M. Di Waldenstrom: il futuro

Anna Maria Frustaci
ASST GOM Niguarda

Disclosures of Name Surname

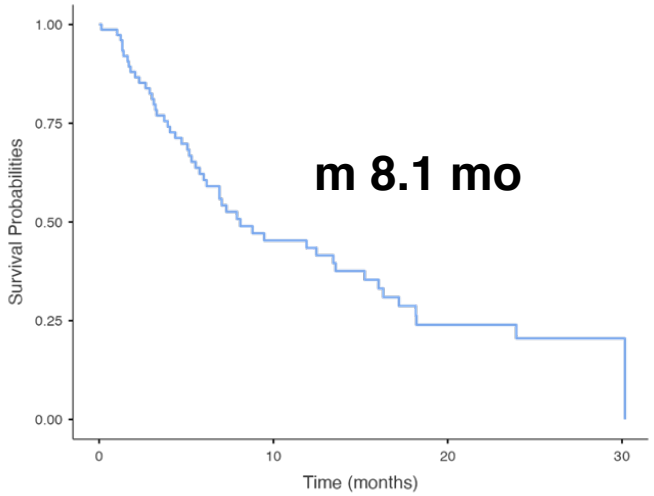
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BeOne			x			x	x
Janssen			x			x	x
Abbvie			x			x	x
AstraZeneca			x			x	x

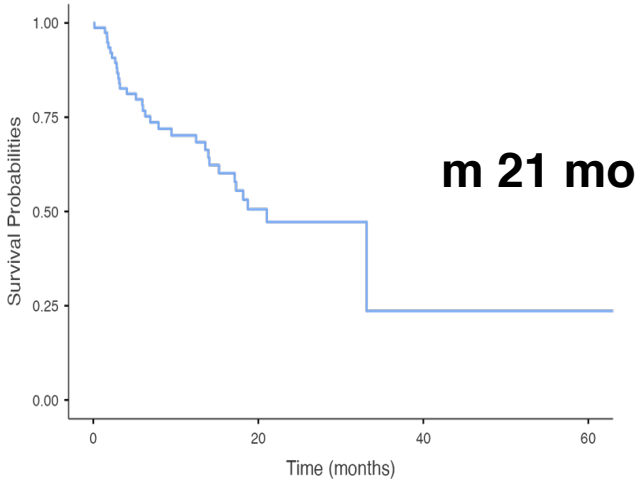
Outcomes of patients receiving a salvage treatment after cBTKi

Progression free survival

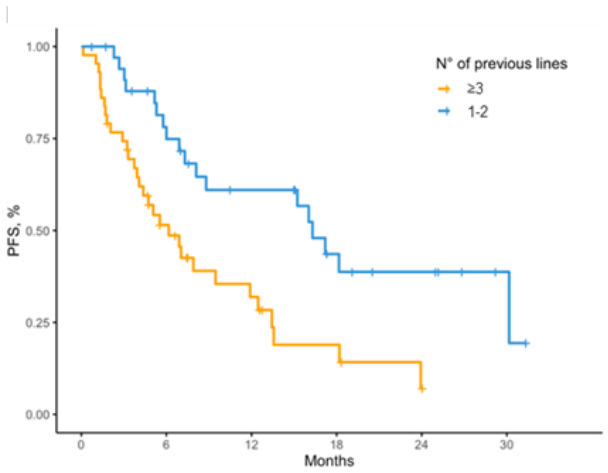
Overall survival

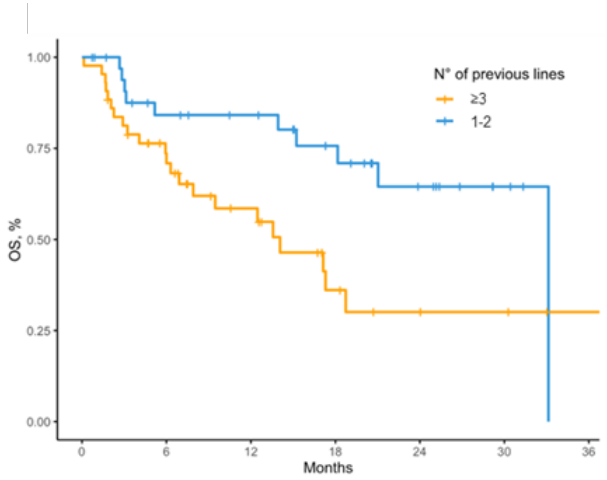
Whole cohort





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





Frustaci, Hemasphere 2025

Potential therapeutic targets in WM

Bispecifics

Non covalent BTKI
Pirtobrutinib
Nemtabrutinib

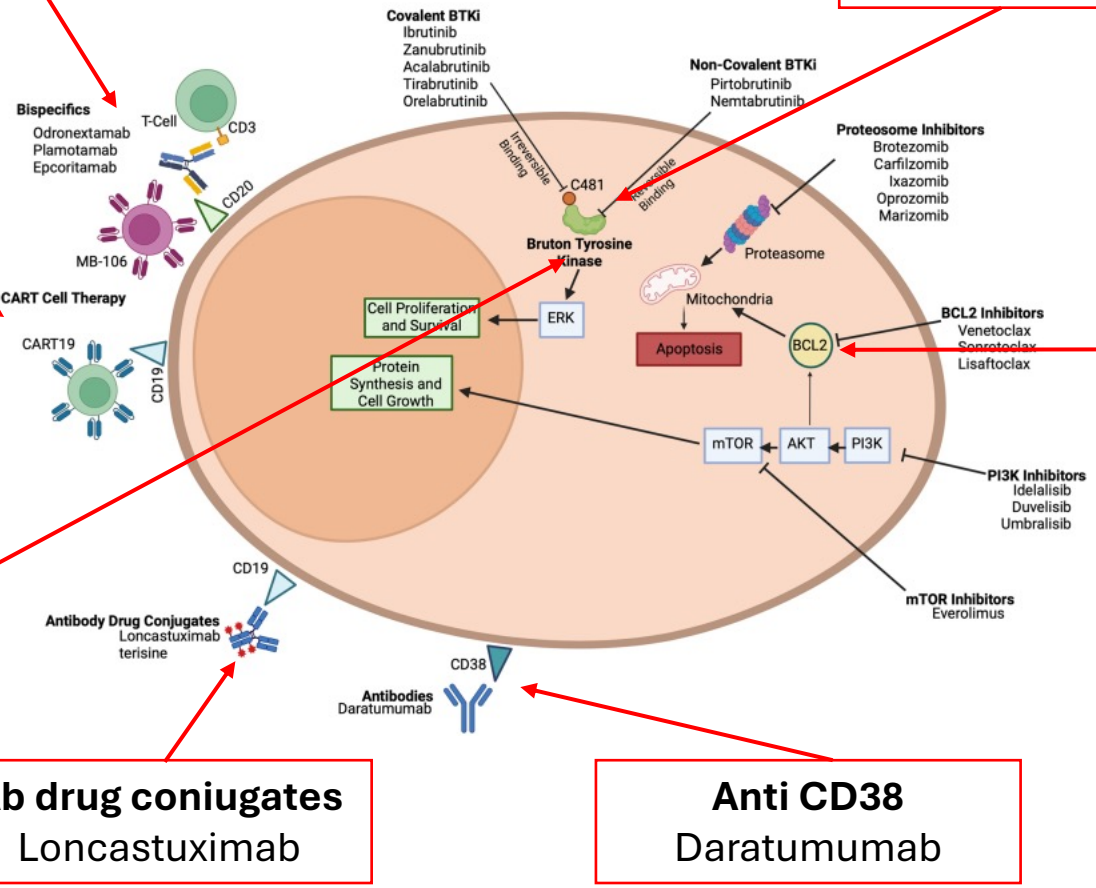
CAR-T

Bcl2 antagonists
Venetoclax
Sonrotoclax
Lisaftoclax

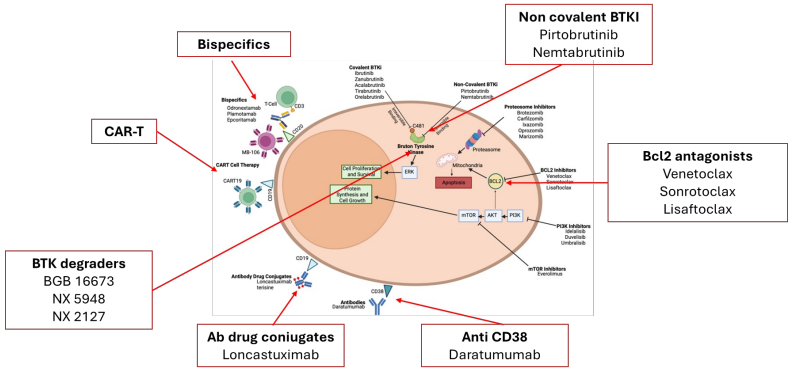
BTK degraders
BGB 16673
NX 5948
NX 2127

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:

- **Venetoclax**
- **pirtobrutinib**

Pirtobrutinib in BTKi-exposed patients: survival

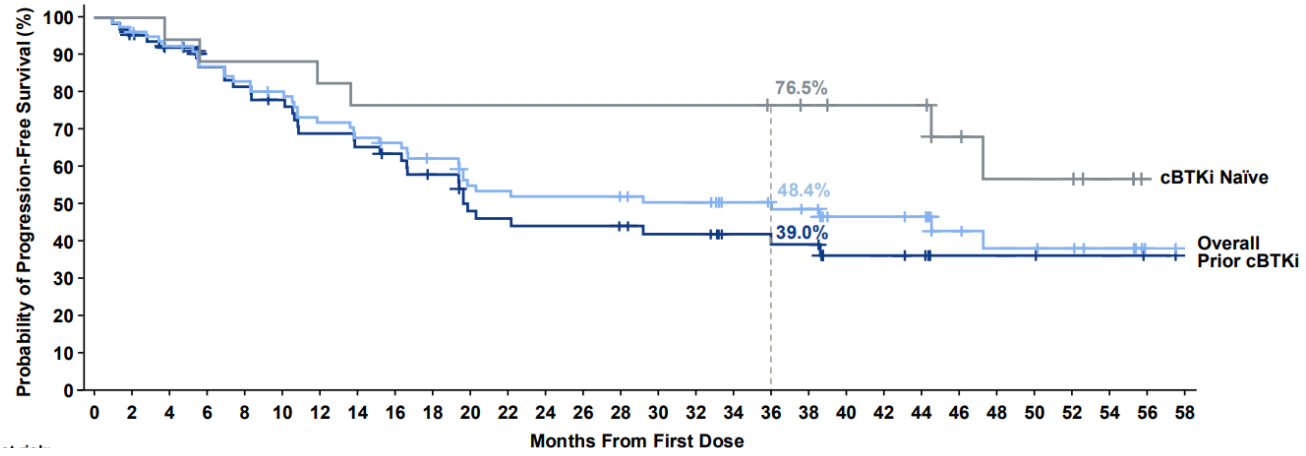
M FU 35 months
Prior BTKi 78%
Prior BTKi+ CIT 64%
m prior lines:3 in BTK-exposed

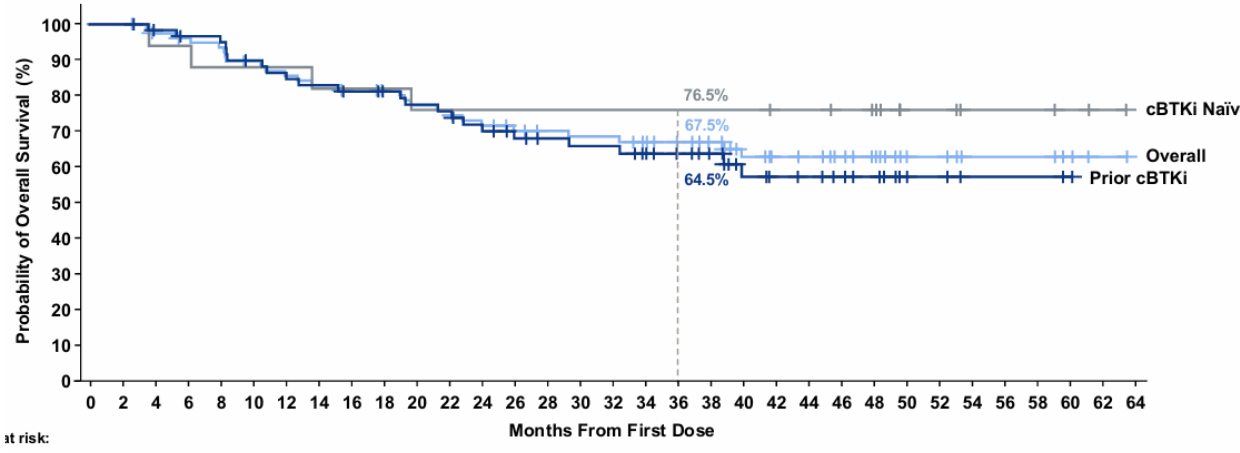
median PFS: 36 mo

19.6 in BTK-exp

NR in BTK-naive

median OS: NR





Cheah ASH 2026

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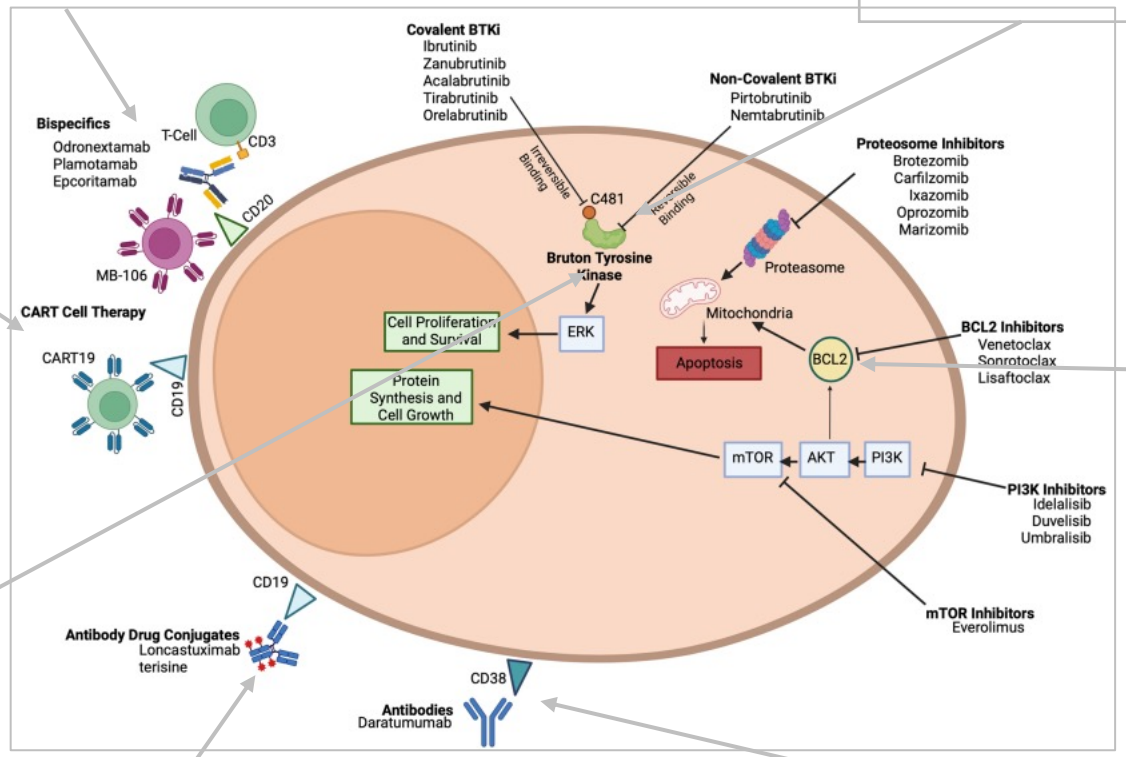

Bcl2 antagonists
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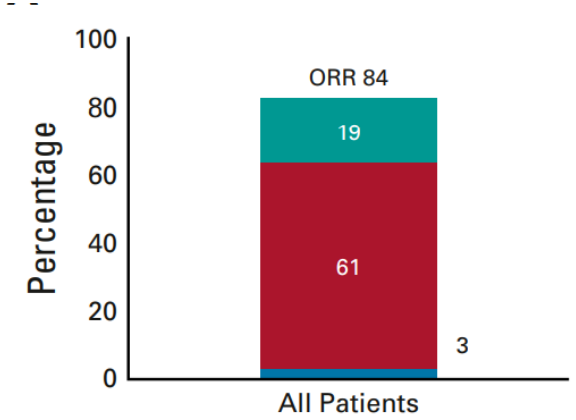
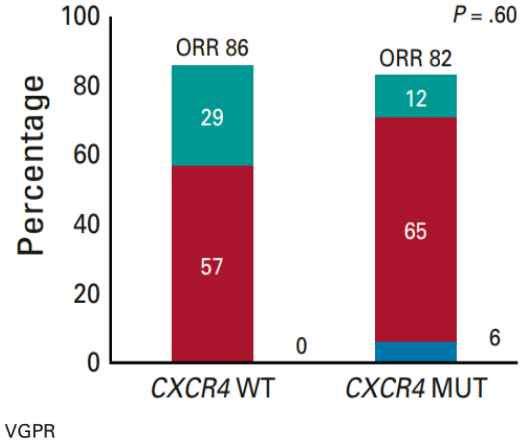
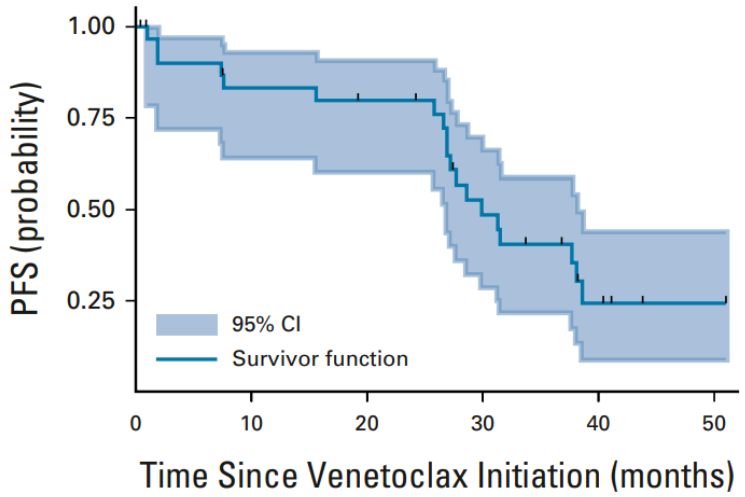
Daratumumab

What next? Fixed-duration venetoclax monotherapy in R/R WM

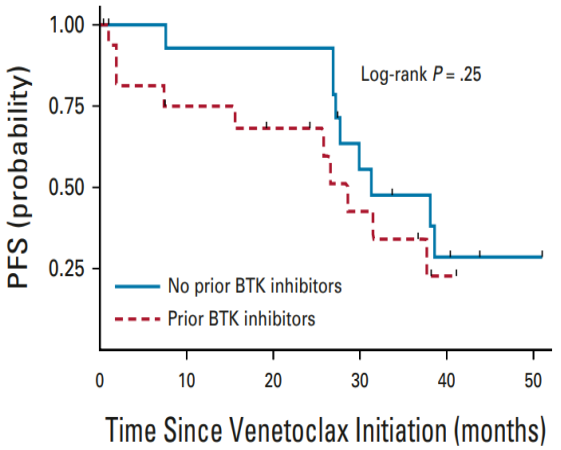
32 pts	
Median prior Tx:	**2(1-10)**
Prior BTKi:	**66%**
MYD88^{mut}:	**100%**
CXCR4^{mut}:	**53%**



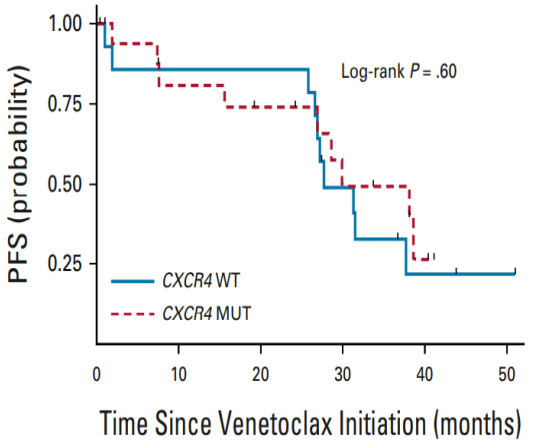




Accord to prior BTKi exp



Accord to CXCR4 status



Castillo et al 2021

Ibrutinib + venetoclax in TN WM

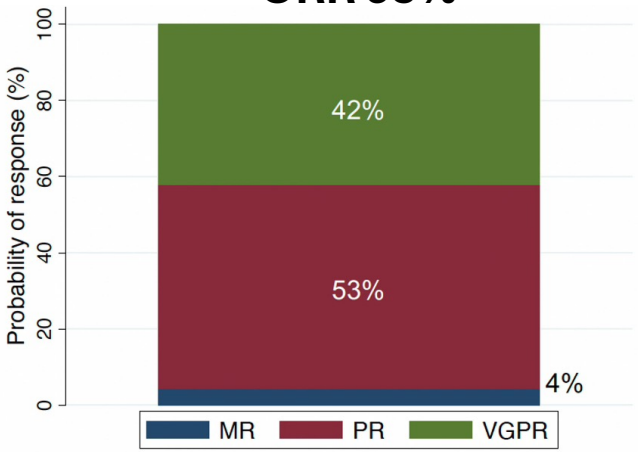
Safety

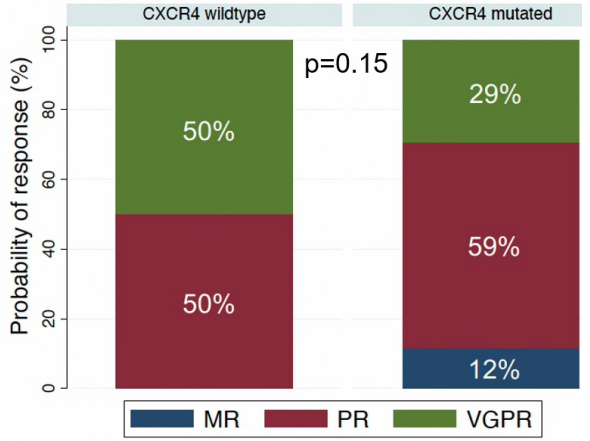
Adverse events	Grade 3	Grade 4	Grade 5	Total
Anemia	2			3
Atrial fibrillation	2	1		4
Diarrhea	1			9
Reflux				10
Mucositis	2			9
Nausea				5
Neutropenia	10	3		14
Hyperphosphatemia				8
Muscle/joint pain	2			16
Skin rash				6
Ventricular arrhythmia		1	2	4
Laboratory TLS	2			2

Efficacy

Median tx exposure 11 months

ORR 95%





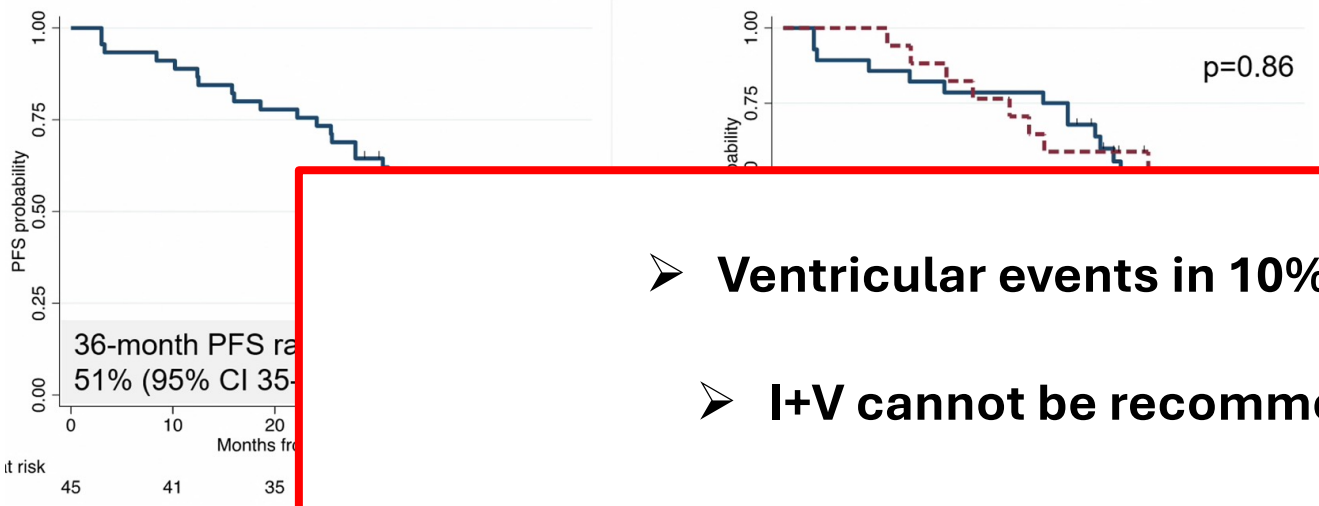
CXCR4 mut vs WT

- No differences in Hb response
- Lower IgM reduction

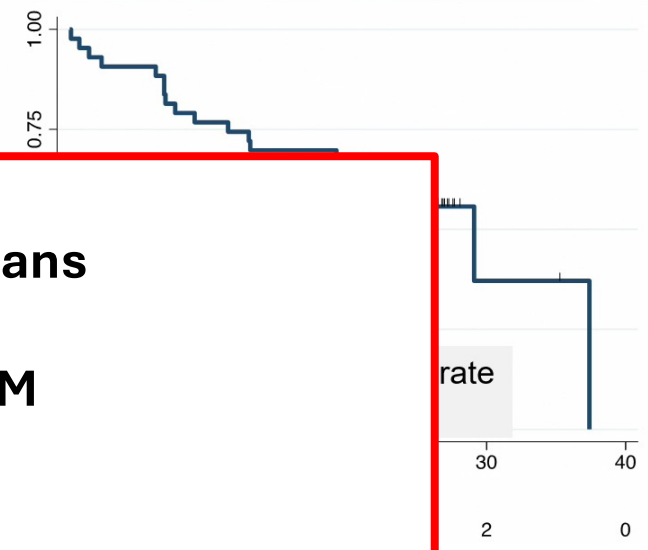
Castillo ASH 2023, Castillo IwWM 2024

Ibrutinib + venetoclax in TN WM

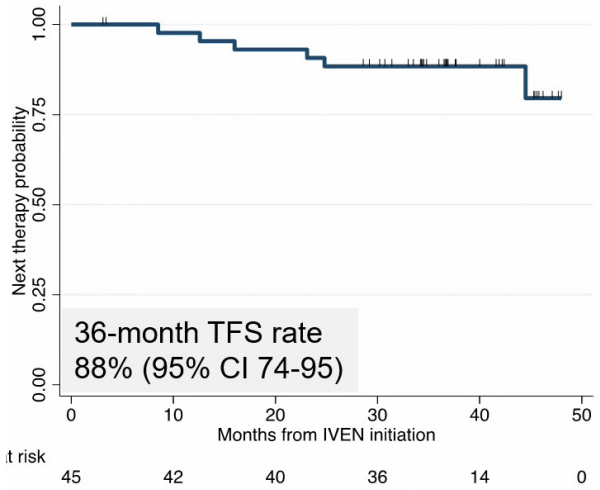
PFS

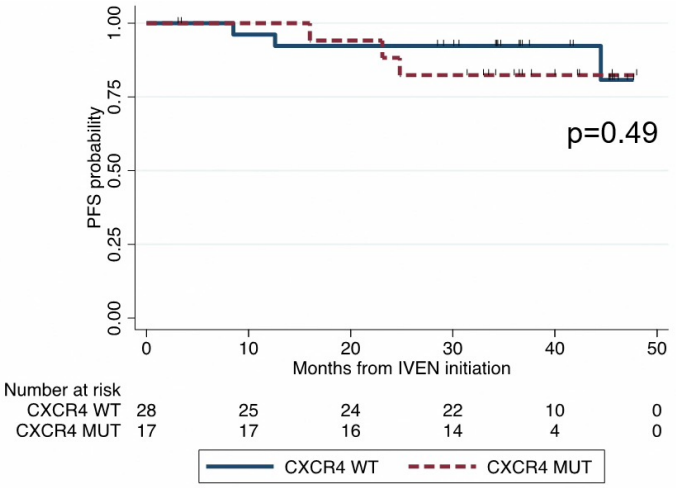


PFS from the end of treatment



- **Ventricular events in 10% of participans**
- **I+V cannot be recommended in WM**





PFS from the end of treatment independent from:

- CXCR4 status
- VGPR vs PR
- <12 mo vs >12 mo of treatment

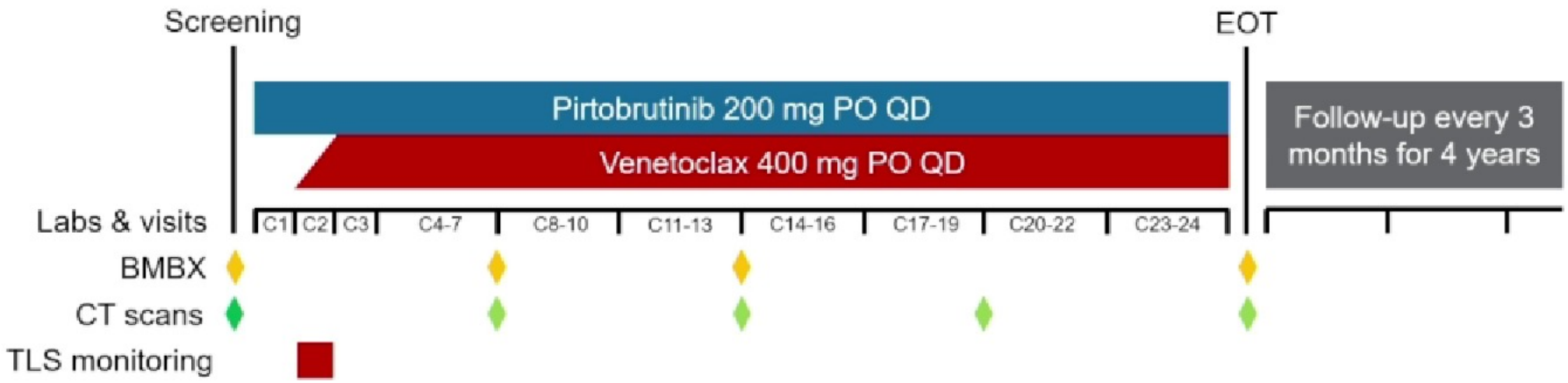
Castillo IwWM 2024

Fixed-duration venetoclax pirtobrutinib in R/R WM

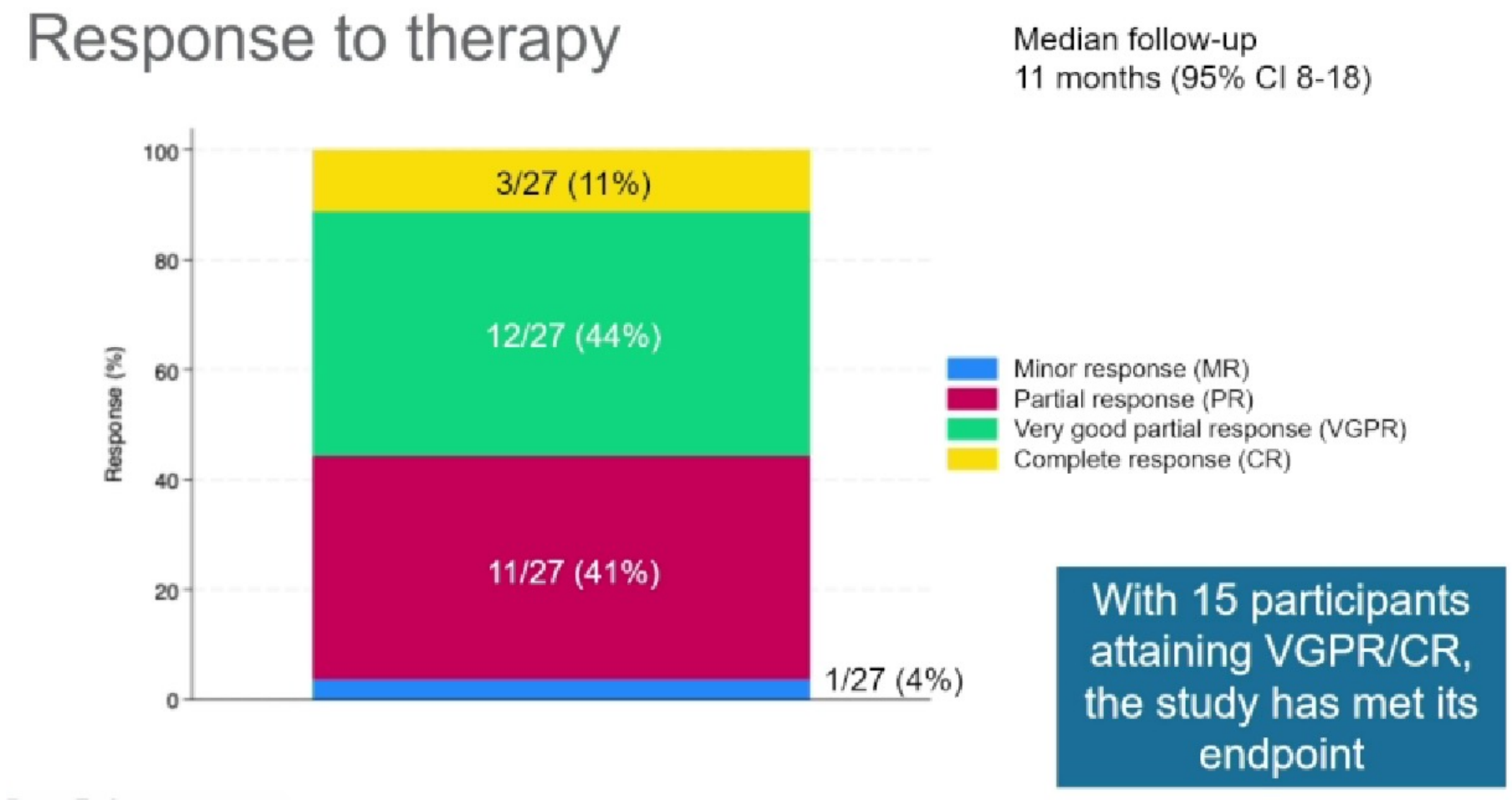
Treatment schema

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



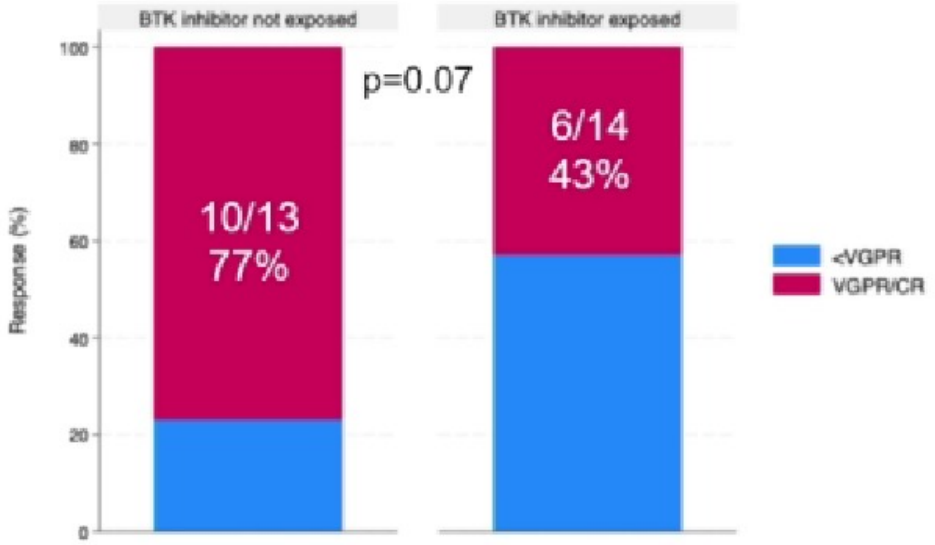
Fixed-duration venetoclax pirtobrutinib in R/R WM



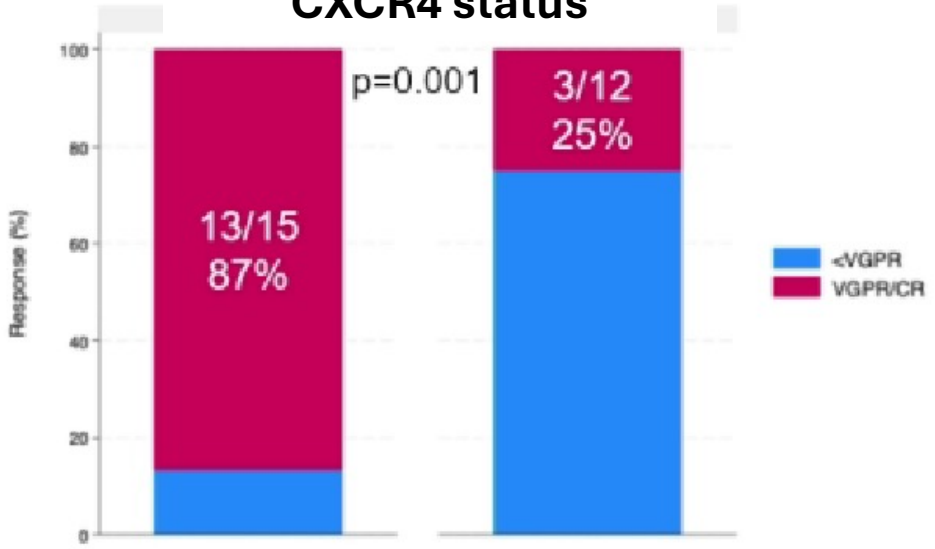
Fixed-duration venetoclax pirtobrutinib in R/R WM

Response to therapy

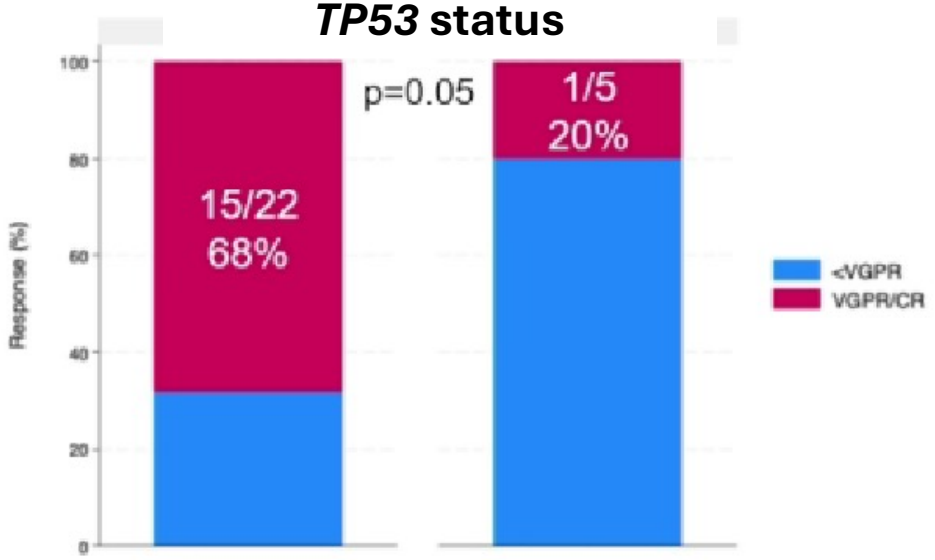
Prior BTKi exposure



CXCR4 status

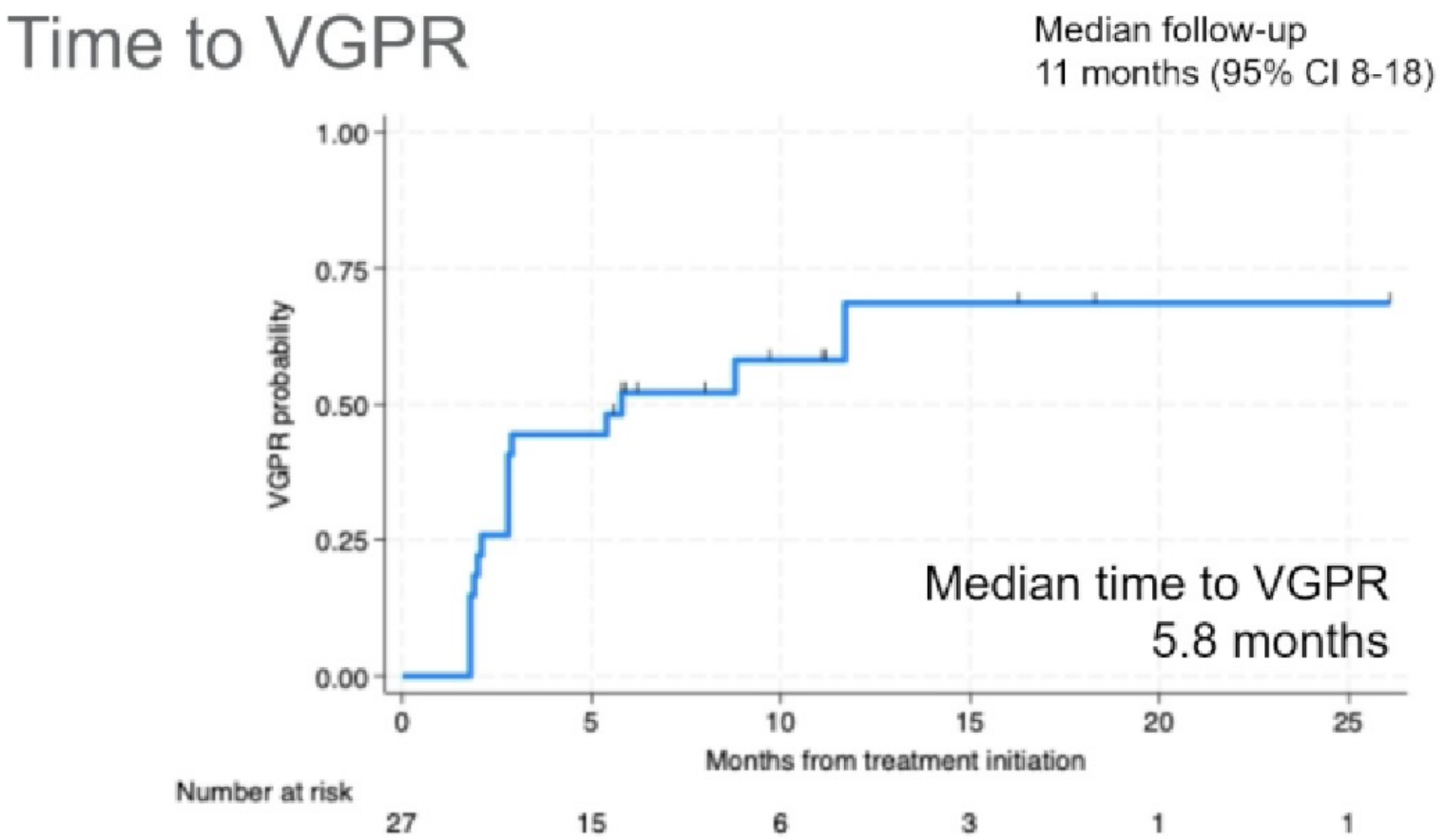


TP53 status

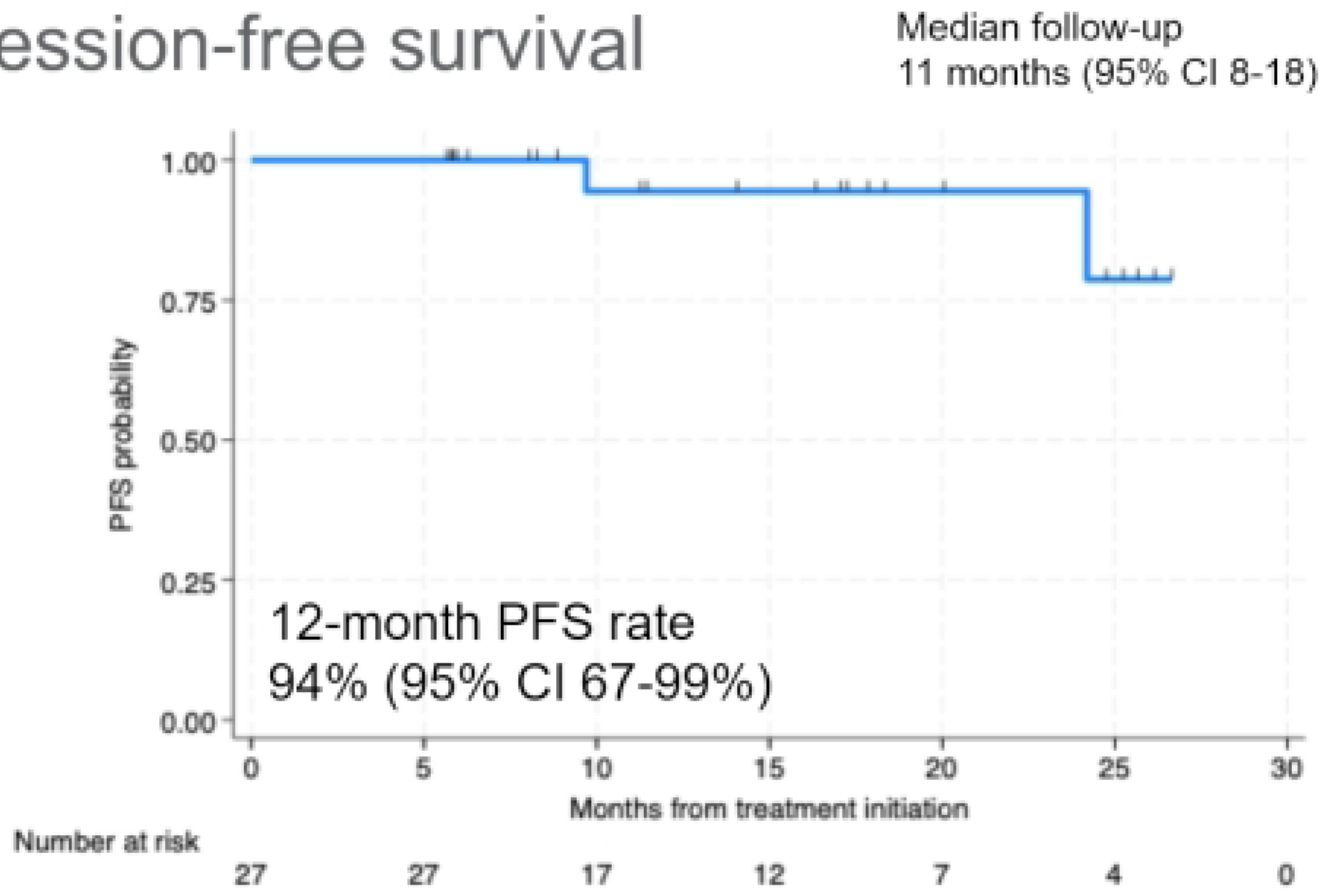


Dana-Farber Cancer Institute

Fixed-duration venetoclax pirtobrutinib in R/R WM

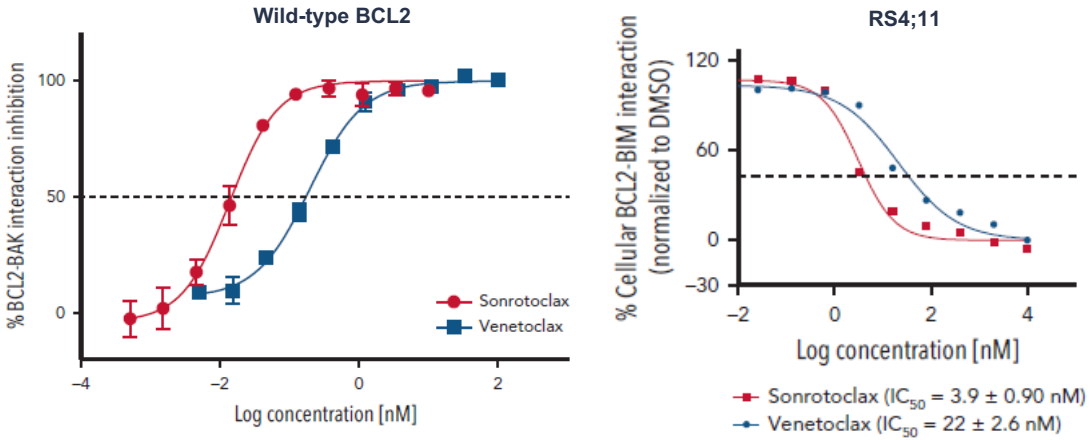


Fixed-duration venetoclax pirtobrutinib in R/R WM

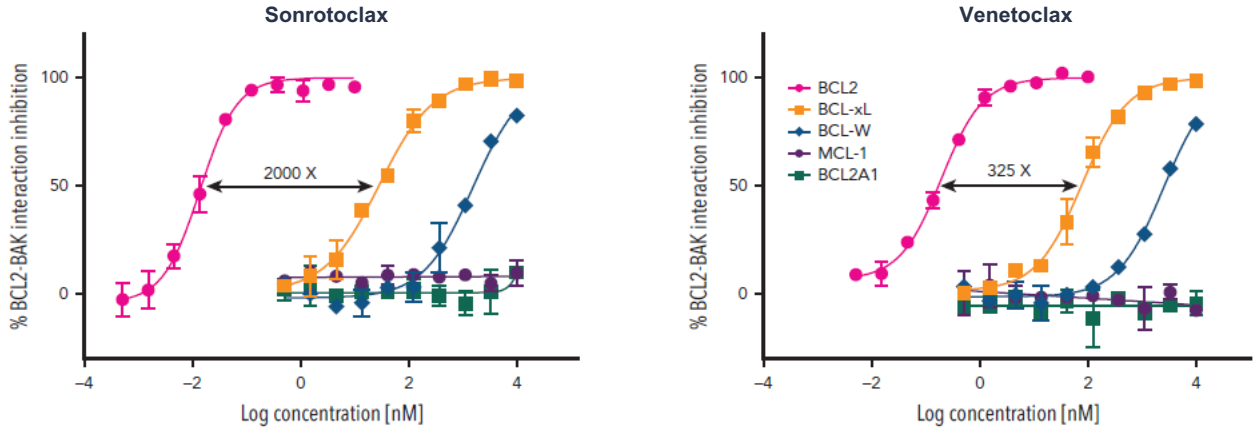


Next generation Bcl2 inhibitor sonrotoclax in R/R WM

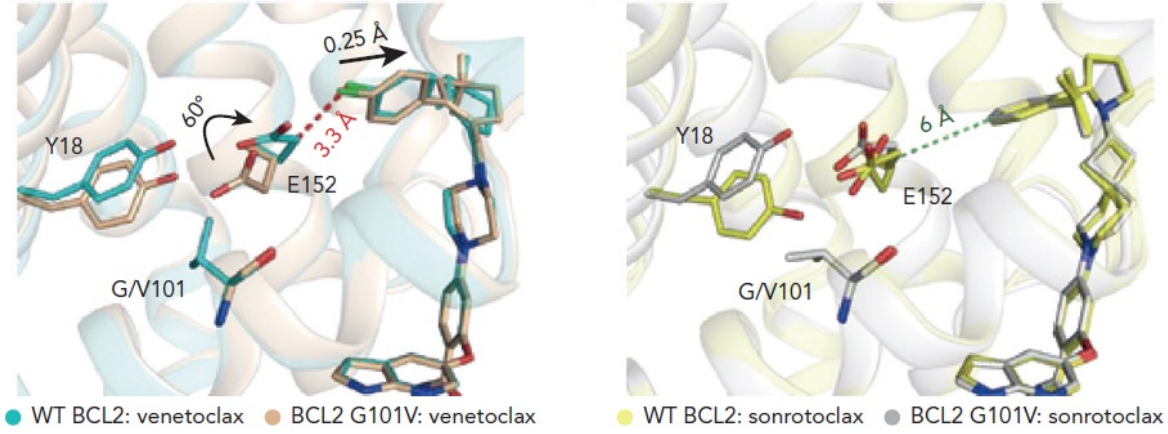
Increased potency



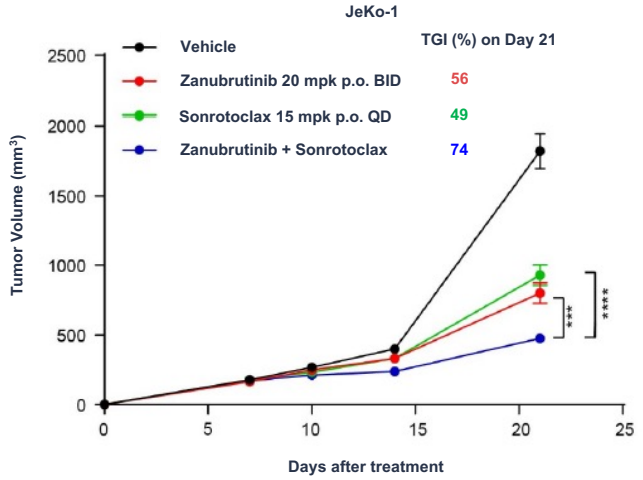
Increased selectivity toward BCL-xL



Sonrotoclax maintains high potency against the BCL2 G101V mutant



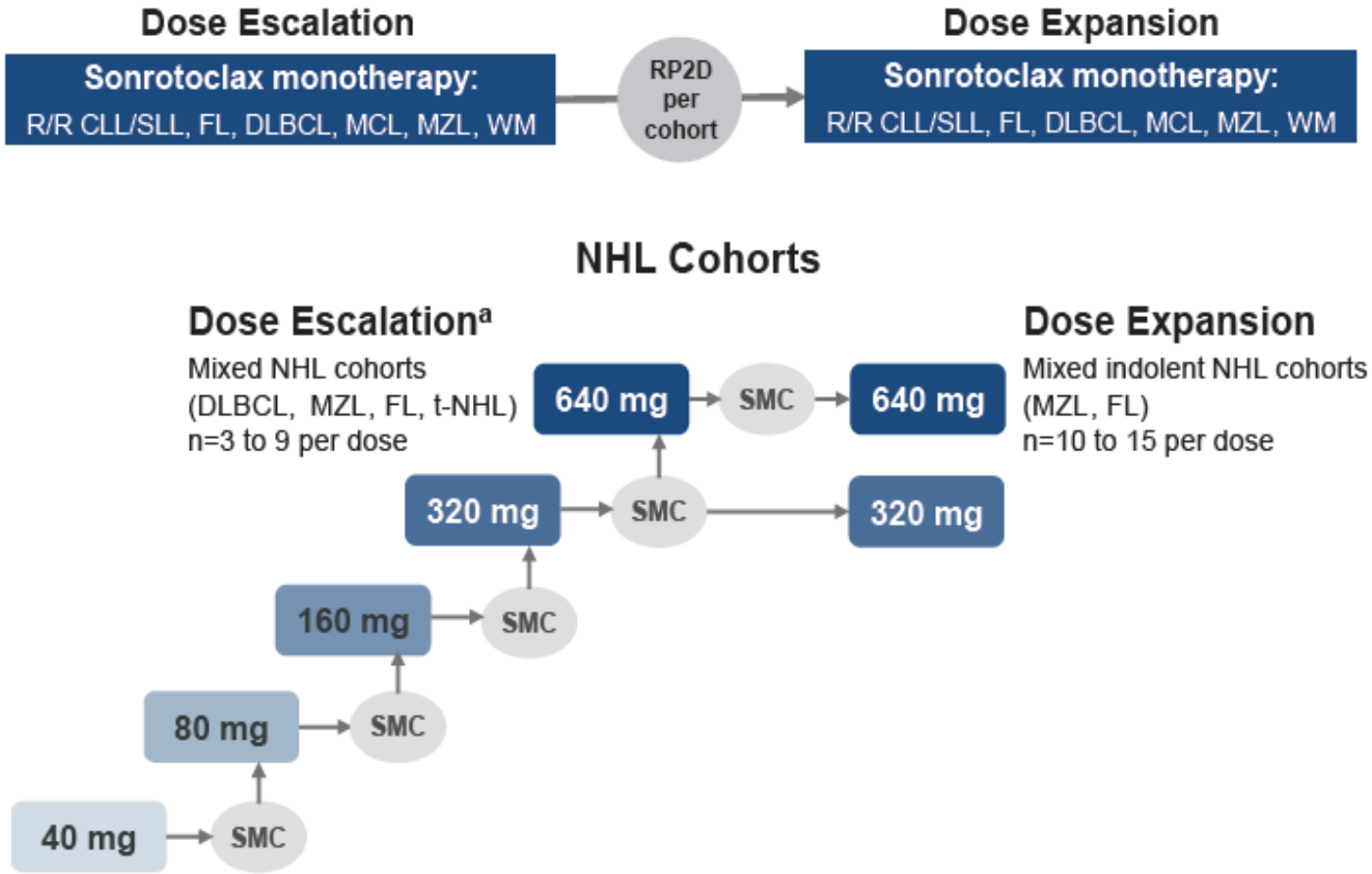
Increased activity of sonrotoclax + zanubrutinib than either single agent



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 R/R NHL and CLL

Sonrotoclax monotherapy



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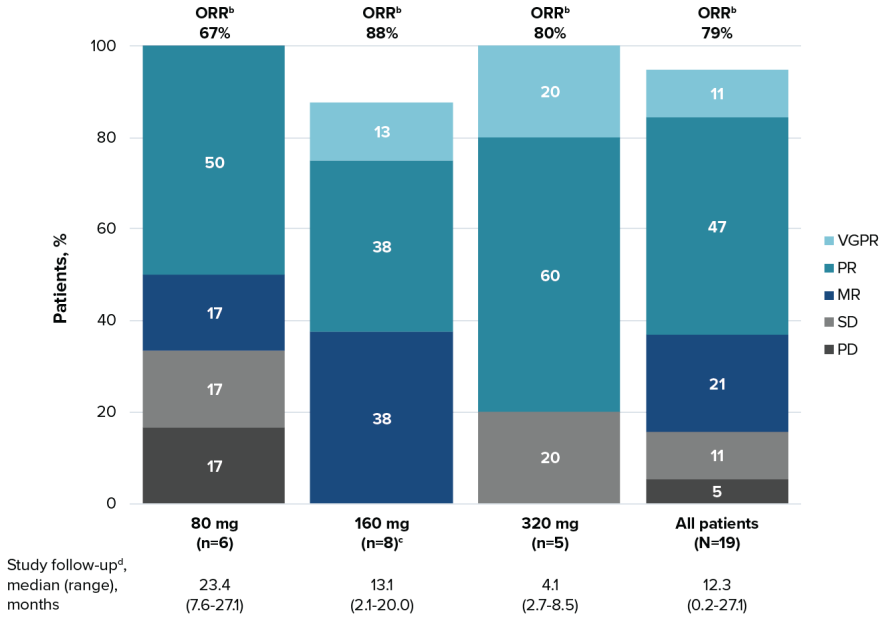
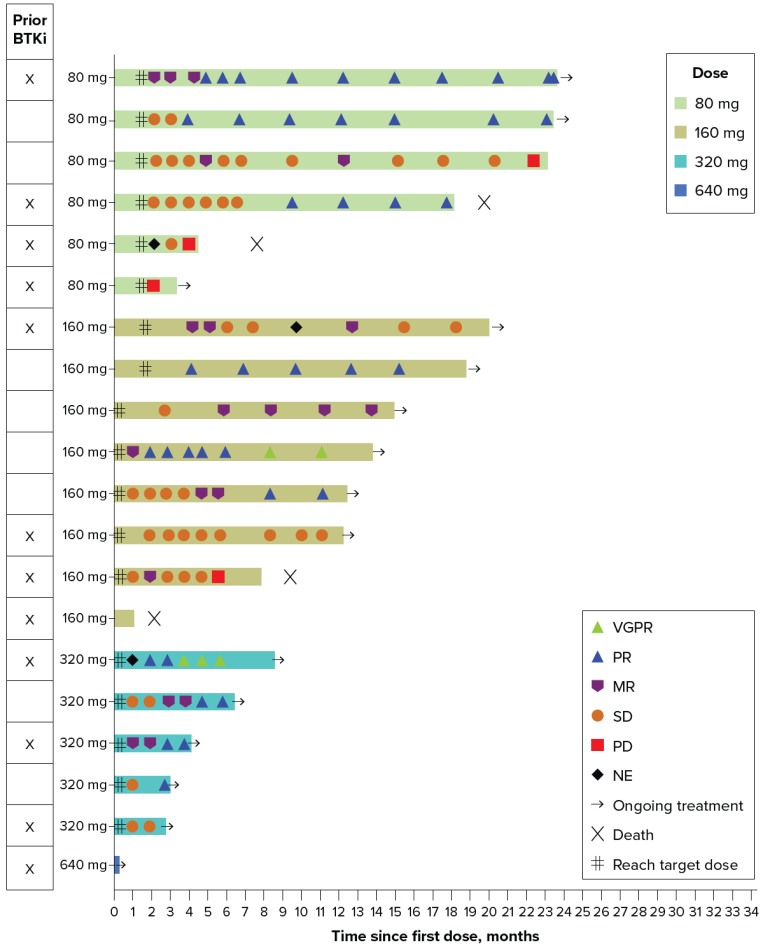
Sonrotoclax in WM cohort: efficacy

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: 45%





Cheah, EHA 2024

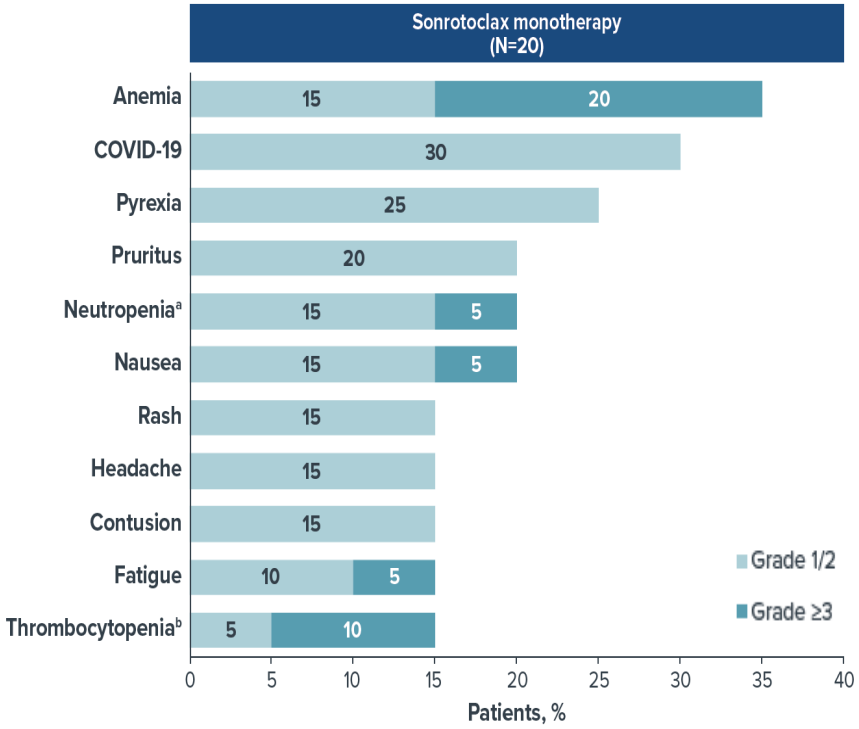
Sonrotoclax in WM cohort: safety

	WM[2] (N=20)
Any grade TEAE	95%
Grade ≥3	35%
Serious AEs	30%
Leading to death	10%
Leading to discontinuation	10%
Leading to dose interruption	25%
Leading to dose reduction	0

- No MTD reached
- No clinical TLS reported

Grade 1-2 *vs* Grade 3-4 AEs

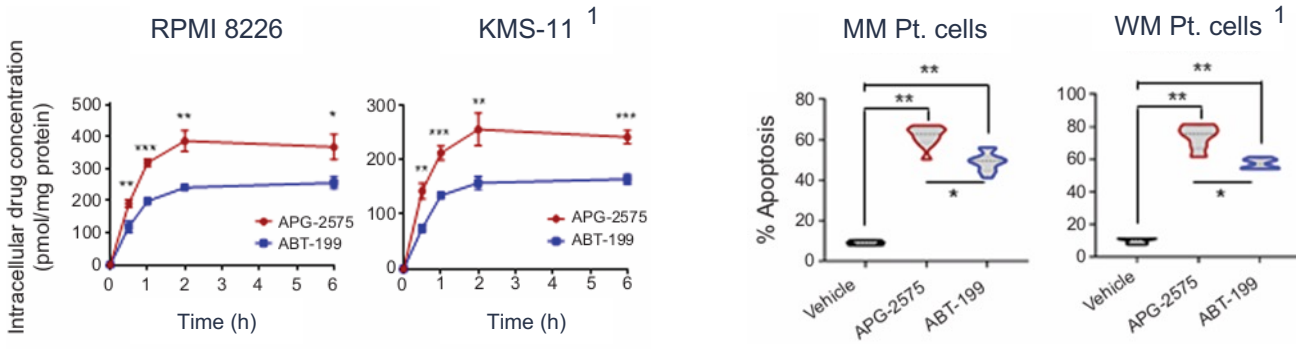
(WM)[2]



Cheah, EHA 2024

Lisaftoclax (APG-2575), a novel BCL-2 inhibitor in B-cell malignancies

Lisaftoclax *vs* venetoclax



[1]

[2]

	Any grade (≥15%)	Grade 3/4
Adverse event, *n* (%)		
Diarrhea	25 (48.1)	1 (1.9)
Fatigue	18 (34.6)	1 (1.9)
Nausea	16 (30.8)	2 (3.8)
Anemia	15 (28.8)	5 (9.6)
Thrombocytopenia	15 (28.8)	7 (13.5)
Neutropenia	14 (26.9)	11 (21.2)
Constipation	13 (25.0)	1 (1.9)
Vomiting	12 (23.1)	—
Headache	11 (21.2)	2 (3.8)
Peripheral edema	9 (17.3)	2 (3.8)
Hypokalemia	9 (17.3)	1 (1.9)
Arthralgia	8 (15.4)	—

- **Higher C_{max} and lower systemic exposure compared to venetoclax[2]**
- **Daily ramp-up[2]**
- **No TLS reported[2]**
- While effective in CLL, on preliminary data **no major responses in NHL cohort** (7 SD; 1 minor response)[2]

BCL-2, B-cell lymphoma-2; CLL, chronic lymphocytic leukemia; C_{max}, maximum plasma concentration; h, hours; KMS, Kawasaki Medical School; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; Pt, patient; RPMI, Roswell Park Memorial Institute; SD, stable disease; TLS, tumor lysis syndrome; WM, Waldenstr€om macroglobulinemia.
Adapted from 1) Deng J et al. Clin Cancer Res. 2022;28(24):5455-5468; 2) Ailawadhi S et al. Clin Cancer Res. 2023;29(13):2385-2393.

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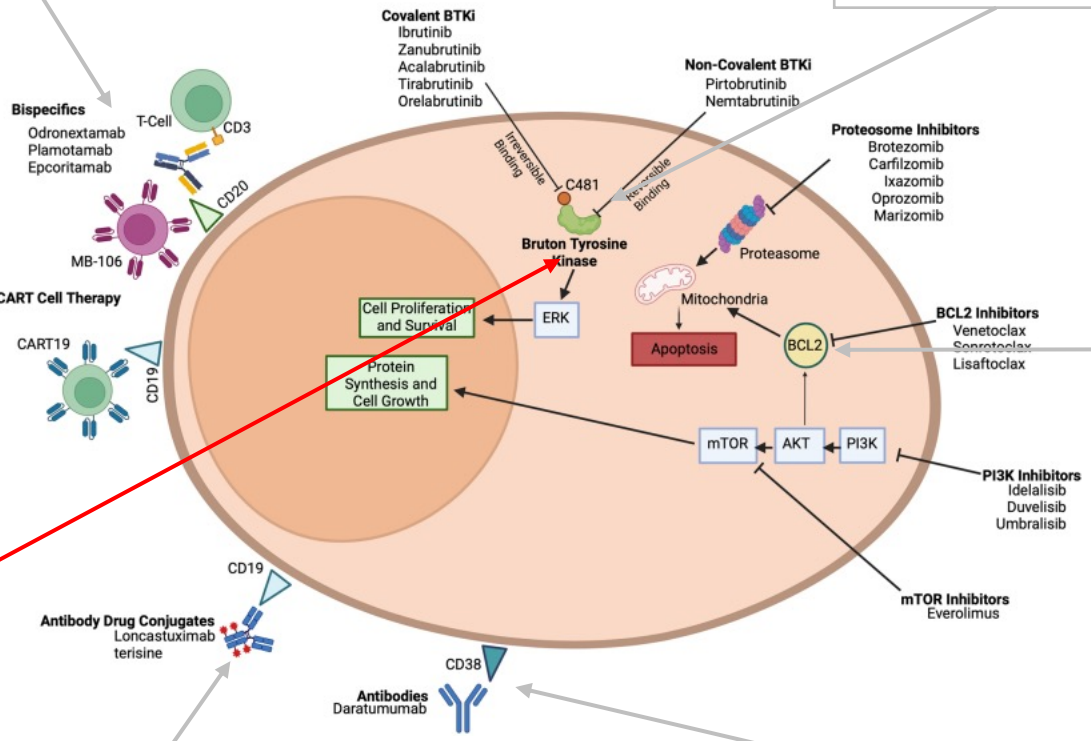

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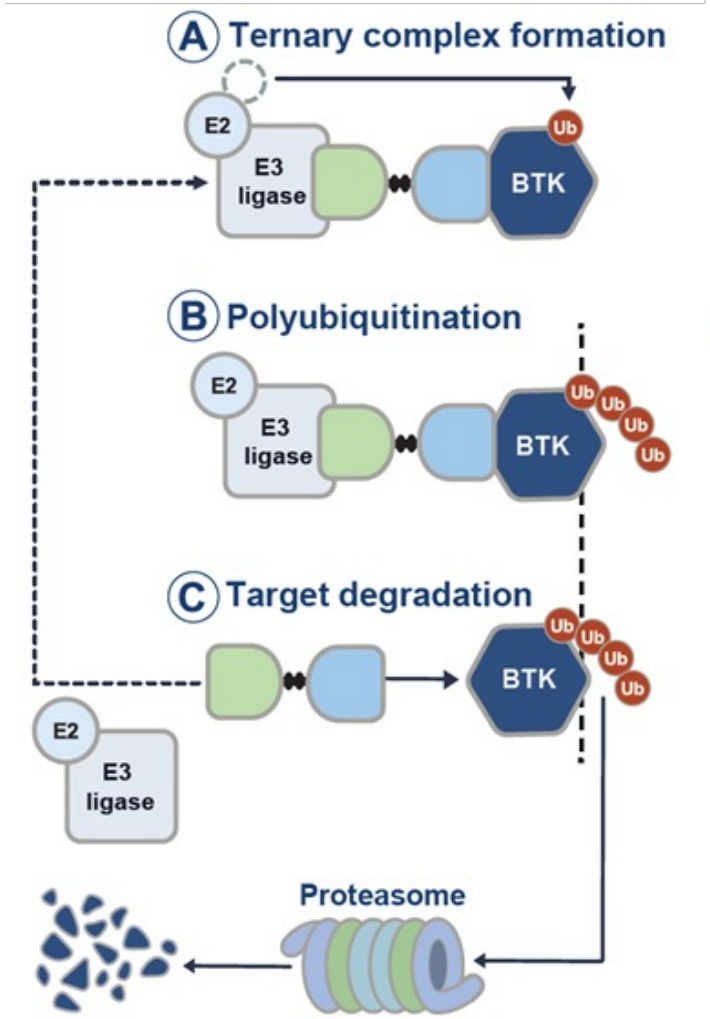
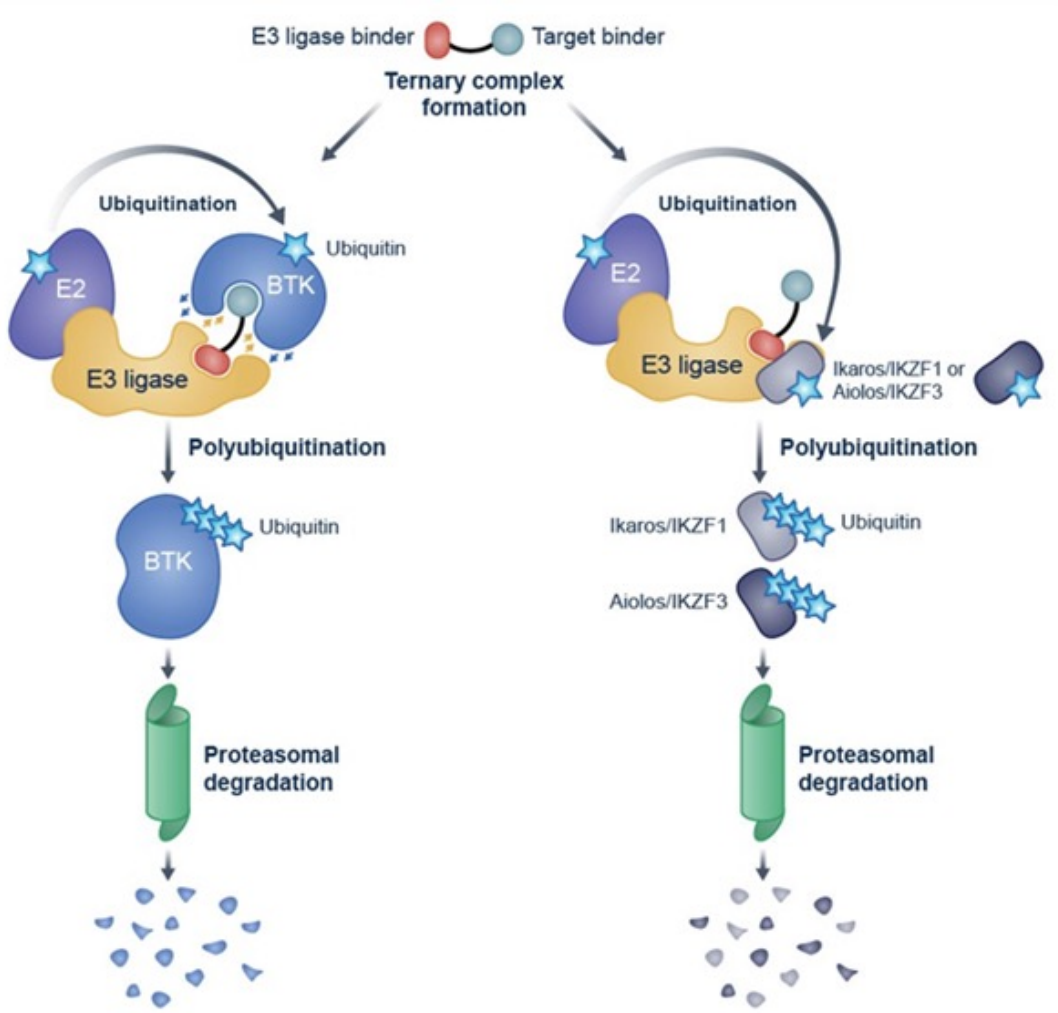




BGB16673-101 in WM

Baseline Patient Characteristics
Heavily pretreated with high rate of poor risk features

	Total (N=36)
Age, median (range), years	72.0 (49-81)
Male, n (%)	22 (61.1)
ECOG PS, n (%)	
0	17 (47.2)
1	17 (47.2)
2	2 (5.6)
Hemoglobin, median (range), g/L	102 (60-146)
Hemoglobin ≤110 g/L, n/N with known status (%)	25/34 (73.5)
Neutrophils, median (range), 10^9/L	2.6 (0.2-7.4)
Neutrophils ≤1.5×10^9/L, n/N with known status (%)	11/33 (33.3)
Platelets, median (range), 10^9/L	153.5 (14.0-455.0)
IgM, median (range), g/L	35.1 (0.3-92.6)

	Total (N=36)
Mutation status, n/N with known status (%)[a]	
MYD88 mutation present	31/35 (88.6)
CXCR4 mutation present	19/35 (54.3)
BTK mutation present	11/31 (35.5)
TP53 mutation present	16/31 (51.6)
No. of prior lines of therapy, median (range)	3 (1-11)
Prior therapy, n (%)	
cBTK inhibitor	36 (100)
Anti-CD20 antibody	36 (100)
Chemotherapy	34 (94.4)
Proteasome inhibitor	11 (30.6)
BCL2 inhibitor	9 (25.0)
ncBTK inhibitor[b]	7 (19.4)
Discontinued prior BTK inhibitor due to PD, n (%)	30 (83.3)

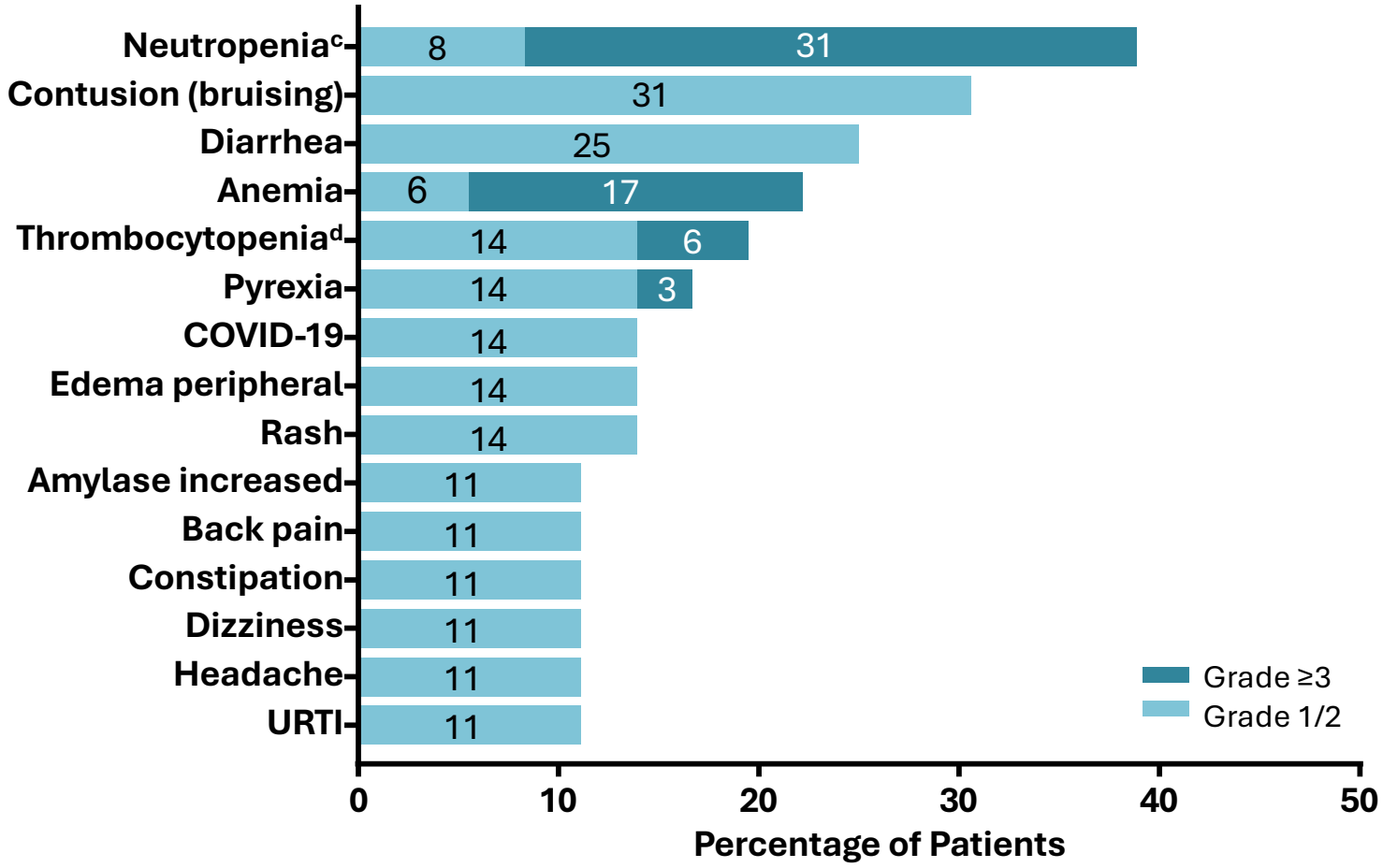
Frustaci, EHA 2025

Safety Summary and All-Grade TEAEs in ≥10% of All Patients

Well tolerated with no treatment-related TEAEs leading to death

- Most common TEAEs were neutropenia in 39% and contusion (bruising) in 31% of patients
- No atrial fibrillation, major hemorrhage[a], febrile neutropenia, or pancreatitis

Patients, n (%)	Total (N=36)
Any TEAE	32 (88.9)
Any treatment-related	25 (69.4)
Grade ≥3	22 (61.1)
Treatment-related grade ≥3	14 (38.9)
Serious	12 (33.3)
Treatment-related serious	4 (11.1)
Leading to death[b]	1 (2.8)
Treatment-related leading to death	0
Leading to treatment discontinuation	2 (5.6)



Data cutoff: March 3, 2025. Median follow-up: 8.2 months (range, 0.6-30.6 months).
[a]Grade ≥3, serious, or any central nervous system bleeding. [b]Septic shock (200-mg dose level), note in the context of PD. [c]Neutropenia combines preferred terms *neutrophil count decreased* and *neutropenia*. [d]Thrombocytopenia combines preferred terms *platelet count decreased* and *thrombocytopenia*.
IgM, immunoglobulin M; PD, progressive disease; PR, partial response; TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection.

Frustaci, EHA 2025

Overall Response Rate
High response rates across all risk groups

- Responses were observed at all dose levels and in patients with prior chemoimmunotherapy (25/30), cBTK inhibitor (27/32), or ncBTK inhibitor (4/4)

	Total (N=32)[a]
Best overall response, n (%)	
VGPR	10 (31.3)
PR	14 (43.8)
MR	3 (9.4)
SD	3 (9.4)
PD	1 (3.1)
Discontinued prior to first assessment	1 (3.1)
ORR, n (%)[b]	27 (84.4)
Major response rate, n (%)[c]	24 (75.0)
Time to first response, median (range), months[d]	1.0 (0.9-3.7)

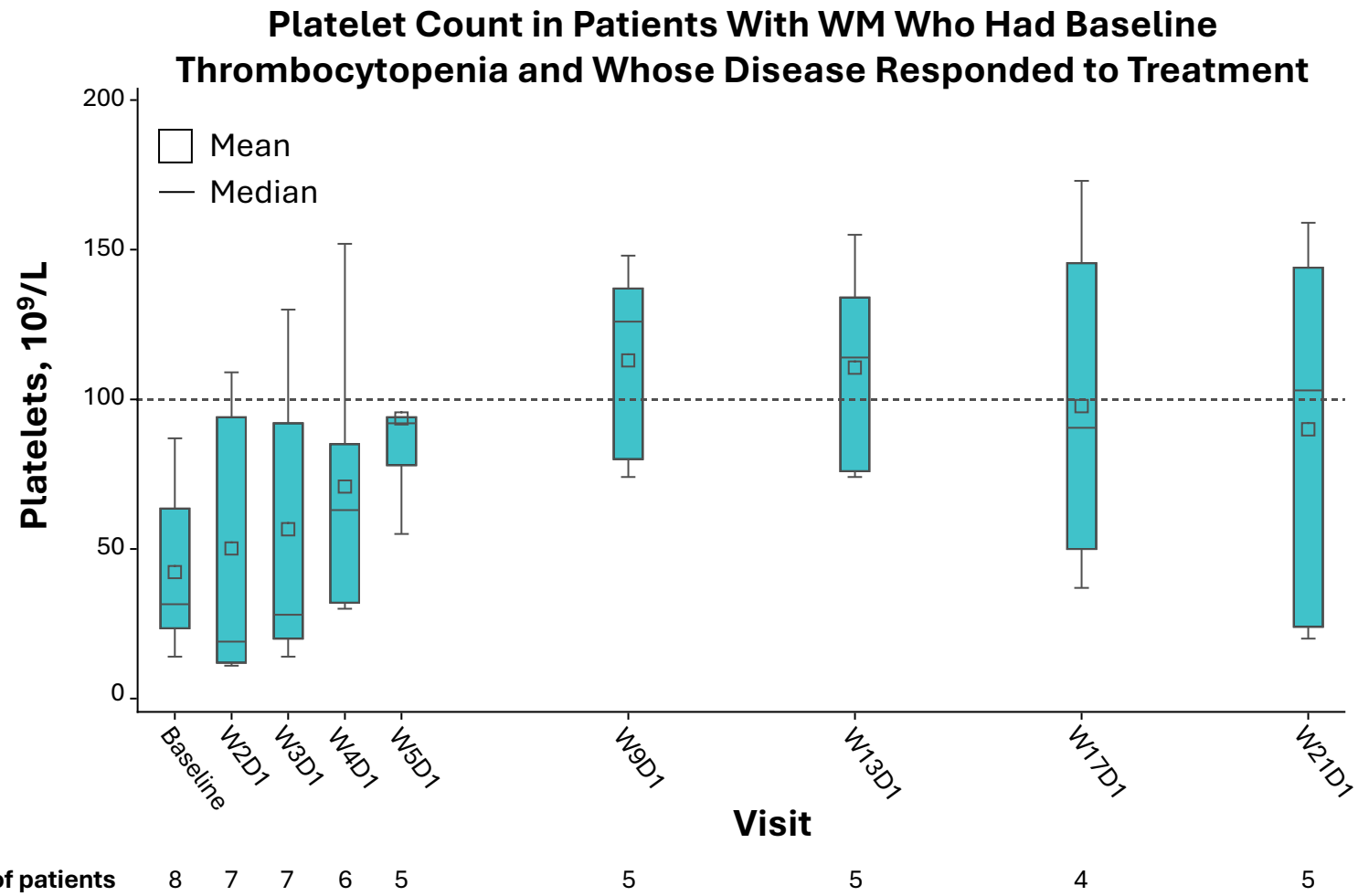
Mutation status, n/N tested (%)	ORR (N=32)[a]
BTK	
Mutated	11/11 (100)
Unmutated	15/19 (78.9)
Unknown	1/2 (50.0)
MYD88	
Mutated	25/28 (89.3)
Unmutated	2/3 (66.7)
Unknown	0/1 (0)
CXCR4	
Mutated	16/17 (94.1)
Unmutated	11/14 (78.6)
Unknown	0/1 (0)
TP53	
Mutated	15/15 (100)
Unmutated	11/15 (73.3)
Unknown	1/2 (50.0)

[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

	Baseline	W9D1
Neutrophil count, median, 10^9/L	0.9	1.1
Hemoglobin level, median, g/L	98.0	114.0
Platelet count, median, 10^9/L	39.5	126.0

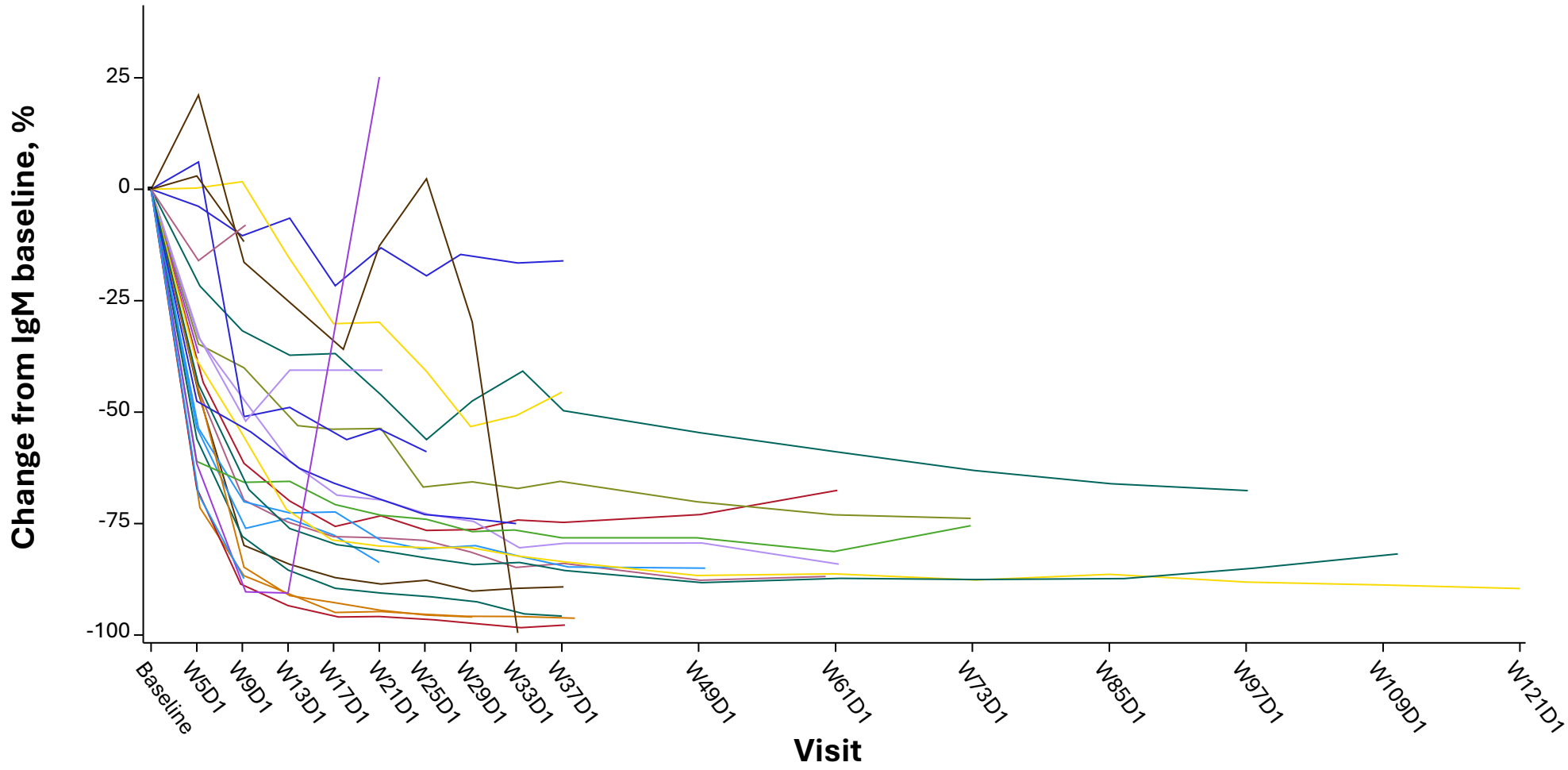


D, day; W, week; WM, Waldenström macroglobulinemia.

Frustaci, EHA 2025

IgM Decreased in All Patients

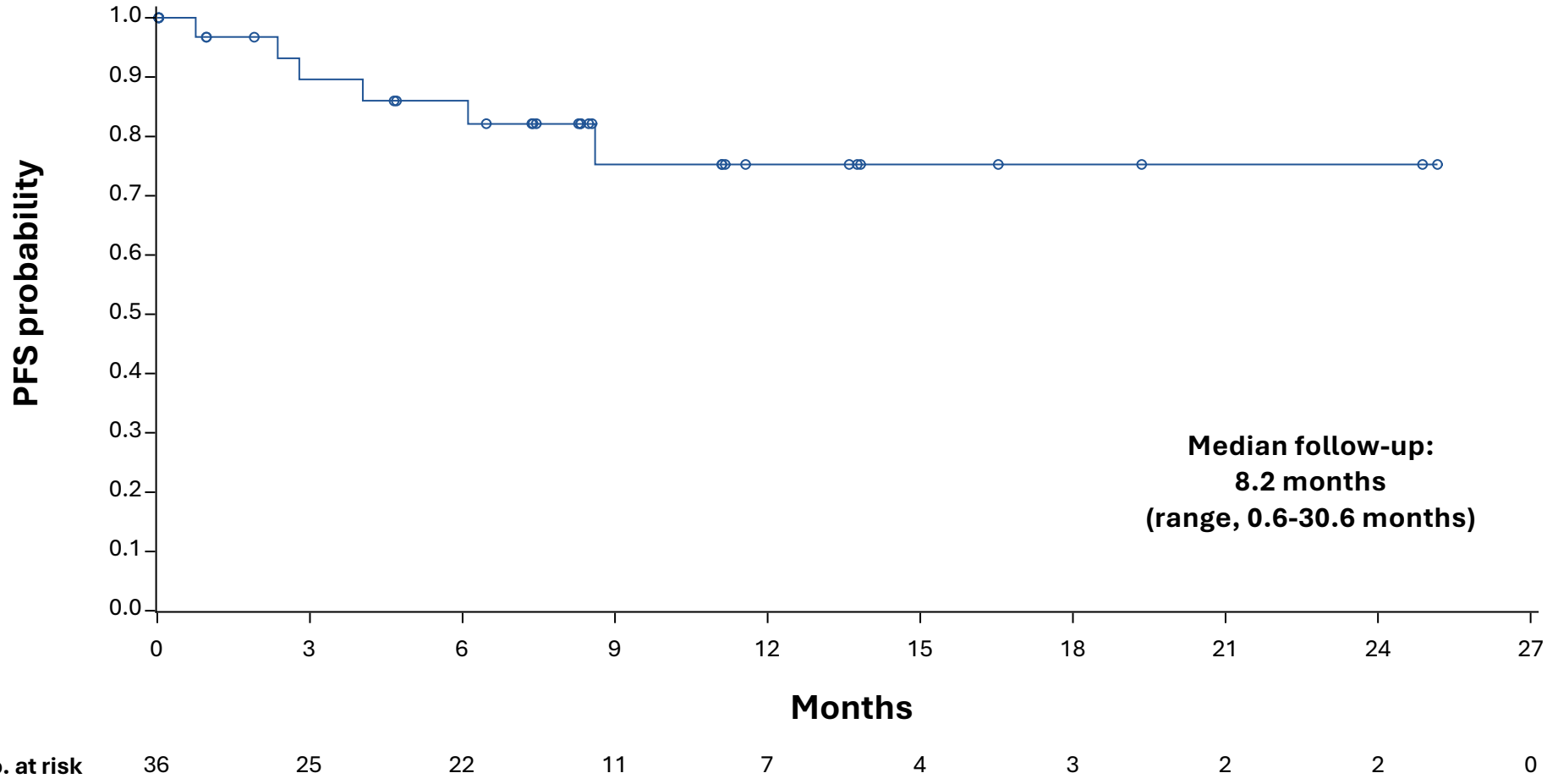
Rapid and sustained decrease in IgM in most patients



Patient with rapid IgM increase had *BTK, MYD88, CXCR4*, and *TP53* mutations at baseline, paused treatment for 2-3 weeks due to COVID-19 infection, and developed rapid progression shortly after restarting treatment.
D, day; IgM, immunoglobulin M; W, week.

Frustaci, EHA 2025

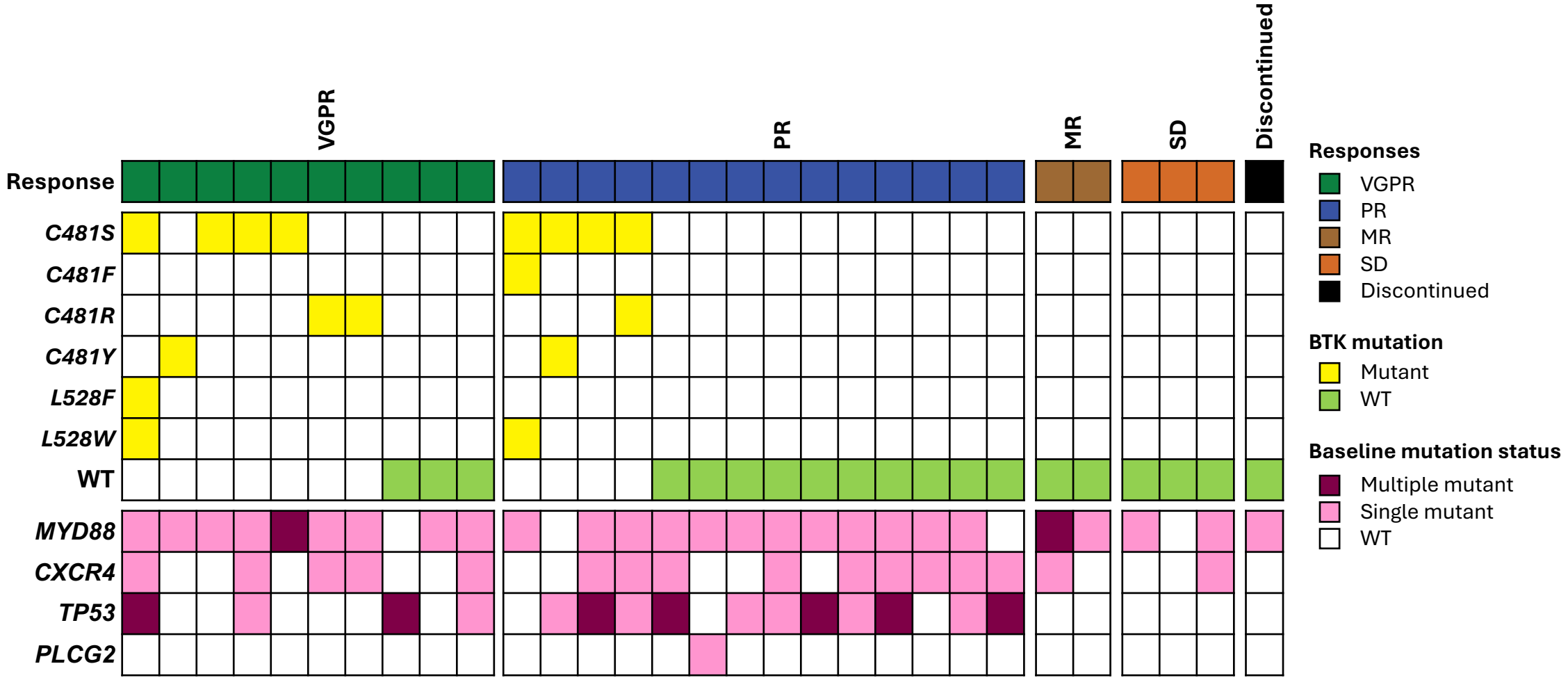
Median PFS Was Not Reached



PFS, progression-free survival.

Frustaci, EHA 2025

Responses Occurred Regardless of Baseline Mutations
(Best Overall Response vs Baseline Mutation)[a]



[a]Genomic mutations were centrally assessed by targeted next-generation sequencing.
BTKi, Bruton tyrosine kinase inhibitor; MR, minor response; NE, not evaluable; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

Frustaci, EHA 2025

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

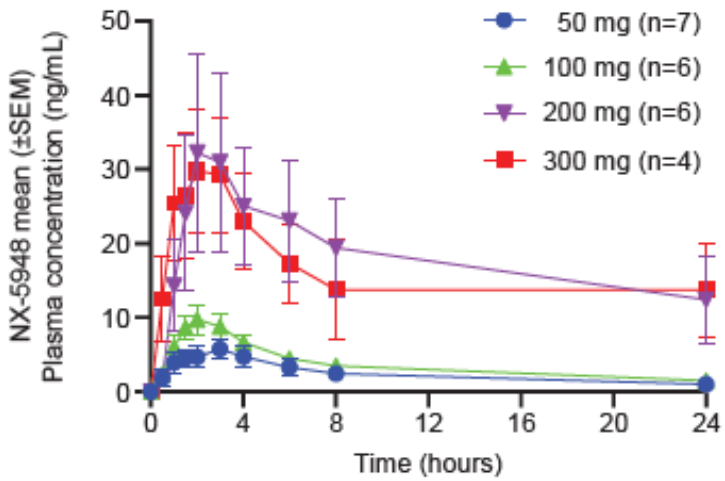
Dose levels: 40 mg → 640 mg

48 NHL/WM[1]

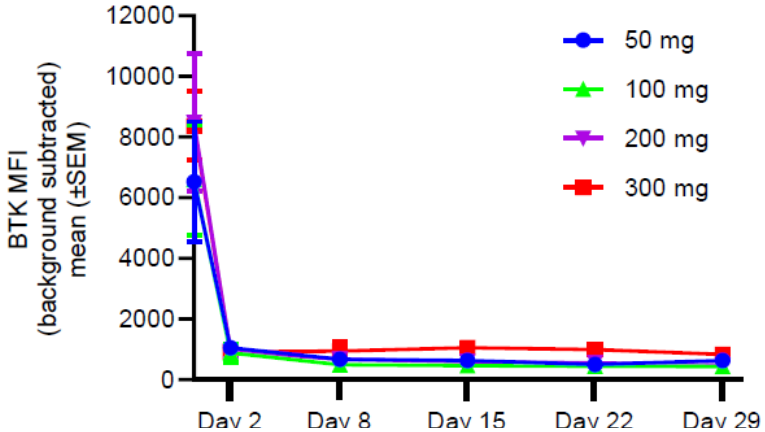
- Median age 66.5 years
- Median prior lines: 4
- CNS involvement 20.8%
- Prior cBTKi: 60.4%
- Prior ncBTKi: 14.6%
- Prior BCL2i: 14.6%
- Prior CAR-T/Bispecifics 22.9%/14.6%
- *TP53* mutations 9.5%

- ➢ *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.

Potential therapeutic targets in WM

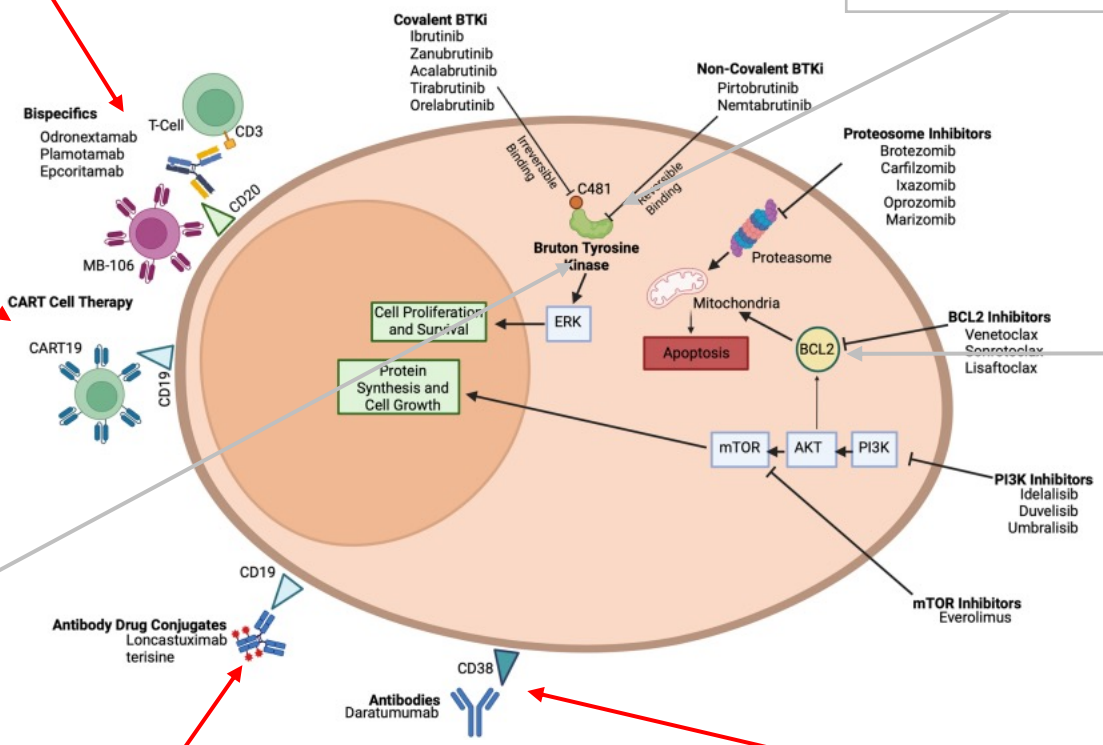
Bispecifics

CAR-T

BTK degraders
BGB 16673
NX 5948
NX 2127

Non covalent BTKI
Pirtobrutinib
Nemtabrutinib

Bcl2 antagonists
Venetoclax
Sonrotoclax
Lisaftoclax



Ab drug coniugates
Loncastuximab

Anti CD38
Daratumumab

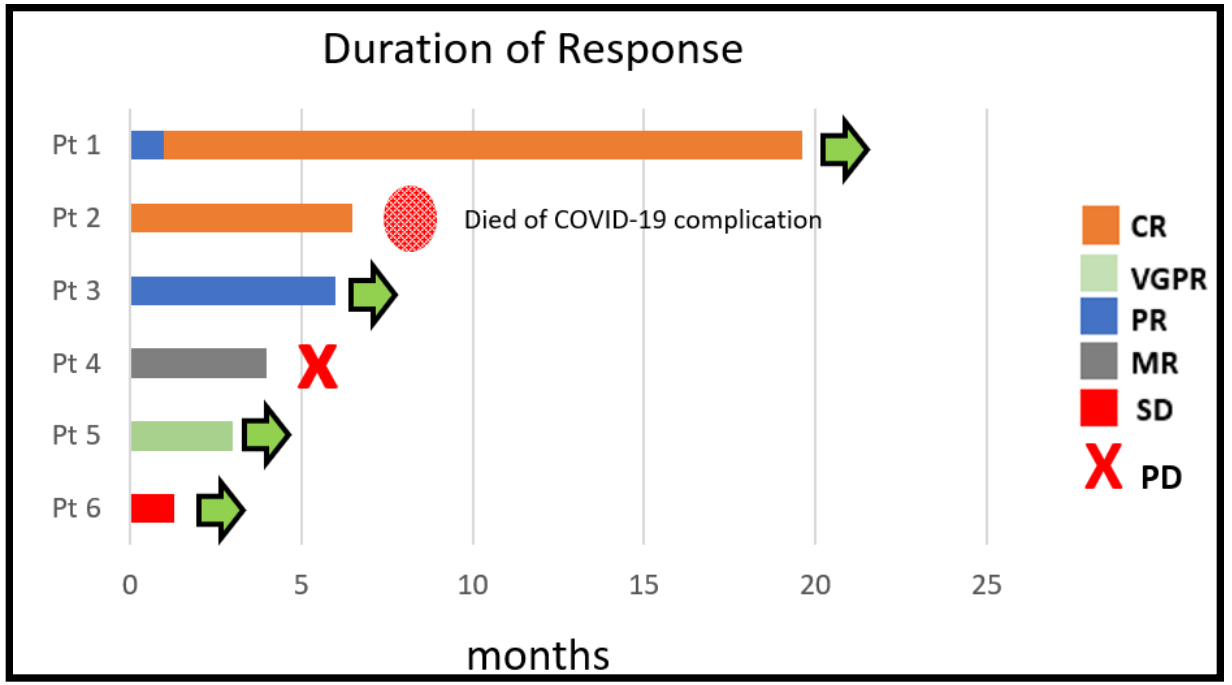
CD20 CAR-T Cell Therapy

Patient characteristics (N=6)	
Age, median (range)	69 (51-79)
Female, n (%)	2 (33%)
Prior lines of therapy, median (range)	6.5 (2-12)
Prior Bruton tyrosine kinase inhibitor	6 (100%)

Best response by IWWM-7† (N=6)	
CR	2 (33%)
VGPR	1 (16.7%)
PR	1 (16.7%)
MR	1 (16.7%)
SD	1 (16.7%)

Major response rate: 67%

Safety (N=6)				
	G1	G2	G3	G4
CRS	2 (33%)	3 (50%)	0	0
ICANS	1 (16%)	0	0	0



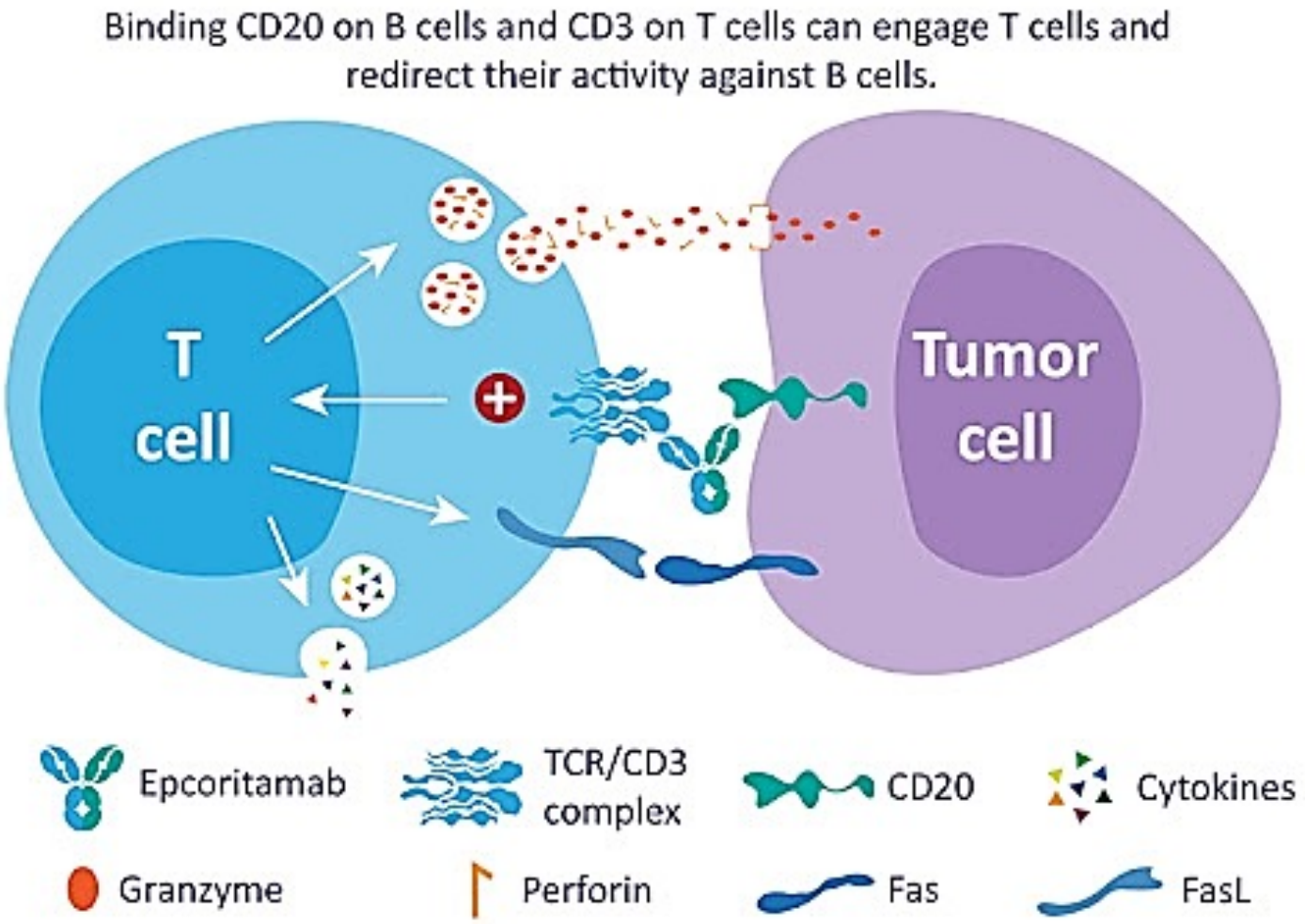
No patient has started new anti-WM treatment after MB-106

†Dimopoulos MA, et al. *Blood.* 2014;124(9):1404-1411. VGPR = Very good partial response, MR = Minor response; Updated at EHA June 9, 2023, Presented by Mazyar Shadman, MD (FHCC), at the EHA2023 Congress.

Bispecific Antibody Therapy for WM

Epcoritamab in R/R WM

- ❑ ≥1 prior line
- ❑ Have to undergo plasmapheresis before 1° infusion id IgM >4000 mg/dl
- ❑ BNS excluded

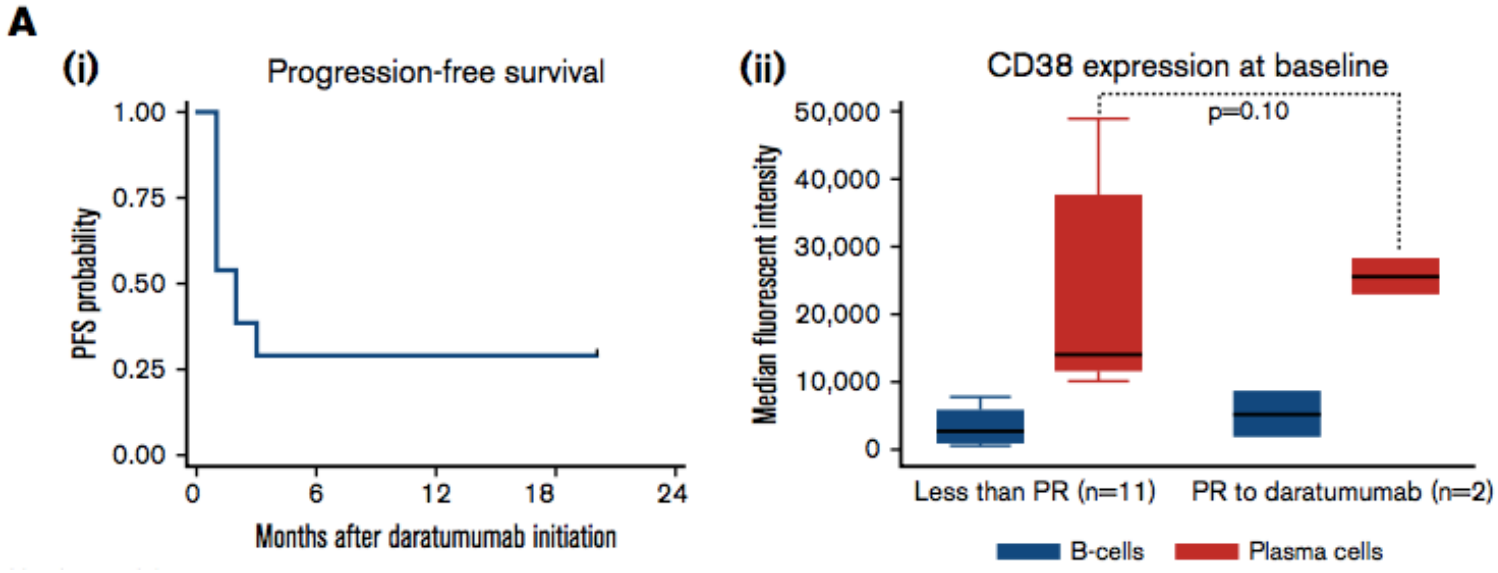


Actively recruiting

A Phase II Study of Daratumumab Plus Ibrutinib in Patients With WM

2020 Daratumumab monotherapy RR WM (13 pts, 4 RR cBTKi)
daratumumab monotherapy induced lower than expected responses in WM, despite effective in MM

ORR	**23%**
MR	15%
Clinical benefit	54%



M number of Dara cycles: 2
11/13 discontinued due to PD/no response

Castillo JJ et al, blood advances 2020

Conclusions

- **Promising development of next generation Bcl2 inhibitors, nc BTKi and BTK degraders in cBTKi-refractory patients**
  - *Should WM follow CLL road-map?*

- **No data on cellular therapy/bispecifics**
  - *May be effective, expecially if sensitized by BTKi*

- **Chemo-free fixed-duration regimen both in first and salvage treatment may be an effective strategy to avoid long-term toxicities and resistance**