88^{MUT} WM

Eligible Patients

- Histologic diagnosis of WM
- Meeting ≥1 criterion for treatment initiation[1]
- If treatment naïve (TN*), must be considered unsuitable for standard chemoimmunotherapy
- No prior BTK inhibitors

Cohort 1

***MYD88^{MUT}* WM patients**
N=201 (164 R/R)

R
1:1

Stratification factors

- *CXCR4* status (*CXCR4^{WHIM}* vs *CXCR4^{WT}* vs missing)
- Number of prior lines of therapy (0 vs 1-3 vs >3)

Arm A: Zanubrutinib
n= 102
160 mg BID until PD

Arm B: Ibrutinib
n= 99
420 mg QD until PD

Cohort 2

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

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

EUDRACT 2016-002980-33; NCT03053440

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

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

Tam, Blood 2020

ASPEN Study: Zanubrutinib vs Ibrutinib in *MYD88^{MUT}* WM

44.3 mo FU

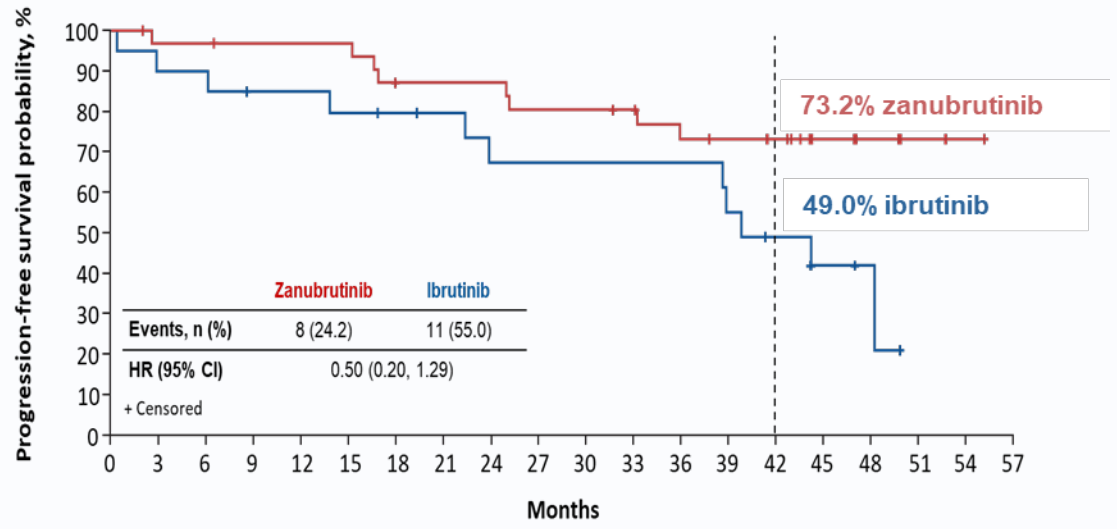
ASPEN Phase 3 trial: zanubrutinib vs ibrutinib in WM

Response Assessment by *CXCR4* Status[a]

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

Bold blue text indicates >10% difference between arms

PFS in Patients with *MYD88^{MUT}CXCR4^{MUT}*



Dimopoulos MA et al. J Clin Oncol. 2023;41(33)

ASPEN Study Design: Zanubrutinib in cohort 2 of *MYD88^{WT}* WM

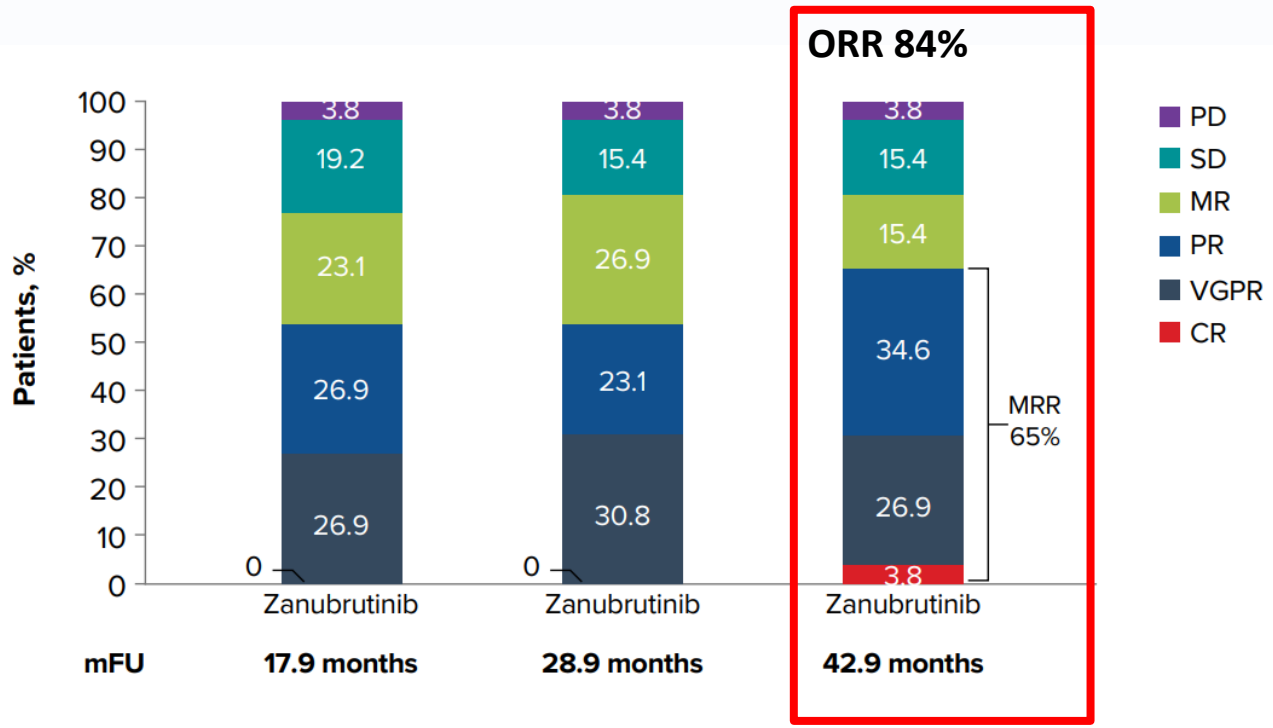
42.9 mo FU

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

→

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

Responses Overtime



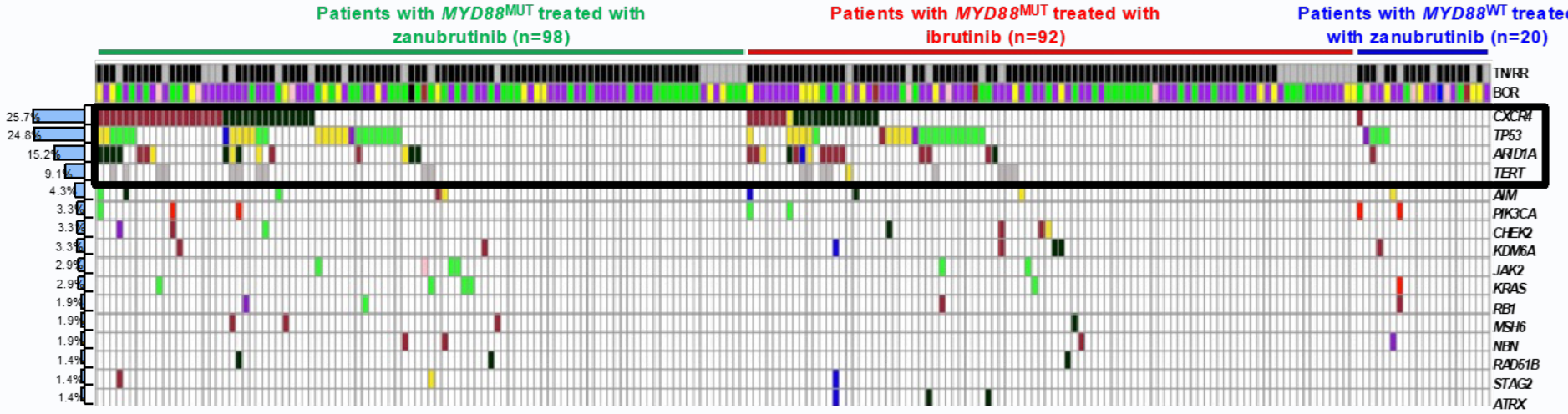
At 42 months:

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

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

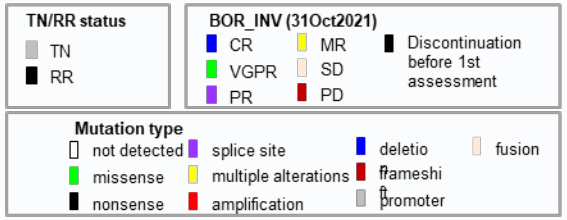
Dimopoulos MA et al. J Clin Oncol. 2023;41(33)

CHALLENGE #2:
High rates of TP53 aberrant (data from the ASPEN trial)



In zanubrutinib-treated vs ibrutinib-treated *MYD88*^{MUT} cohorts, the *CXCR4*^{NS} rate is 14.2% (14/98) vs 14.1% (13/92), and the *CXCR4*^{FS} rate is 19.4% (19/98) vs 7.6%(7/92), respectively

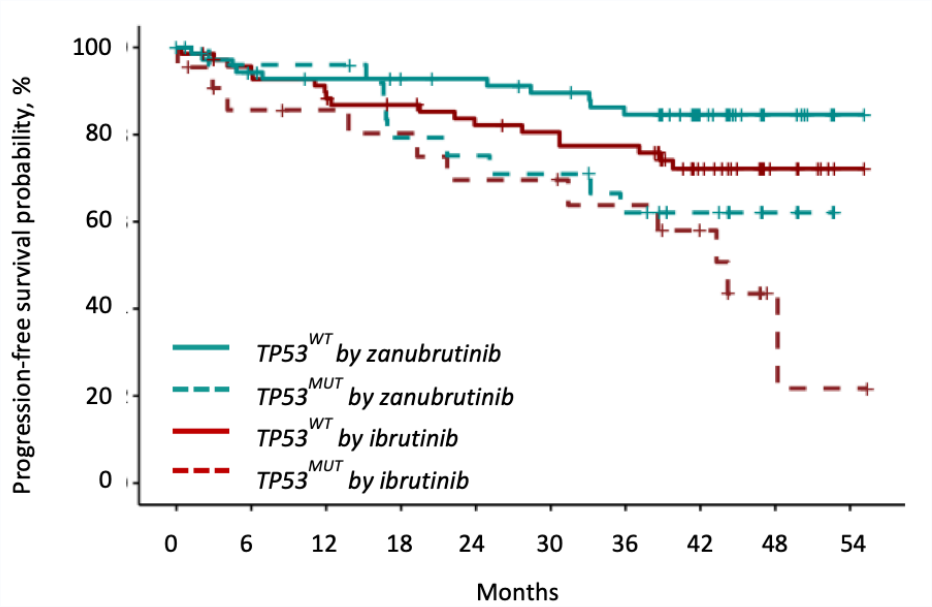
Mutation rate, % (n)	*MYD88*^{WT} (n=20)	*MYD88*^{MUT} (n=190)	*CXCR4*^{WT} (n=156)	*CXCR4*^{MUT} (n=54)	CXCR4^{FS} (n=27)	CXCR4^{NS} (n=27)
TP53	4 (20%)	48 (25.3%)	33 (21.2%)	**19 (35.2%)**	8 (29.6%)	**11 (40.7%)**
TERT	0	**19 (10%)**	6 (3.9%)	**13 (24.1%)**	**4 (14.8%)**	**9 (33.3%)**
ARID1A	1 (5%)	**31 (16.3%)**	9 (5.8%)	**23 (42.6%)**	**11 (40.7%)**	**12 (44.4%)**



Presented by Constantine Tam at the 11th IWWM; October 27-30, 2022

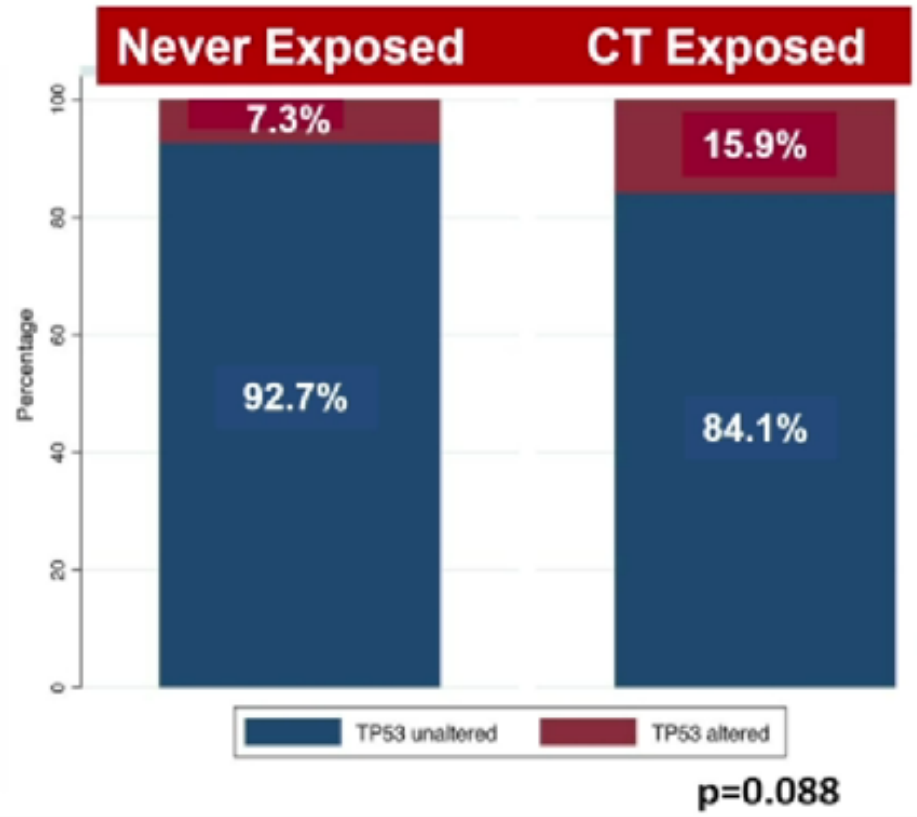
Reduced PFS in *TP53*^{mut} with both cBTKi, but deeper responses with zanubrutinib

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)



Presented by Constantine Tam at the 11th IWWM; October 27-30, 2022

Prior CT exposure: higher rate of TP53 aberrant



Multivariate Logistic Regression

Term	p-value	OR
Prior AA or NA	0.102	2.89
CXCR4 Mutated	0.118	2.28
Age at Biopsy	0.589	1.01
>1 Prior Therapy	0.945	0.96
Actively Progressing	0.909	1.06

Double-hit TP53^{ALT}
18.8% who received both AA and NA
6.1% who received either AA or NA
3.6% who received no CT
p=0.069

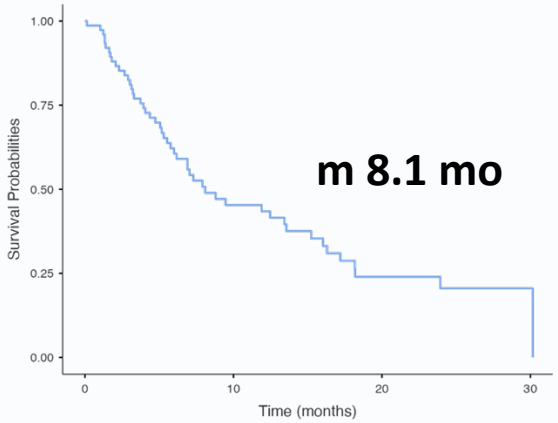
Treon, ASH 2025

CHALLANGE #3:
Outcomes of patients receiving a salvage treatment after cBTKi

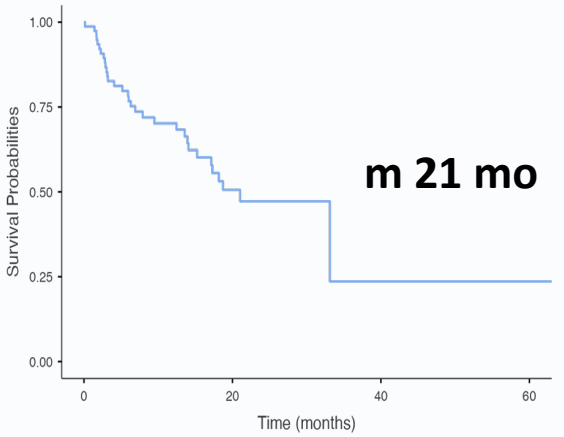
Progression free survival

Overall survival

Whole cohort

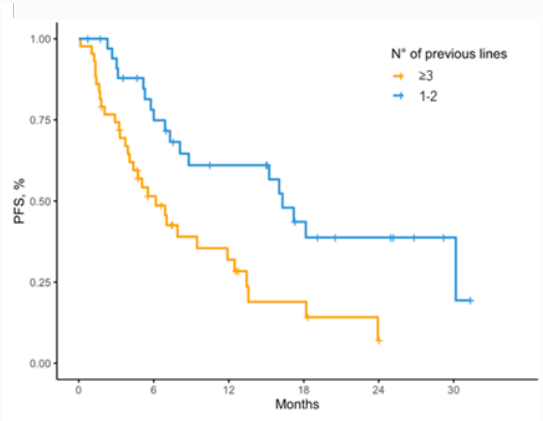


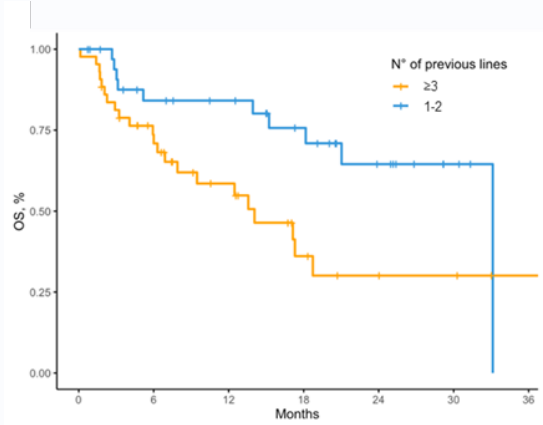
m 8.1 mo



m 21 mo

According to number of lines <u>before</u> cBTKi





Frustaci, Hemasphere 2025

Potential therapeutic targets in WM

Bispecifics

Non covalent BTKI
Pirtobrutinib
Nemtabrutinib

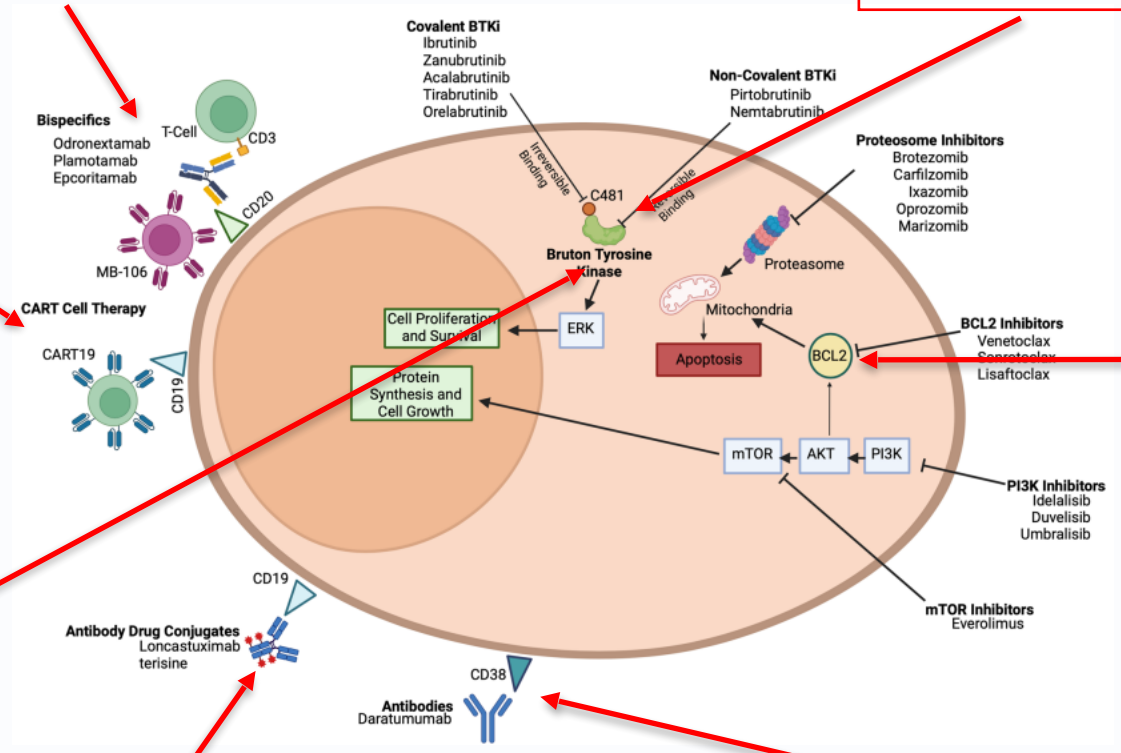
CAR-T

Bcl2 antagonists
Venetoclax
Sonrotoclax
Lisaftoclax

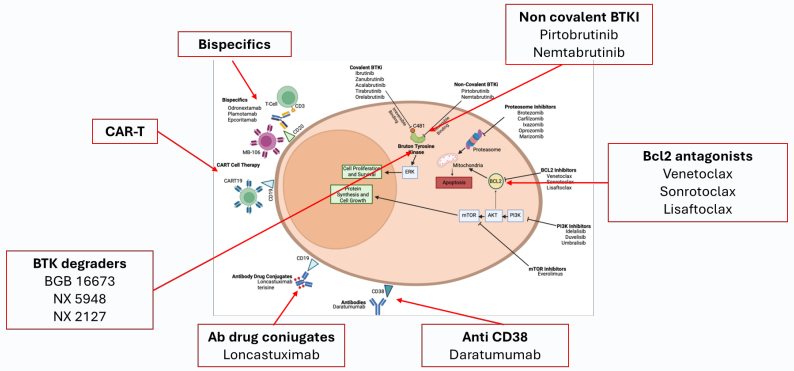
BTK degraders
BGB 16673
NX 5948
NX 2127

Ab drug coniugates
Loncastuximab

Anti CD38
Daratumumab



EMA approved targets in iNHL



	FL	MCL	MZL	WM
CIT[1]	✓	✓	✓	✓
cBTKi[2,3]	Zanu	Ibru	Zanu	Zanu, Ibru
ncBTKi[4]		Pirto		
Bispecifics[5]	Epcor			
CAR-T[6]	Tisa, Axi, Liso	Brexu		

In clinical practice CUP available for:

- **Pirtobrutinib**
- **Venetoclax**

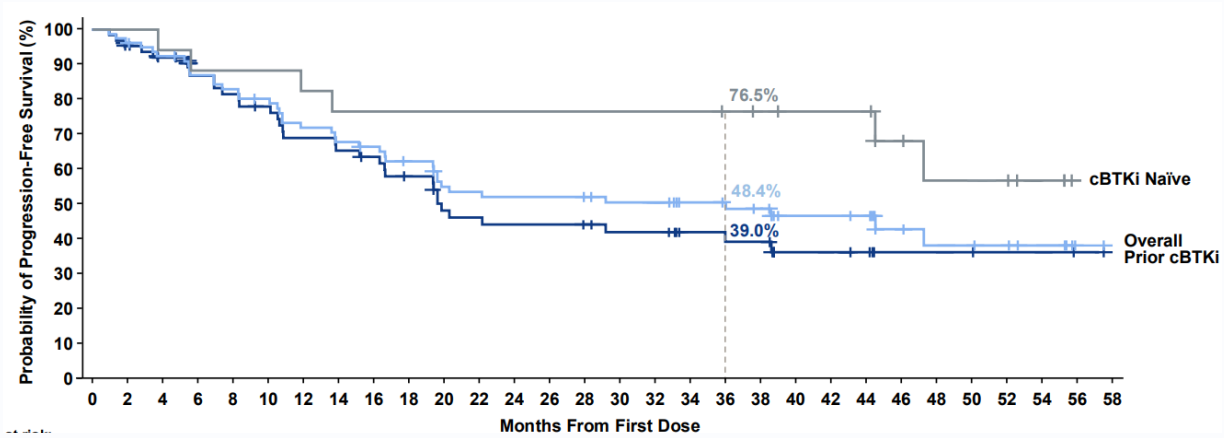
Pirtobrutinib in BTKi-exposed patients: survival

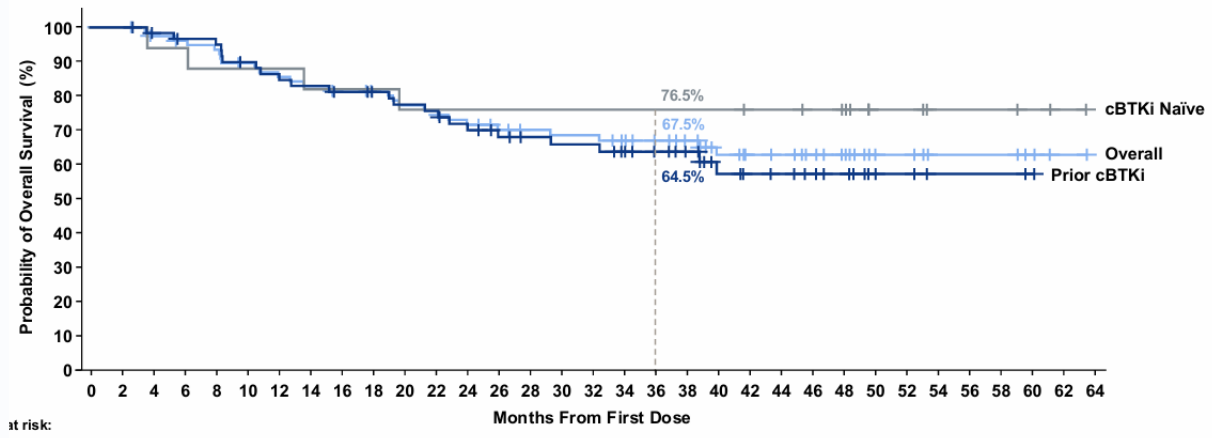
M FU 35 months
Prior BTKi 78%
Prior BTKi+ CIT 64%
m prior lines:3 in BTK-exposed

median PFS: 34 mo

- **19.6 in BTK-exp**
- **NR in BTK-naive**

median OS: NR

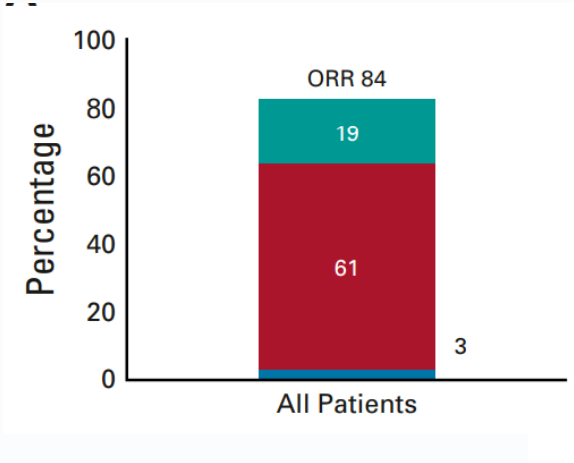


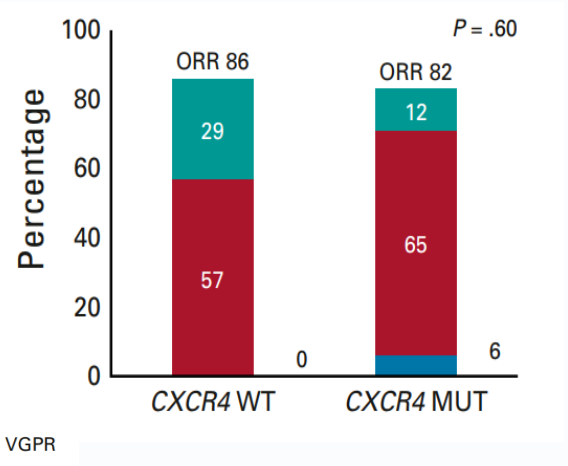


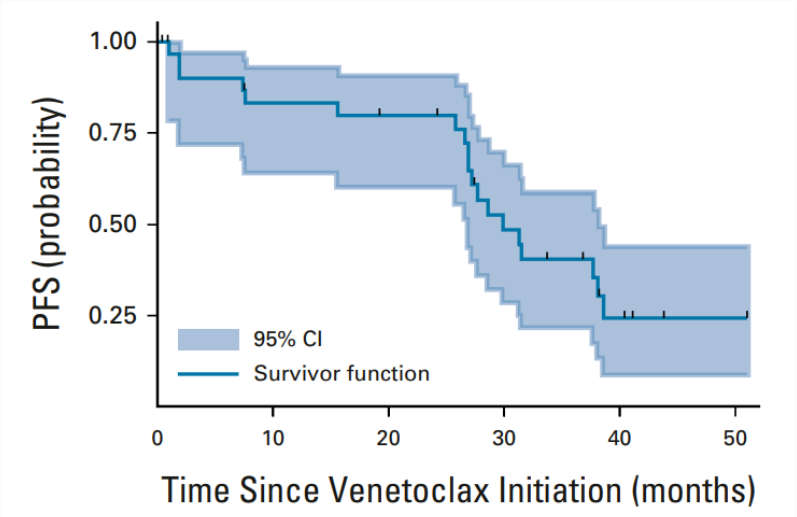
Cheah ASH 2025

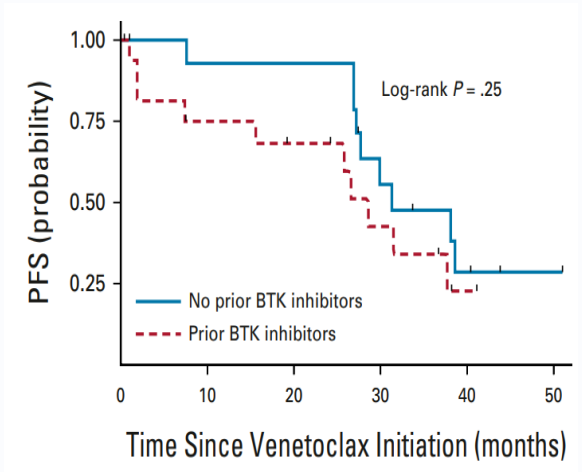
Fixed-duration venetoclax monotherapy in R/R WM

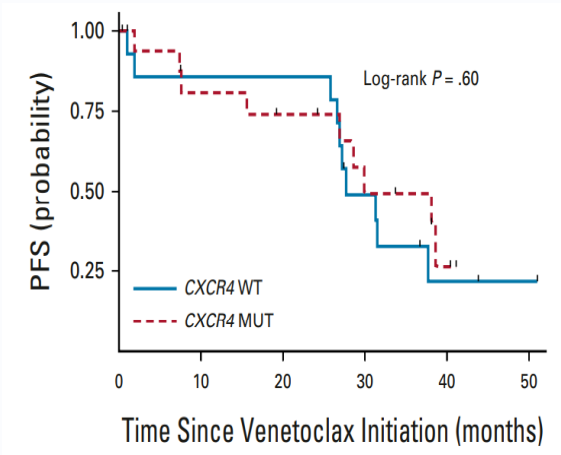
32 pts	
Median prior Tx:	**2(1-10)**
Prior BTKi:	**66%**
MYD88^{mut}:	**100%**
CXCR4^{mut}:	**53%**











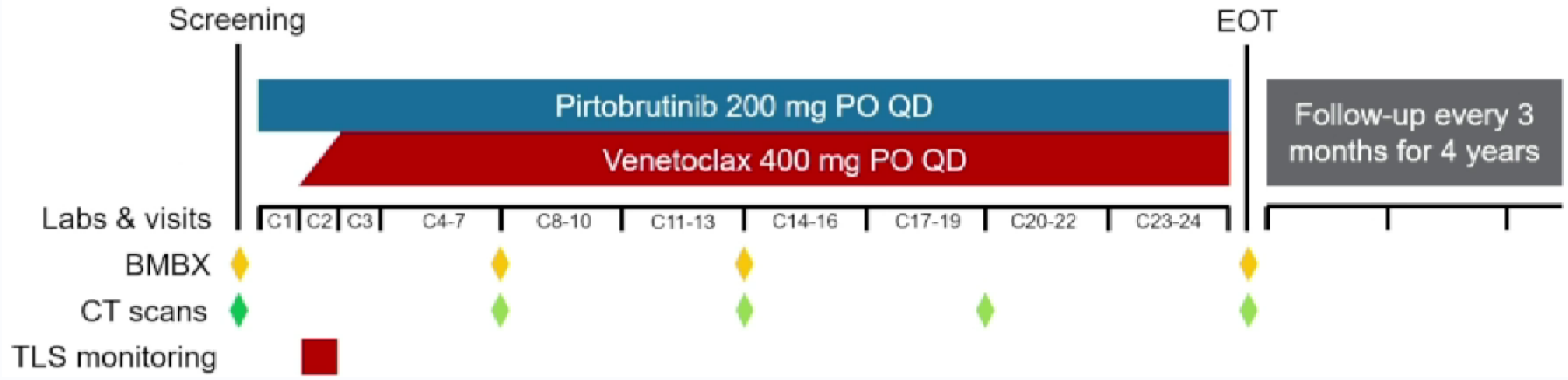
Castillo et al 2021

Fixed-duration venetoclax pirtobrutinib in R/R WM

Treatment schema

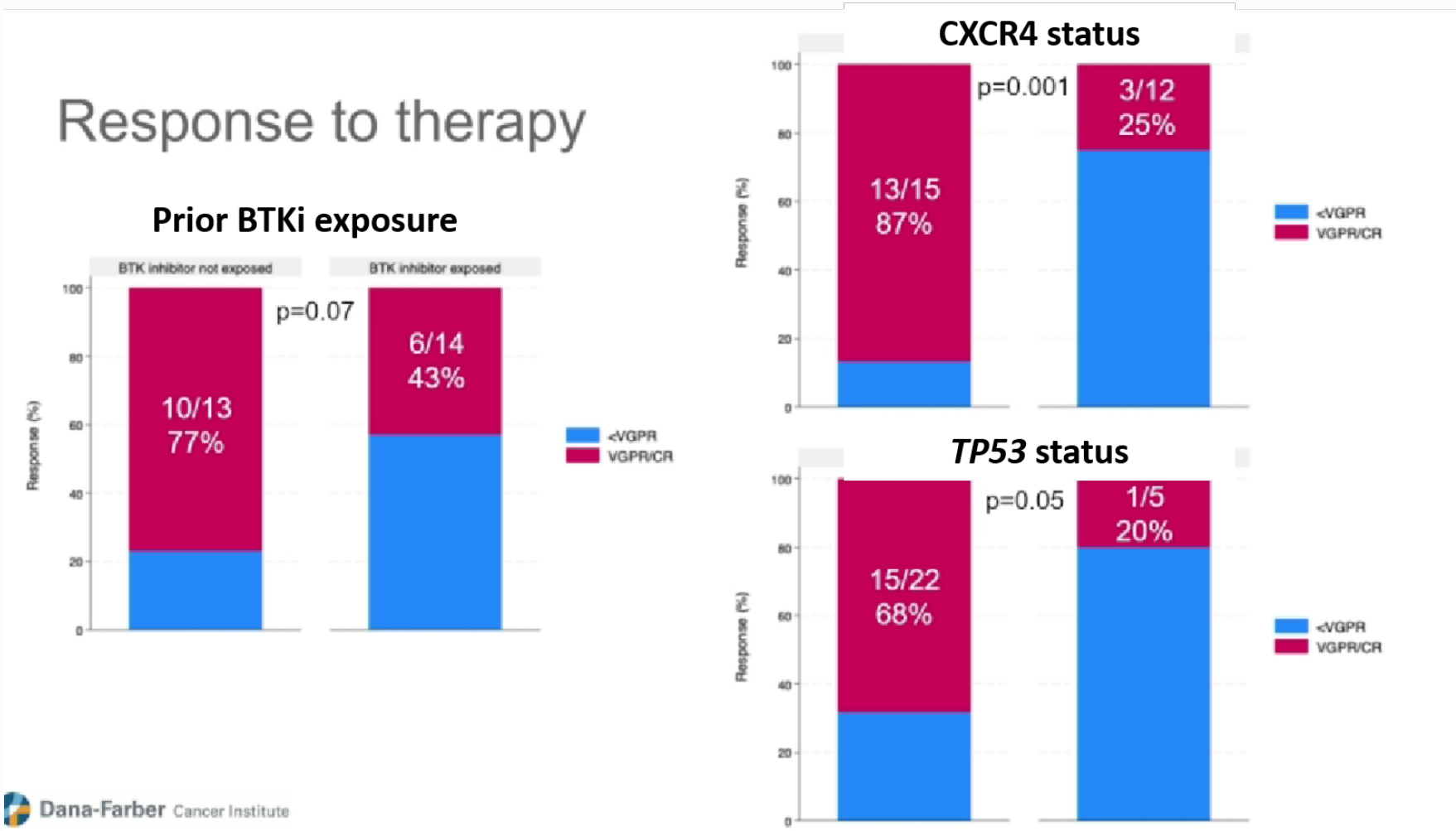
Key inclusion criteria
18+ years
Diagnosis and need for treatment per IWWM2
MYD88 L265P present
1+ previous therapy

Key exclusion criteria
CNS involvement
Pregnancy
Active HIV, HBV, HCV infection
Previous non-covalent BTK inhibitor

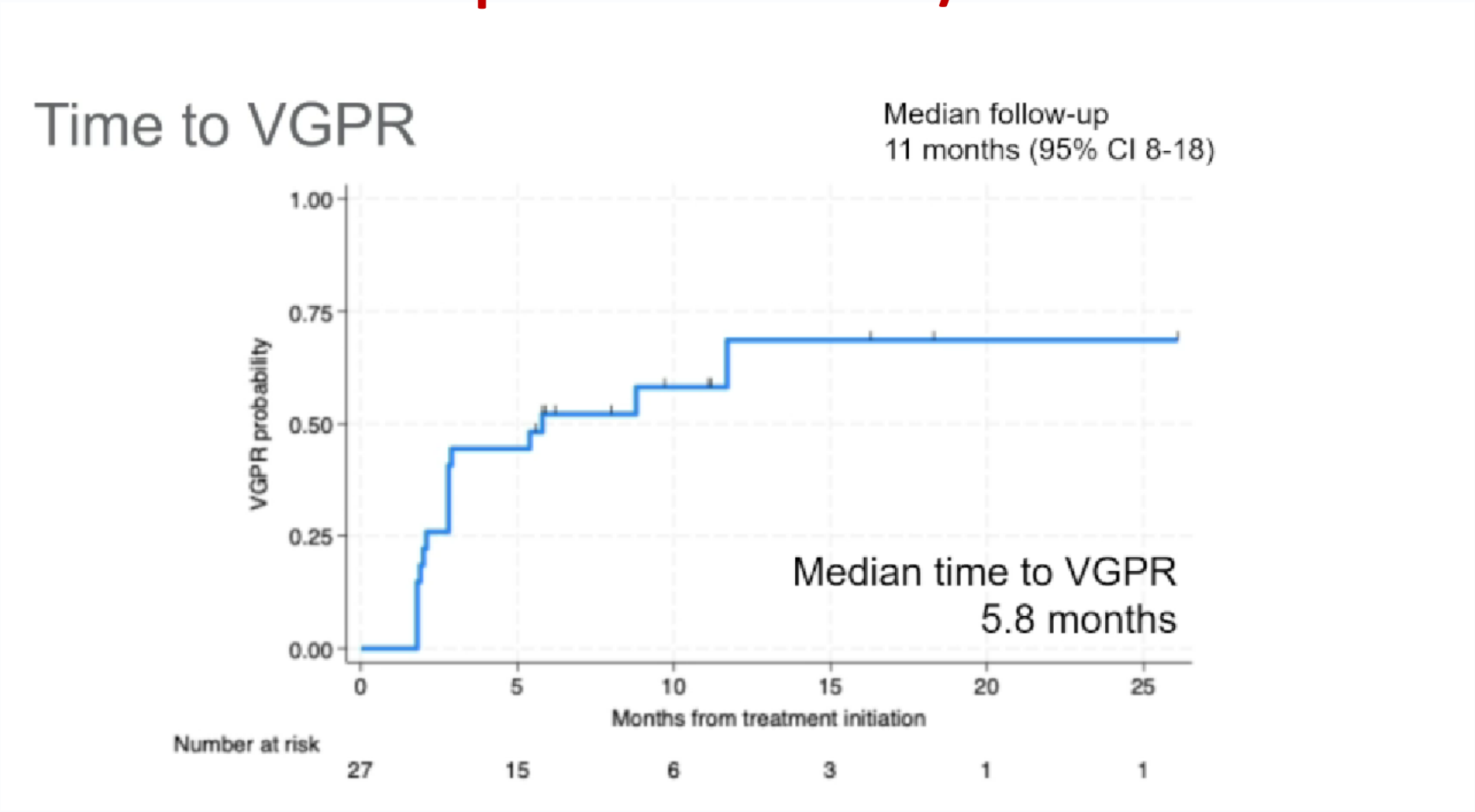


Fixed-duration venetoclax pirtobrutinib in R/R WM

100% ORR
85% VGPR

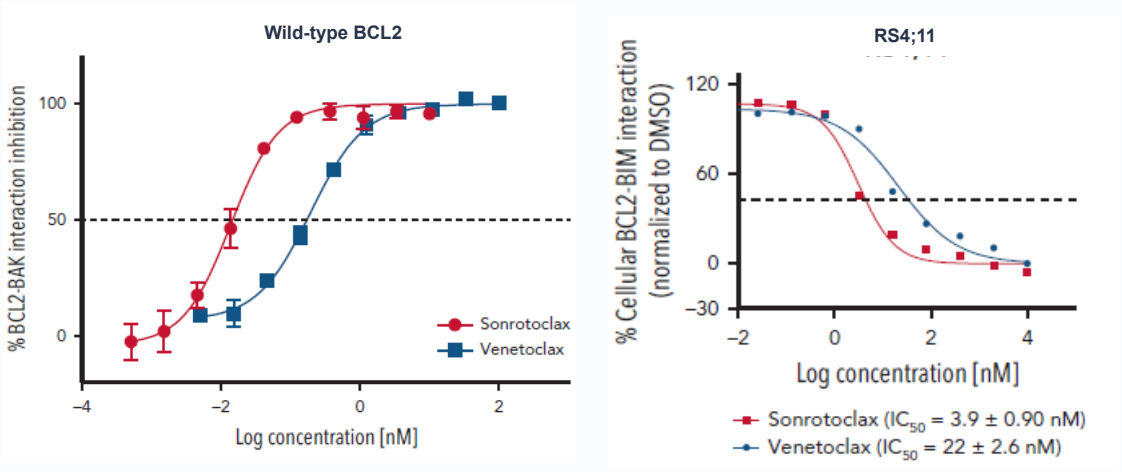


Fixed-duration venetoclax pirtobrutinib in R/R WM

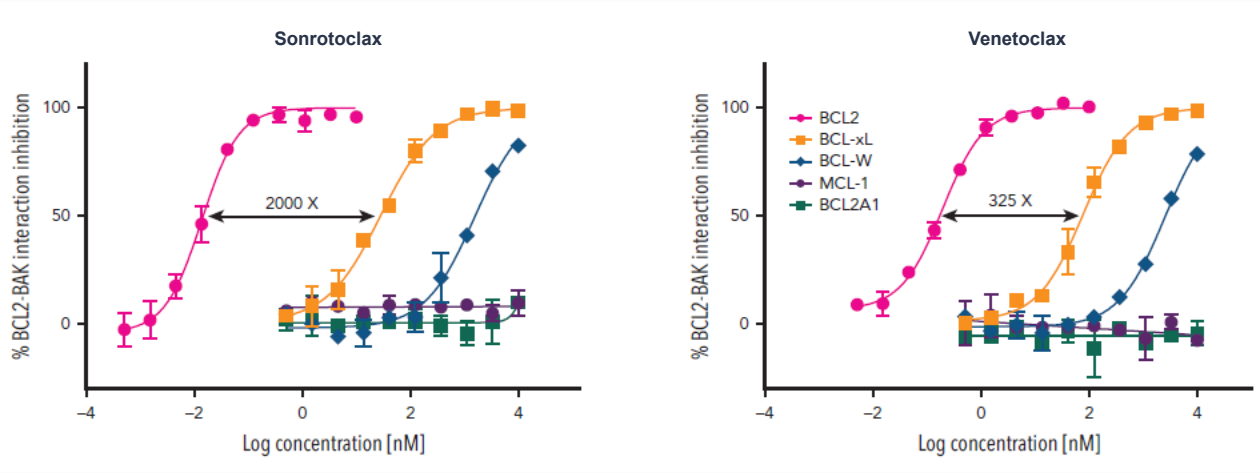


Next generation Bcl2 inhibitor sonrotoclax in R/R WM

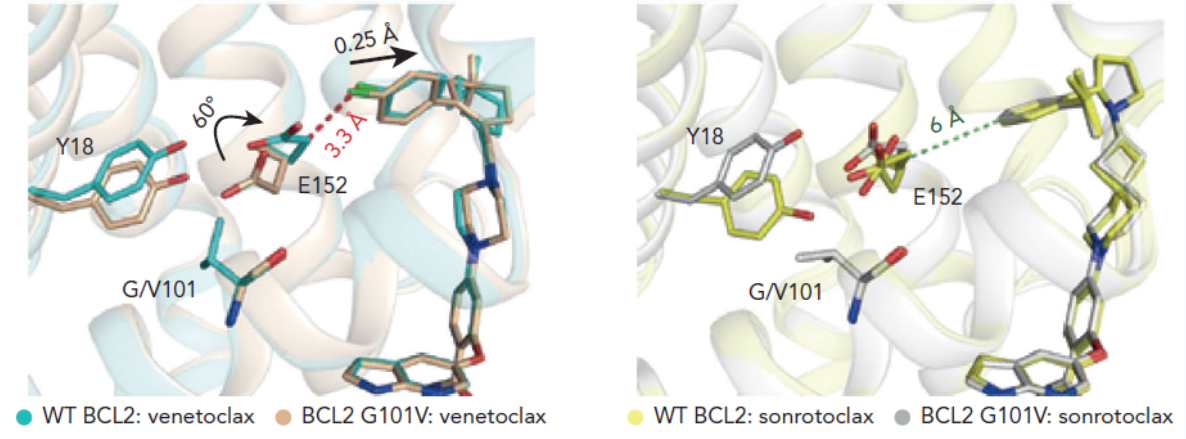
Increased potency



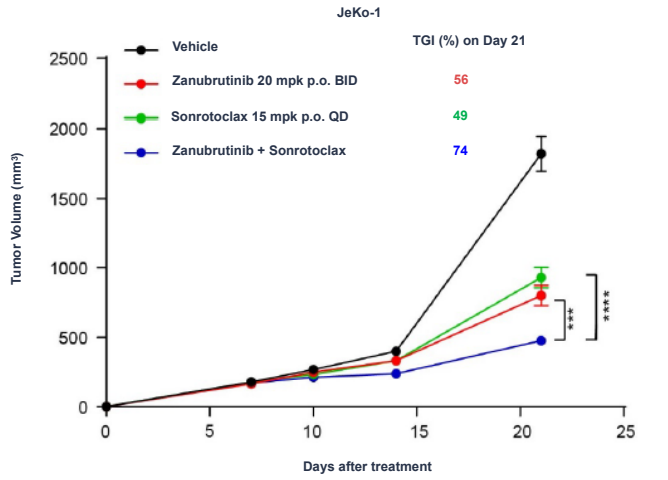
Increased selectivity toward BCL-xL



Sonrotoclax maintains high potency against the BCL2 G101V mutant



Increased activity of sonrotoclax + zanubrutinib than either single agent



BCL2A1, B-cell lymphoma-2-related protein A1; BCL2i, B-cell lymphoma-2 inhibitor; BCL-w, B-cell lymphoma-w; BCL-xL, B-cell lymphoma-L-extra large; BID, twice daily; MCL-1, myeloid cell leukemia-1; QD, once daily; TGI, total growth inhibition; WT, wild type.
Adapted from Liu J et al. Blood. 2024;143(18):1825-1836.

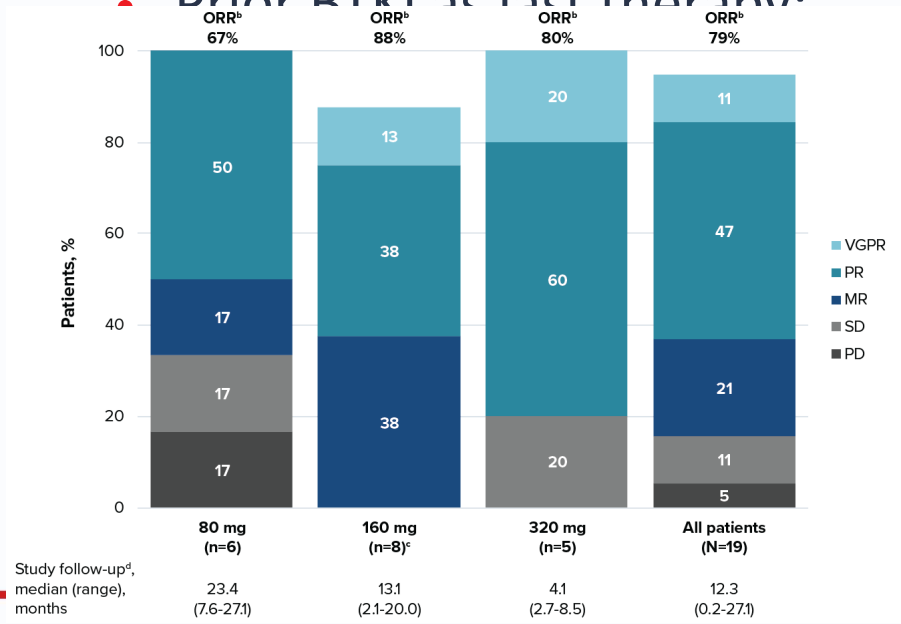
Sonrotoclax in WM cohort: efficacy

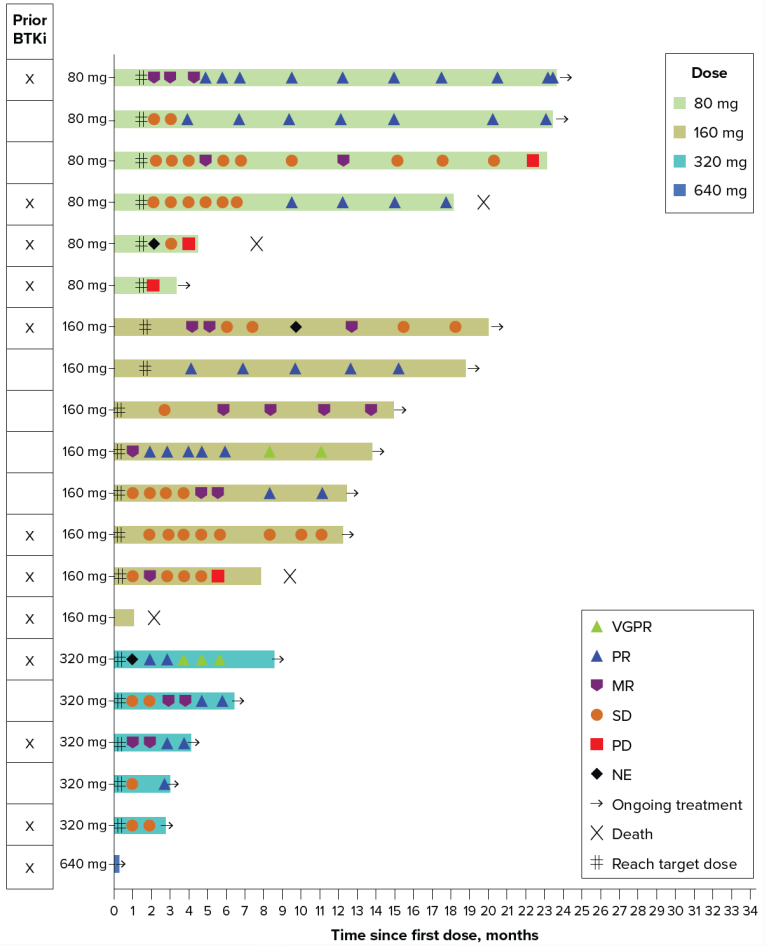
Dose levels: 80 mg → 640 mg

20 WM → 14 (70%) on treatment at last data cut-off

20 WM (mFU 12.3 months)

- Median age: 68.5 yrs
- No. prior lines: 2.5
- Prior BTKi: 60%
- Prior BTKi as last therapy:



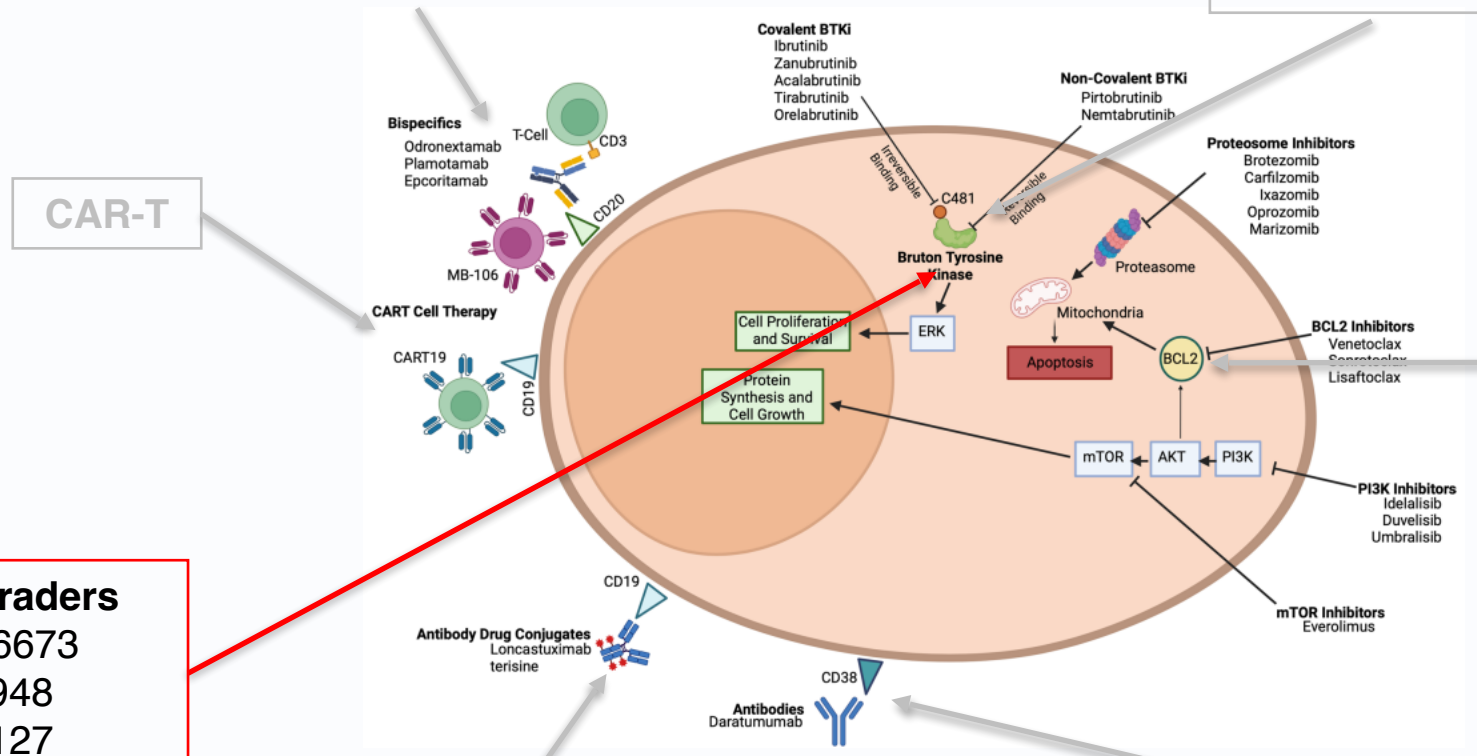


Cheah, EHA 2024

Potential therapeutic targets in WM

Non covalent BTKI
Pirtobrutinib
Nemtabrutinib

Bispecifics



CAR-T

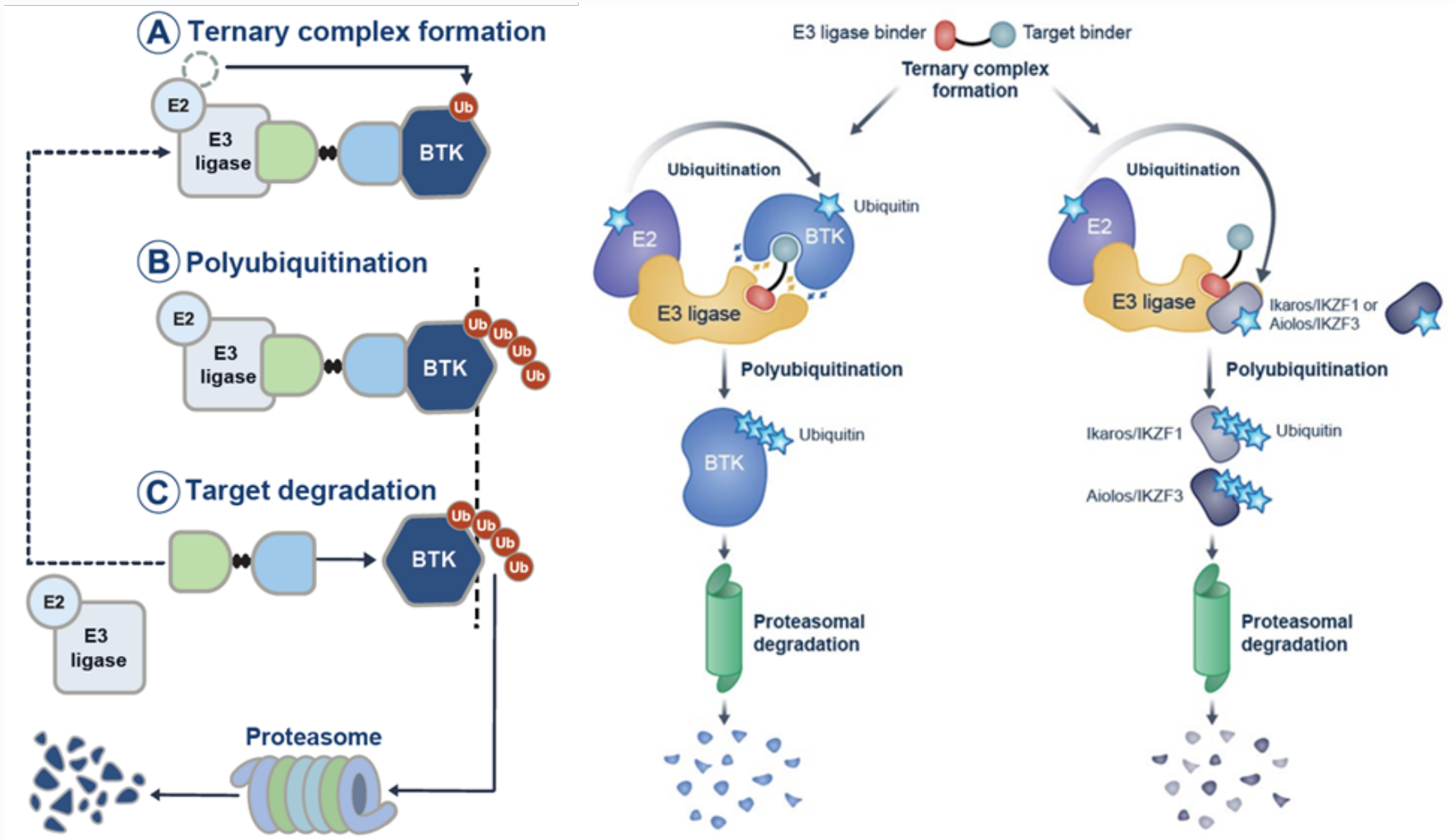
Bcl2 antagonists
Venetoclax
Sonrotoclax
Lisaftoclax

BTK degraders
BGB 16673
NX 5948
NX 2127

Ab drug coniugates
Loncastuximab

Anti CD38
Daratumumab

BTK degradation



BGB16673-101 in WM

Baseline Patient Characteristics

Heavily pretreated with high rate of poor risk features

Characteristic	Total (N=43)
Age, median (range), years	72 (46-81)
Male, n (%)	28 (65.1)
ECOG PS, n (%)	
0	20 (46.5)
1	21 (48.8)
2	2 (4.7)
Hemoglobin, median (range), g/L	103.0 (60.0-146.0)
Hemoglobin <110 g/L, n (%)	30 (69.8)
Neutrophils, median (range), 10^9/L	2.7 (0.2-7.4)
Neutrophils <1.5×10^9/L, n (%)	12 (27.9)
Platelets, median (range), 10^9/L	152.0 (14.0-455.0)
Platelets <100×10^9/L, n (%)	9 (20.9)
IgM, median (range), g/L	33.6 (0.3-92.6)
Mutation status at study entry, n/N with known status (%)[a]	
MYD88 mutated	33/42 (78.6)
CXCR4 mutated	19/42 (45.2)
TP53 mutated	23/42 (54.8)
BTK mutated	13/42 (31.0)
PLCG2 mutated	3/42 (7.1)
No. of prior lines of therapy, median (range)	3 (2-11)
Prior therapy, n (%)	
Chemotherapy	40 (93.0)
Anti-CD20 monoclonal antibodies	43 (100)
cBTK inhibitors	43 (100)
ncBTK inhibitors	7 (16.3)
BCL2 inhibitors	10 (23.3)
Proteasome inhibitors	14 (32.6)
Discontinued prior BTK inhibitor due to PD, n (%)	36 (83.7)

Trotman, EHA 2026

Overall Response Rate

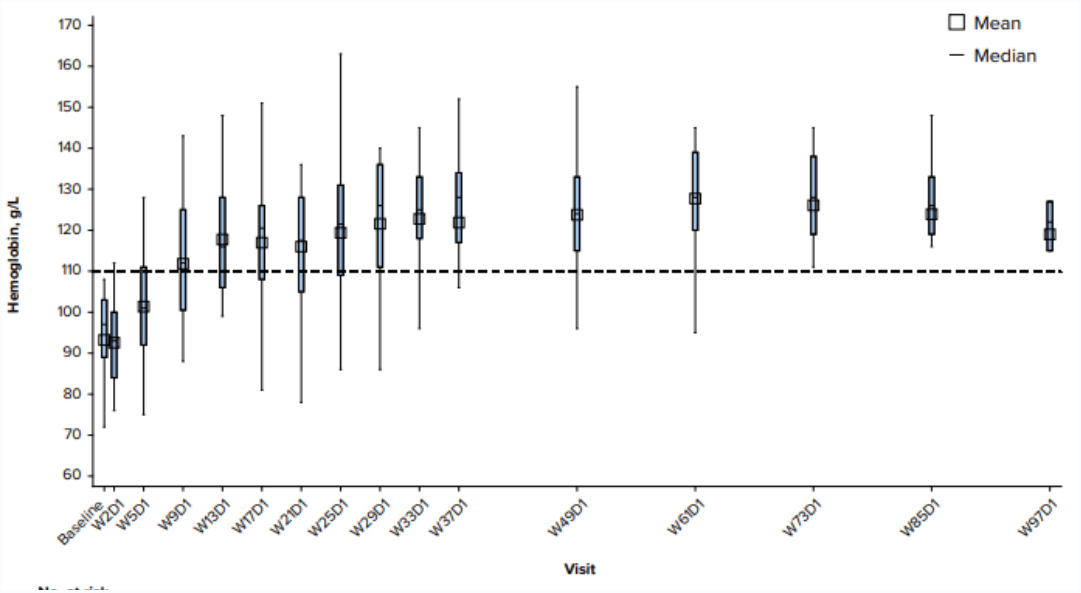
High response rates across all risk groups

Subgroup	ORR, n/N[a] (%)
Overall	36/43 (83.7)
Number of lines of prior anticancer therapies	
<4	20/23 (87.0)
≥4	16/20 (80.0)
Number of prior BTK inhibitor therapies	
≤1	20/25 (80.0)
≥2	16/18 (88.9)
Refractory to last BTK inhibitor[b]	
Yes	24/30 (80.0)
No	3/3 (100.0)
***MYD88* mutation**	
Yes	29/33 (87.9)
No	7/9 (77.8)
***CXCR4* mutation**	
Yes	19/19 (100.0)
No	17/23 (73.9)
***TP53* mutation**	
Yes	21/23 (91.3)
No	15/19 (78.9)
***BTK* mutation**	
Yes	13/13 (100.0)
No	23/29 (79.3)
***PLCG2* mutation**	
Yes	3/3 (100.0)
No	33/39 (84.6)

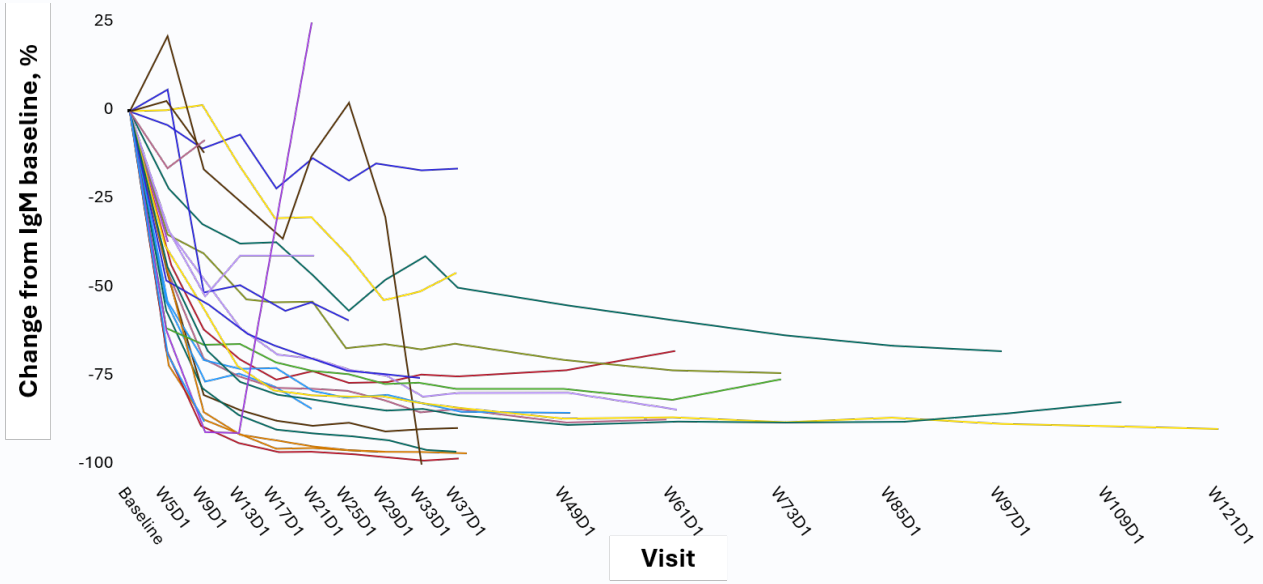
[a]Efficacy-evaluable population; 4 patients were too early in treatment course to be response-evaluable. [b]Includes best overall response of MR or better. [c]Includes best overall response of PR or VGPR. [d]In patients with a best overall response better than SD.
BTK, Bruton tyrosine kinase; cBTK, covalent Bruton tyrosine kinase; MR, minor response; ncBTK, noncovalent Bruton tyrosine kinase; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Frustaci, EHA 2025

Rapid and Significant Cytopenia Improvement Was Observed in Patients With Treatment Response



Trotman, EHA 2026



Frustaci, EHA 2025

NX-5948-301: Phase 1a/b trial in adults with R/R B-cell malignancies

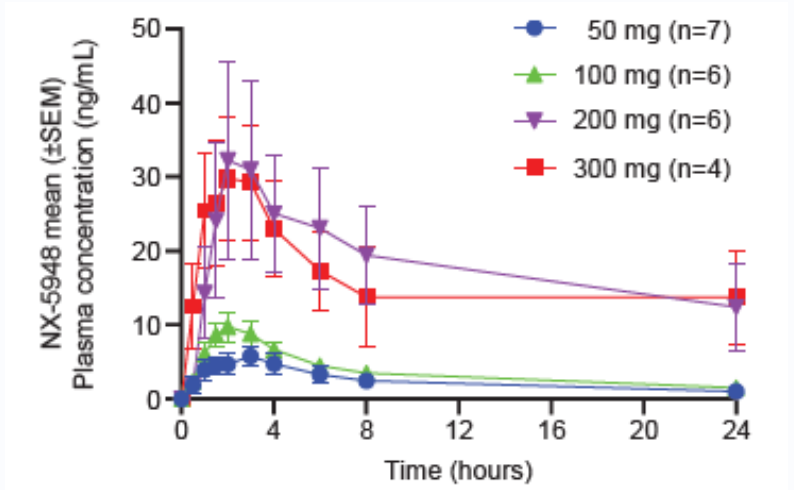
Dose levels: 40 mg → 640 mg

48 NHL/WM[1]

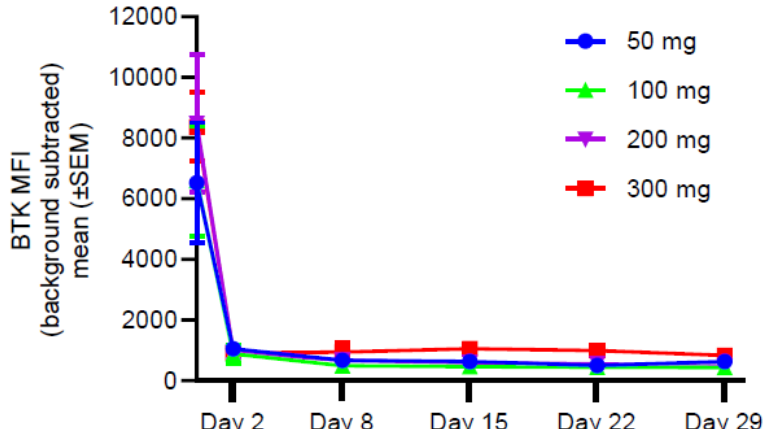
- Median age 66.5 years
- Median prior lines: 4
- CNS involvement 20.8%
- Prior cBTKi: 60.4%
- Prior ncBTKi: 14.6%
- Prior BCL2i: 14.6%
- Prior CAR-T/Bispecifics 22.9%/14.6%
- *TP53* mutations 9.5%

- ***22/48 still on treatment***
- ***Clinical follow-up still ongoing for iNHL/WM cohort***
- ***Clinical efficacy on CNS involvement***

NX-5948 Cycle 1, Day 1 pharmacokinetics



BTK degradation in all patients receiving NX-5948



BCL2i, B-cell lymphoma-2 inhibitor; BTK, Bruton's tyrosine kinase; cBTKi, covalent BTKi; CAR-T, chimeric antigen receptor T-cell; CNS, central nervous system; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MZL, marginal zone lymphoma; ncBTKi, non-covalent BTKi; R/R, relapsed/refractory; *TP53*, tumor protein p53; WM, Waldenström's macroglobulinemia.

1) Linton K al. Presented at the EHA2024 Hybrid Congress; June 13-16, 2024; Madrid, Spain. Available at: https://www.nurixtx.com/wp-content/uploads/2024/06/EHA-2024-Oral-FINAL.pdf;
2) Searle E et al. Presented at the 21st Annual International Ultmann Chicago Lymphoma Symposium; 19–20 April 2024, Chicago, IL, USA. Available at: https://ir.nurixtx.com/static-files/17923ef7-e335-4870-9ed9-aff3b25e127b.

Key points

- **WM is a heterogeneous disease →** treatment should be tailored to patient characteristics, clinical presentation, and disease biology.
- **CIT is still a valid option in 1st line until chemo-free fixed duration treatment are approved in first line or more salvage treatment are available**
- **BTK inhibitors are the mainstay in 2nd** line of therapy
- **Promising development of next generation Bcl2 inhibitors, nc BTKi and BTK degraders in cBTKi-refractory patients →** Should WM follow CLL road-map?