Therapeutic News from the World of Waldenstrom's Macroglobulinemia

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DISCLOSURES

Company	
Abbvie/Pharmacyclics	Research Support
Beigene	Research Support, Consulting
Schrodinger	Consulting
Eli Lilly	Research Support
Johnson and Johnson	Research Support

Sixth International Workshop on Waldenstrom's Macroglobulinemia
Giampaolo Merlini, Enrica Morra, Steve Treon (Co-Organizers)
Venice 2010

Pre-MYD88

WM Treatment Approach

"Hand me down medicines"

Mutated MYD88 Pro-survival Signaling in WM

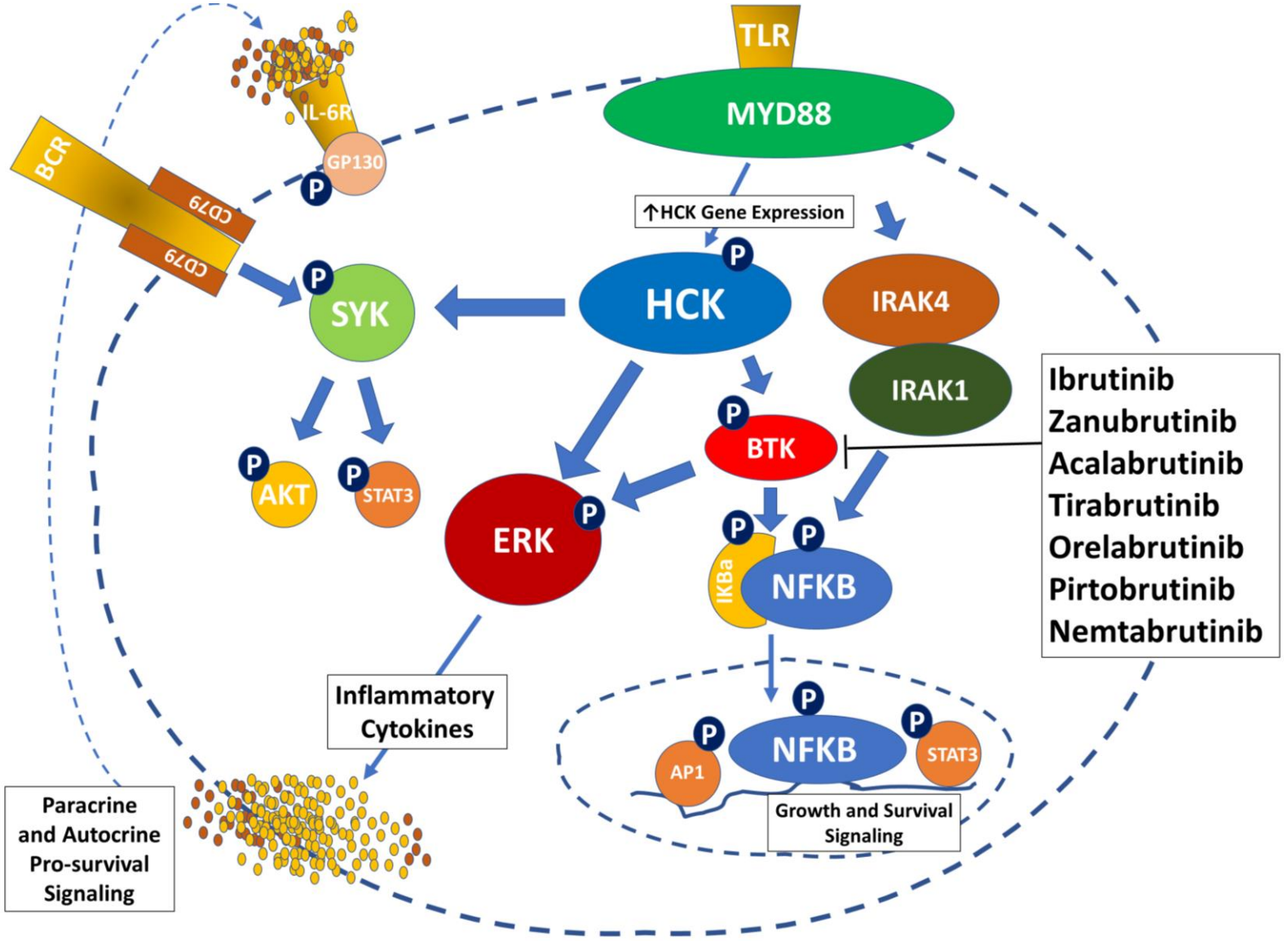
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

MYD88 L265P Somatic Mutation in Waldenström's Macroglobulinemia

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

MYD88 mutations occur in 95-97% WM Patients



Treon, et al. N Engl J Med. 2012;367(9):826-833.
Yang, et al. Blood. 2013;122(7):1222-1232.
Hodge, et al. Blood. 2014;123(7):1055-1058.
Yang, et al. Blood. 2016;127(25):3237-3252.
Chen, et al. Blood. 2018;131(18):2047-2059.
Liu, et al. Blood Adv. 2020;4(1):141-153.
Munshi, et al. Blood Cancer J. 2020;10:12.
Munshi, et al. Blood Adv. 2022.

BTK-Inhibitor Trials in WM

Study	Cohort	Agent (s)	N=	Time to Major Resp.	ORR/Major RR	≥VGPR	PFS
Pivotal Study	R/R	Ibrutinib	63	2 mo.	91% / 79%	30%	54% @ 60 mo.
INNOVATE Arm C	R/R	Ibrutinib	31	2 mo.	87% / 77%	29%	40% @ 60 mo.
Phase 2	TN	Ibrutinib	30	1.9 mo.	100% / 87%	30%	76% @ 48 mo.
INNOVATE Arms A, B	TN, R/R	Ibrutinib Rituximab	150	3 mo.	92% / 76%	31%	68% @ 54 mo.
(MYD88^{WT})							
Phase 2	TN, R/R	Acalabrutinib	106	N/A	94% / 81%	39%	84% TN / 52% R/R (@ 66 mo.)
Phase 2	TN, R/R	Tirabrutinib	27	1.9 TN 2.1 R/R	96% / 93%	33%	93% @ 24 mo.
Phase 2	R/R	Pirtobrutinib	80	N/A	81% / 67% (prior cBTKi) 88% / 88% (cBTKi naïve)	24% (prior cBTKi) 29% (cBTKi naïve)	57% @ 18 mo. (for prior cBTKi) N/A for cBTKi naïve.

Median ORR: 93%; Major RR: 81%; ≥VGPR: 30%; PFS 76% @ 4 yrs

CXCR4 mutations impact WM disease presentation and treatment response.

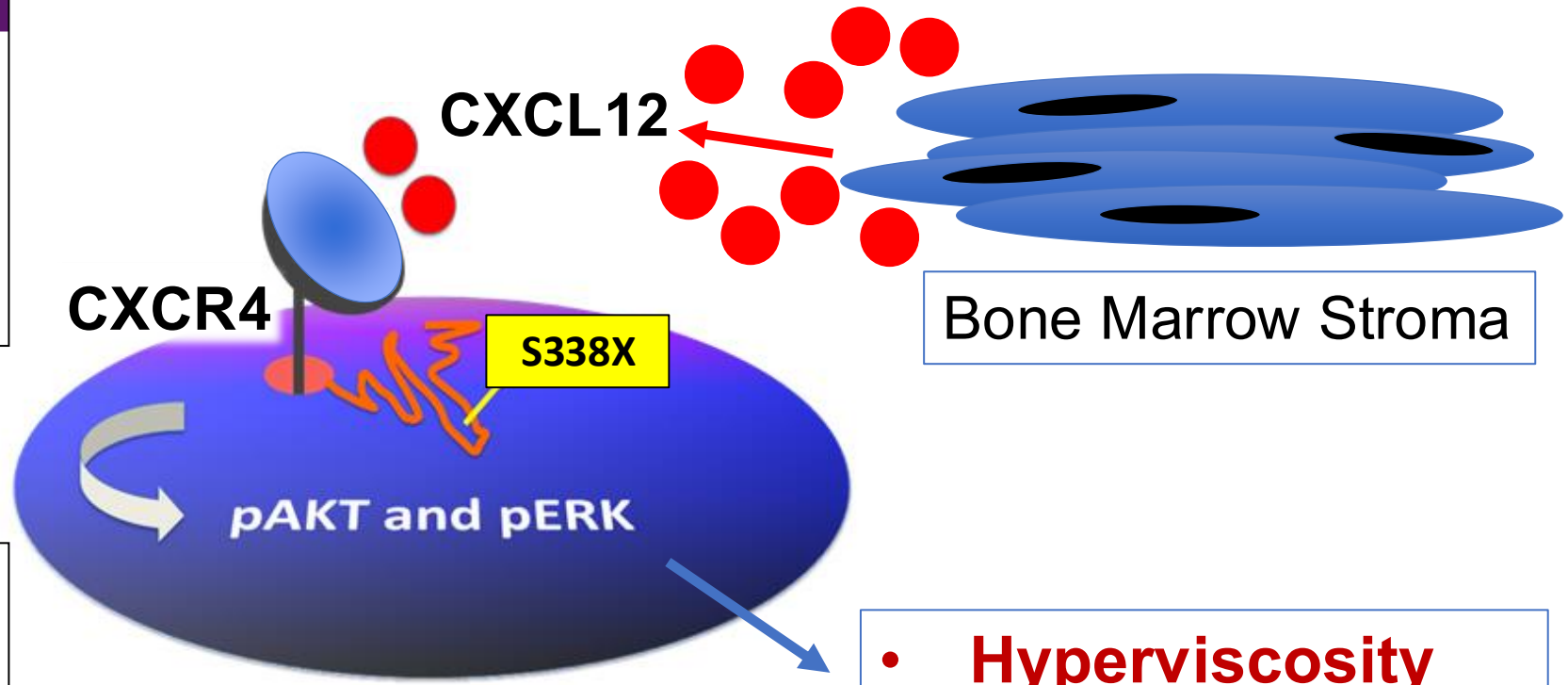
Plenary Paper

LYMPHOID NEOPLASIA

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

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

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



- 30-40% of WM patients are CXCR4 mutated.
- >40 different CXCR4 NS and FS mutations
- Most common is S338X.

- Hyperviscosity Syndrome
- Drug resistance

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

CXCR4 Impact on BTK-Inhibitor Outcomes in WM

Study	Patient Population	Agent (s)	Time to Major Response ($CXCR^{Mut\ vs.\ WT}$)	Major Response Rate ($CXCR^{Mut\ vs.\ WT}$)	≥VGPR ($CXCR^{Mut\ vs.\ WT}$)	PFS ($CXCR^{Mut\ vs.\ WT}$)
Pivotal	R/R	Ibrutinib	4.7 vs.1.8 mo.	68% vs. 97%	9% vs. 47%	38% vs. 70% (@ 60 mo.)
ASPEN Cohort 1	TN, R/R	Ibrutinib	6.6 vs. 2.8 mos.	65% vs. 82%	10% vs. 24%	49% vs. 75% (@ 42 mo.)
	TN, R/R	Zanubrutinib	3.4 vs. 2.8 mos.	70% vs. 82%	18% vs. 34%	73% vs. 81% (@ 42 mo.)

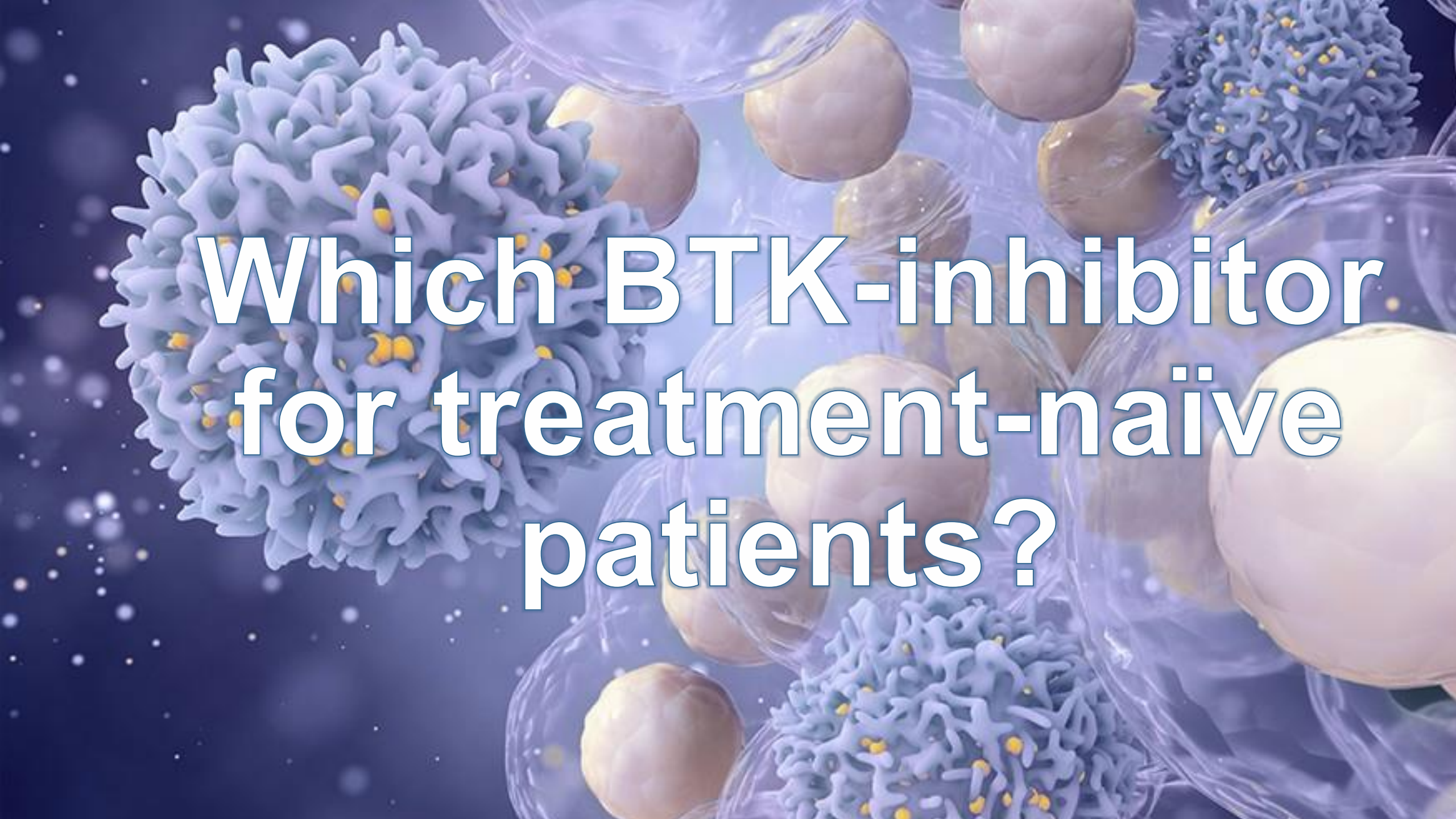
$CXCR4^{Mut}$ vs $CXCR4^{WT}$

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

Median Major RR: 71% vs. 87%

Median ≥VGPR: 14% vs. 41%

PFS: 59% vs. 75% @4 years

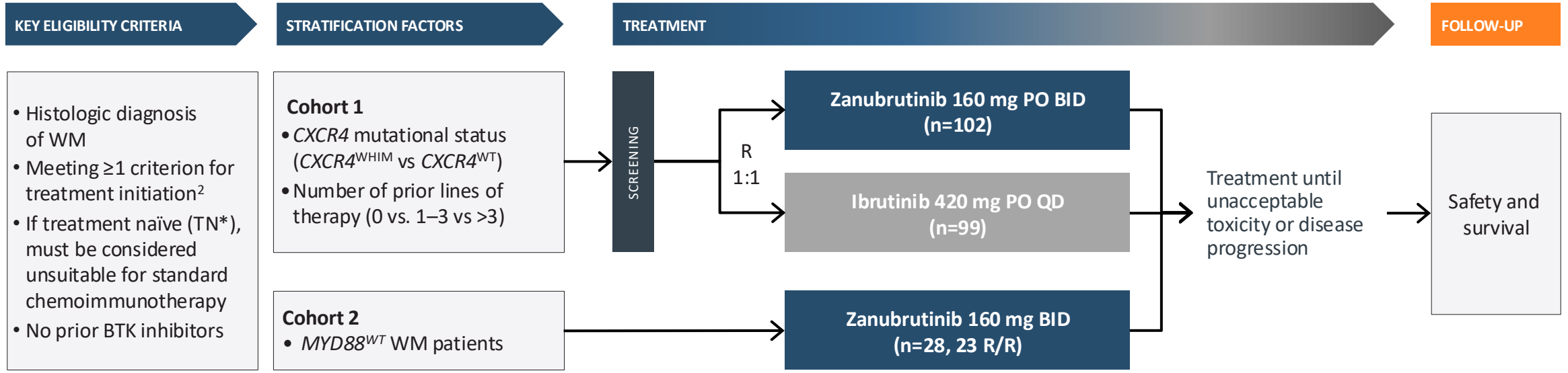

Which BTK-inhibitor
for treatment-naïve
patients?

Long-term f/u for Phase III ASPEN study in WM

PHASE 3

Study Identifier: BGB-3111-302, NCT03053440

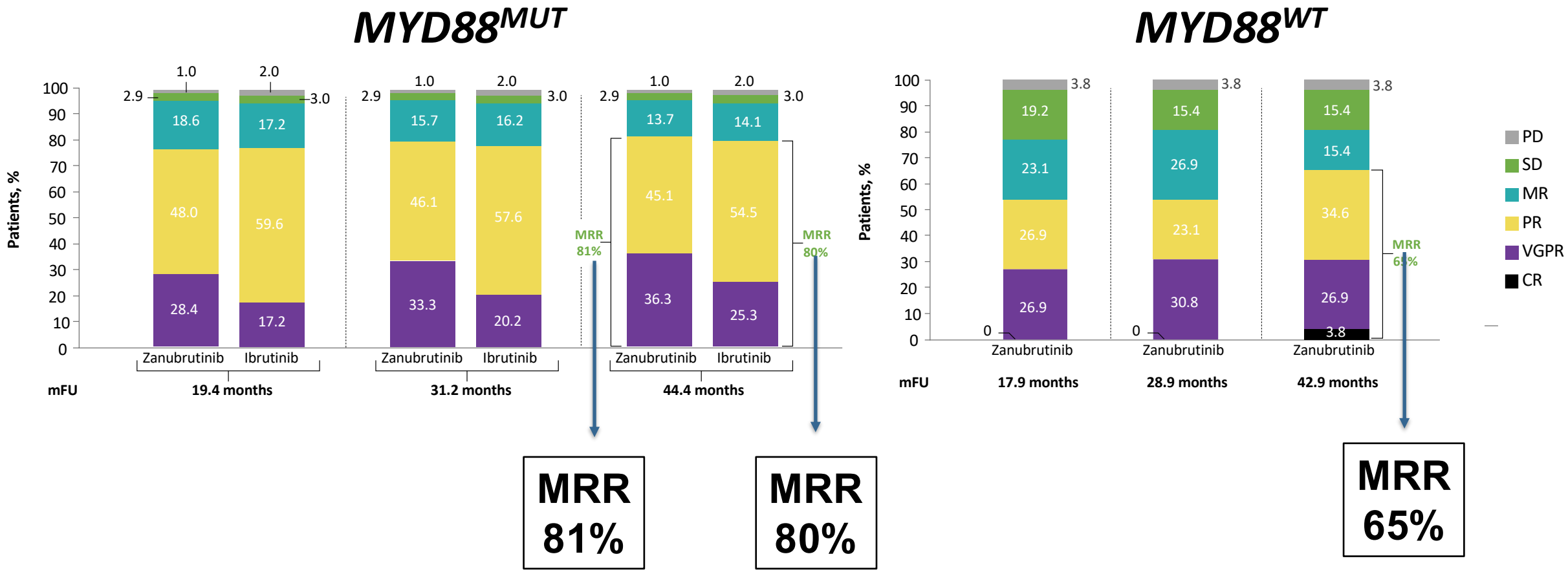
Primary Endpoint: CR/VGPR rate
Key Secondary Endpoints: MRR (≥PR), PFS, OS, DOR, symptom resolution, safety
Exploratory Endpoints: PK, QoL



Dimopoulos et al, IWWM-12, 2024

Best Overall Responses by Investigators

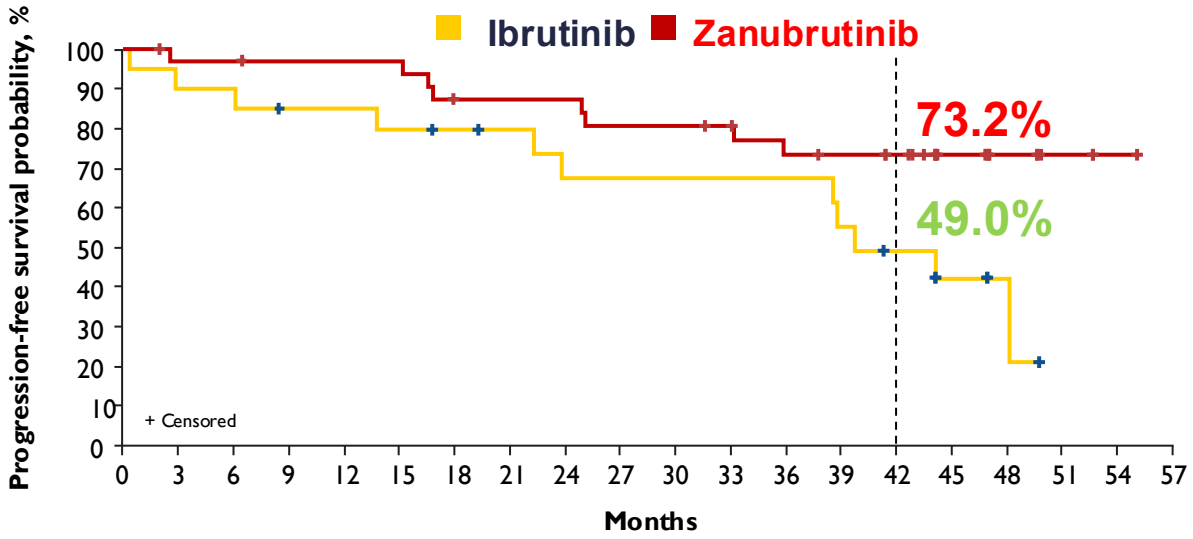
ASPEN – Long-term follow-up



Response Assessment by CXCR4 Mutation Status

ASPEN – Long-term follow-up (Cohort 1)

	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



	Zanubrutinib	Ibrutinib
Events, n (%)	8 (24.2)	11 (55.0)
HR (95% CI)	0.50 (0.20, 1.29)	

PFS impacted by $MYD88^{WT}$ or $TP53^{ALT}$ mutation status following treatment with Zanubrutinib in ASPEN Study

	Cohort 1/MYD88 MUT (n=102)	Cohort 2/MYD88 WT (n=26)
60-mo event-free rate for PFS, % (95% CI)	74.8 (64.5, 82.5)	**39.3 (20.0-58.1)**
$CXCR4^{WHIM}$[a]	70 (50.1-83.2)	NE
$CXCR4^{WT}$[b]	77.4 (64.2-86.3)	31.6 (11.4-54.3)
$TP53^{MUT}$[c]	**57.3 (35-74.4)**	NE
$TP53^{WT}$[d]	81.2 (69.2-88.9)	33.8 (11.8-57.5)
Unknown[e]	75.0 (12.8-96.1)	66.7 (19.5-90.4)
60-mo event-free rate for OS, % (95% CI)	82.8 (73.5-89.1)	79.0 (56.4-90.8)

Adverse Events of Interest (Cohort 1)

ASPEN – Long-term follow-up

	All grades		Grade ≥3	
AEs,[a] n (%)	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/ Non-Skin 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)

Dimopoulos et al, IWWM-12, 2024


BTK-inhibitors or
chemo-immunotherapy
for treatment-naïve
patients?

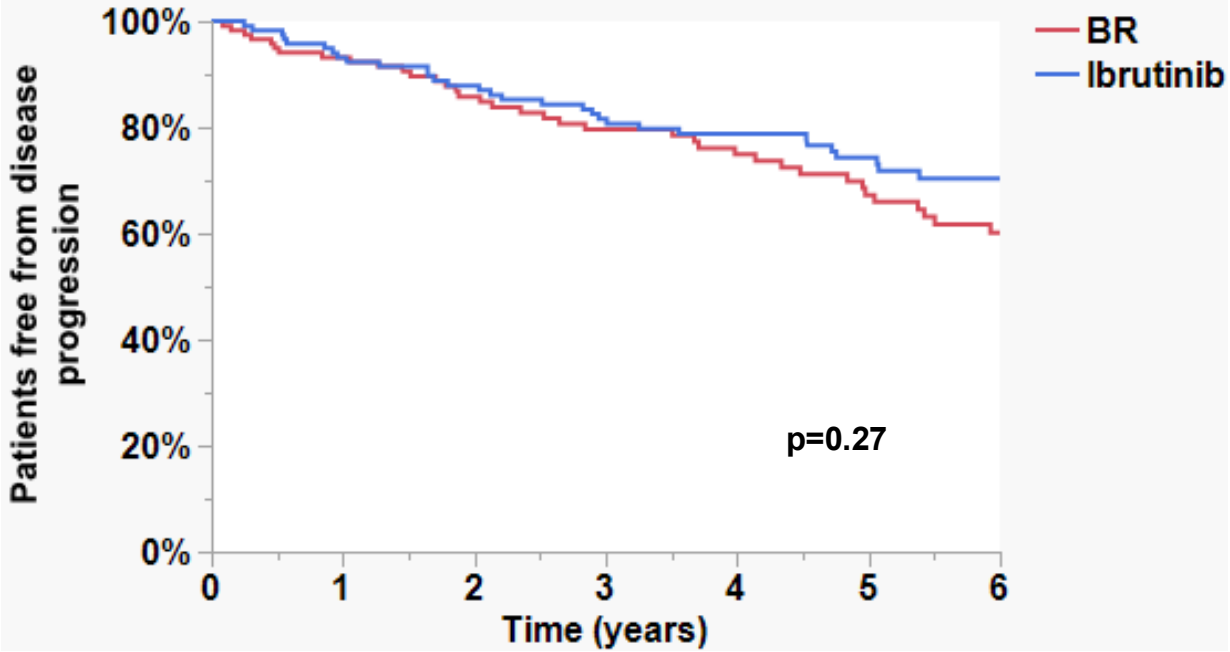
Benda-R vs. Ibrutinib in Treatment-Naïve WM (Multinational Retrospective Study)

Abeykoon et al, IWWM-12, 2024

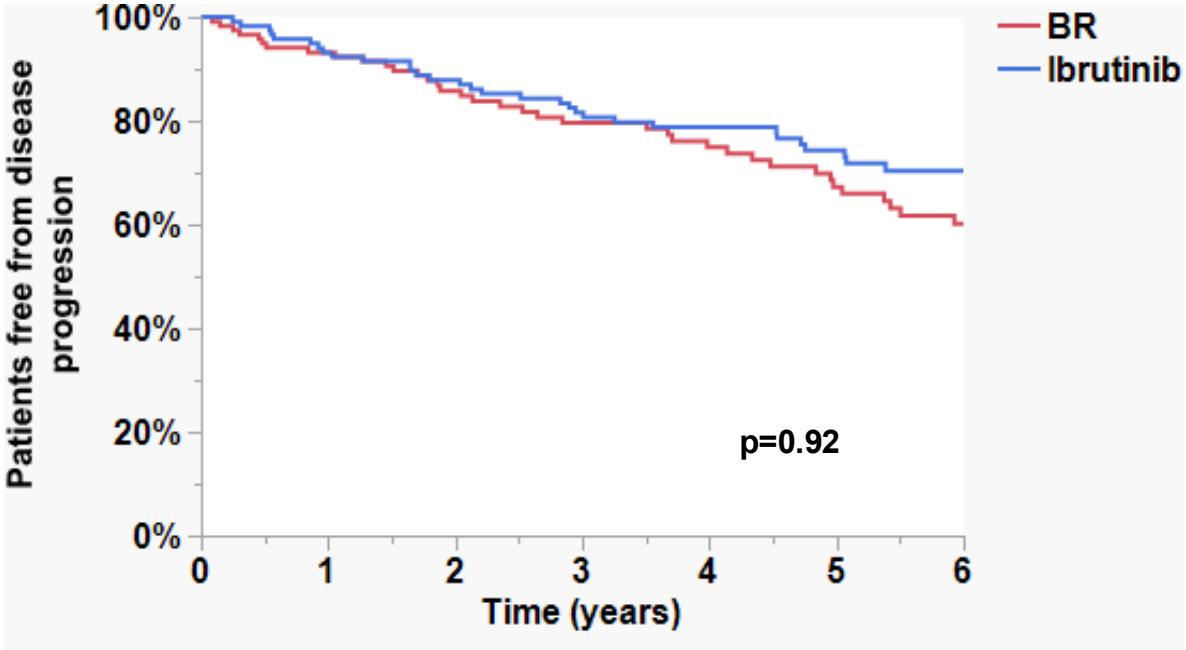
Variable	BR (n=123)	Ibrutinib (n=123)	p-value
Median Follow-up (yrs)	6.0 (5.1-6.6)	6.0 (5.4-6.6)	0.89
Median Age (yrs)	68 (40-86)	68 (39-86)	0.9
IPSS, % Low Intermediate High	 11 33 56	 17 33 48	0.63
Median Cycles	6 (1-6) >4 cycles, 79%	54 (1-114)	
ORR (%)	95	93	0.47
MRR (%)	93	82	**0.014**
CR (%)	17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

Benda-R vs. Ibrutinib: Time-to-event analyses

Progression Free Survival



Overall Survival



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

Abeykoon et al, IWWM-12, 2024

FRENCH INNOVATIVE LEUKEMIA ORGANIZATION

BENDAMUSTINE AND RITUXIMAB (BR) IN WALDENSTROM MACROGLOBULINEMIA (WM): LONG-TERM RESULTS

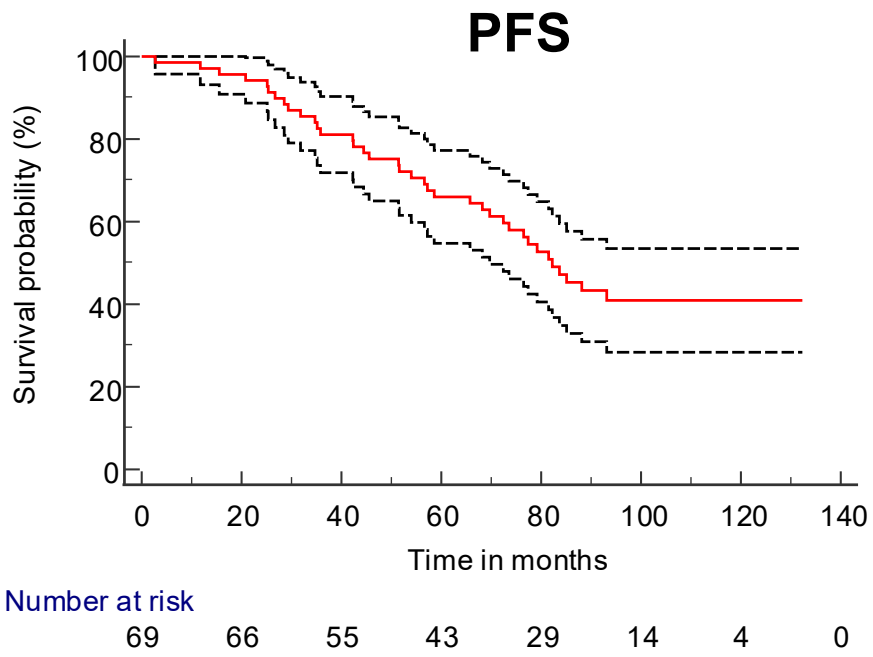
Eveillard JR, Chaoui D, Cavalieri D, Dartigeas C, Willems L, Le Calloch R, Roos-Weil D, Merabet F, Roussel X, Bareau B, Tricot S, Dupuis J, Poulain S, Laribi K, Leblond V

MÉDECINE SORBONNE UNIVERSITÉ

Leblond et al, IWWM-12, 2024

LONG TERM RESPONSE DATA FOR BENDA-R

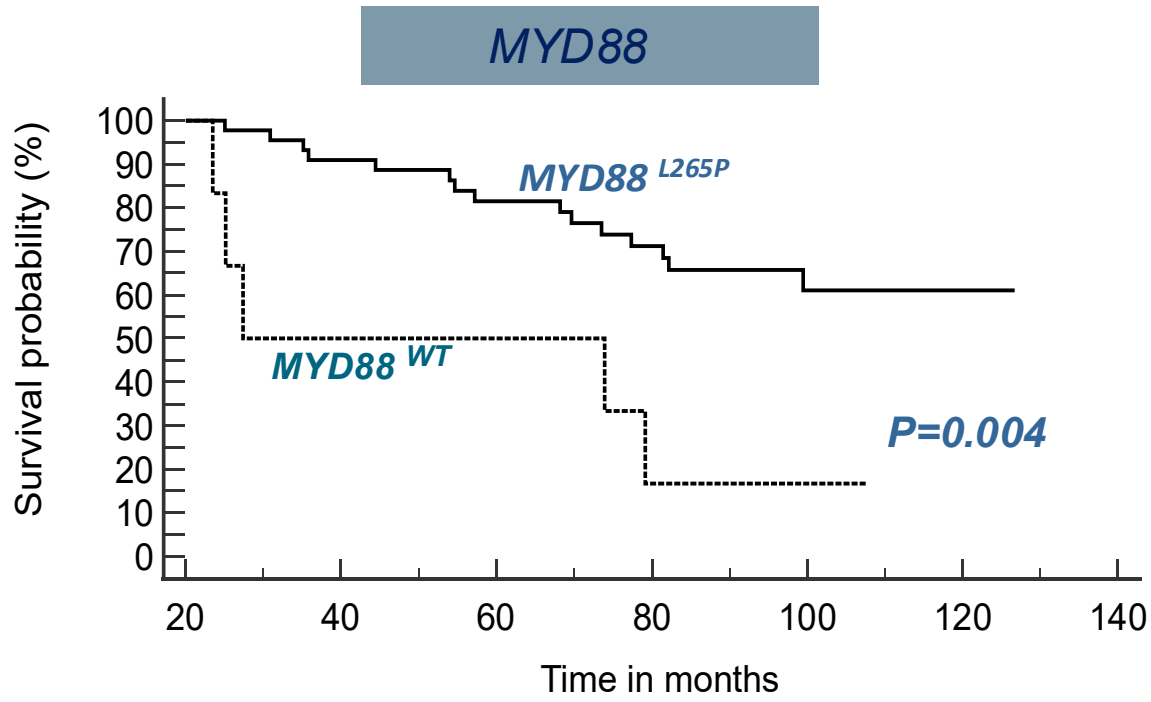
Response	N	%	
ORR	68/69	97%	
MRR	67/69	96%	
VGPR (Neg IFX)	13	19%	56%
VGPR (Pos IFX)	26	37%	
Partial response	28	40%	
Minor response	1		



Median PFS: 82.2 months (69.7-93.1)

LeBlond et al, IWWM-12, 2024

IMPACT OF MUTATIONS ON OVERALL SURVIVAL
MYD88 WT patients



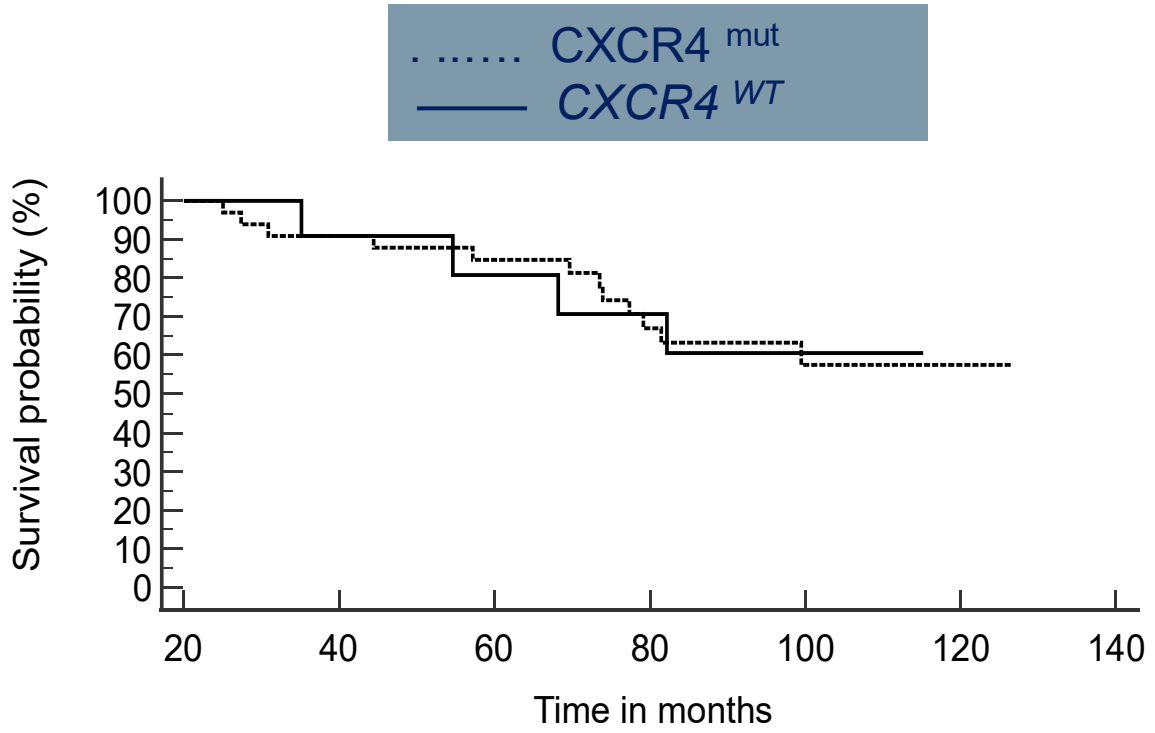
Number at risk

Group: 0

6	3	3	1	1	0	0

Group: 1

45	40	34	26	13	3	0



Number at risk

Group: 0

33	30	27	18	10	3	0

Group: 1

11	10	8	7	4	0	0

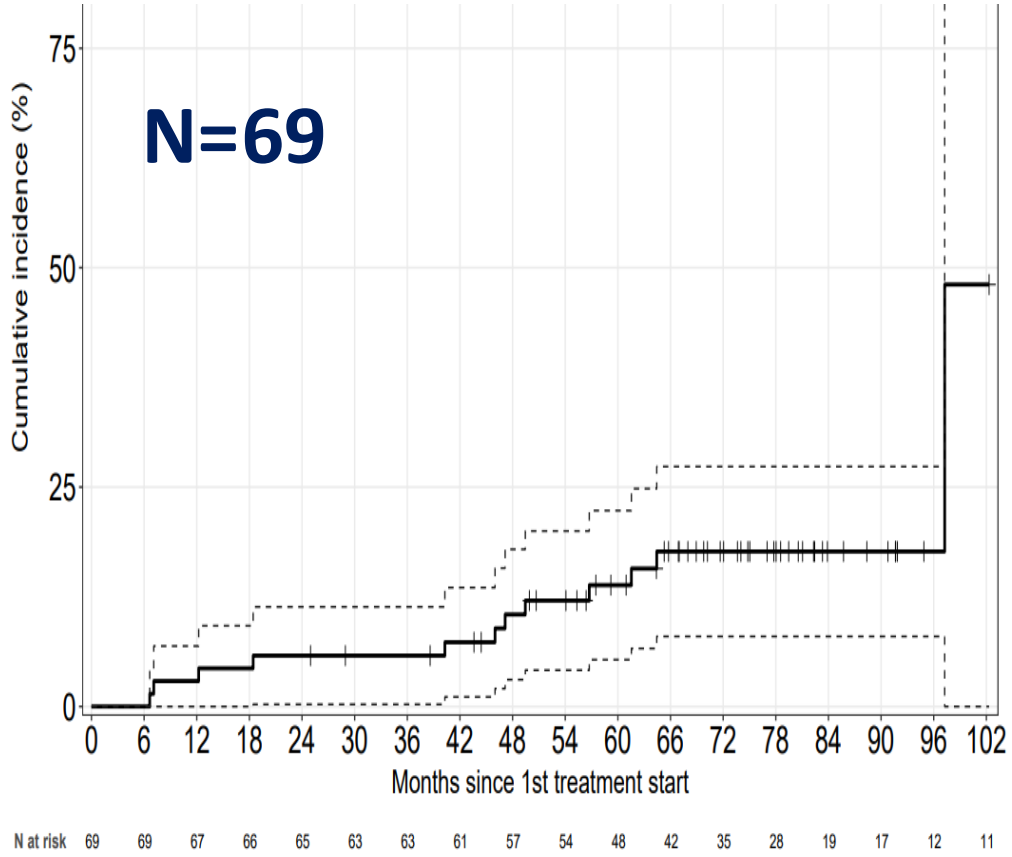
LATE-ONSET TOXICITIES FOR BENDA-R

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

➢ **Long–lasting cytopenia 35 pts (51%)**

➢ **Second malignancies: 12 patients**

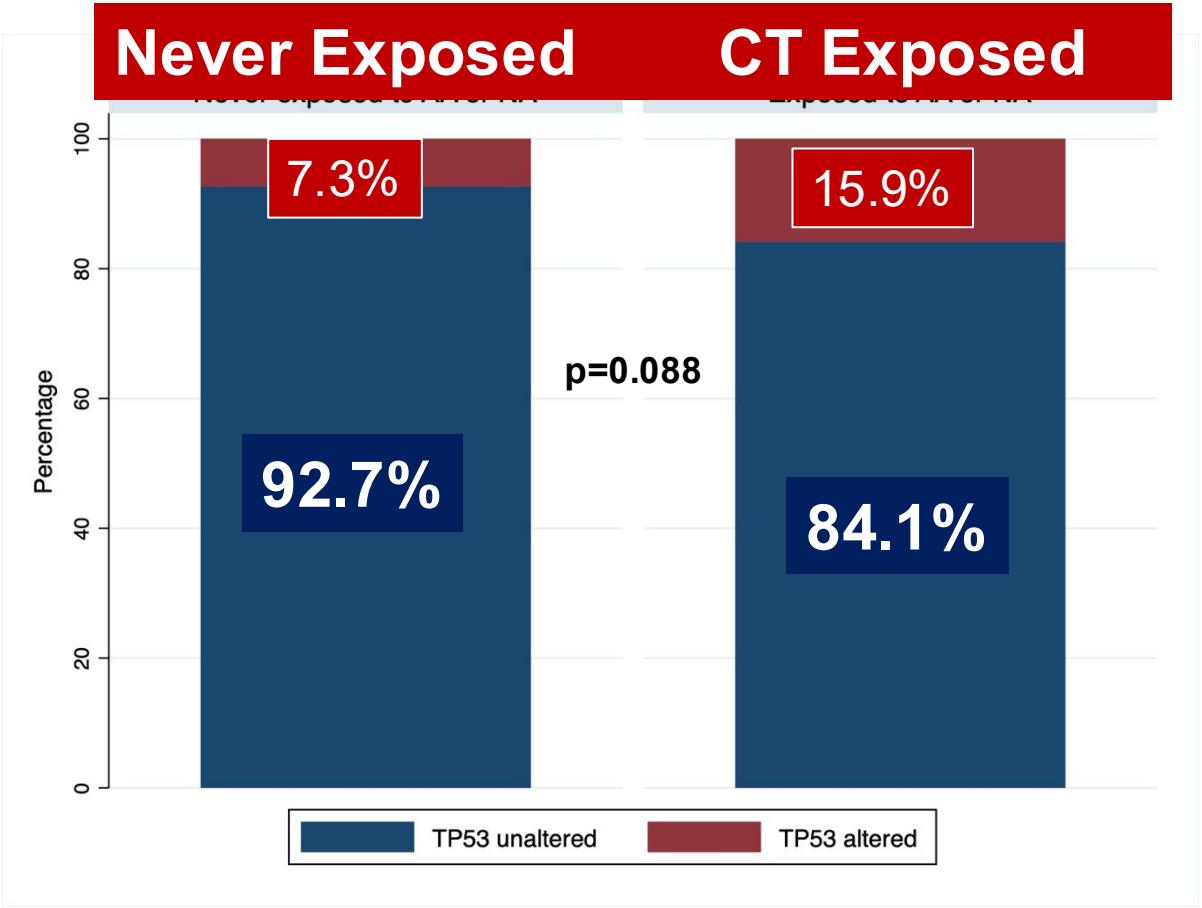
- 9 solid tumors (2 pancreas , 2 gastric, 1 colic, 1 oesophagus 1 lung, 1 skin, 1 breast)
- 3 MDS with 2 AML



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

Leblond et al, IWWM-12, 2024

TP53 ALT Were More Common in CT- vs. Non-CT-Exposed Patients



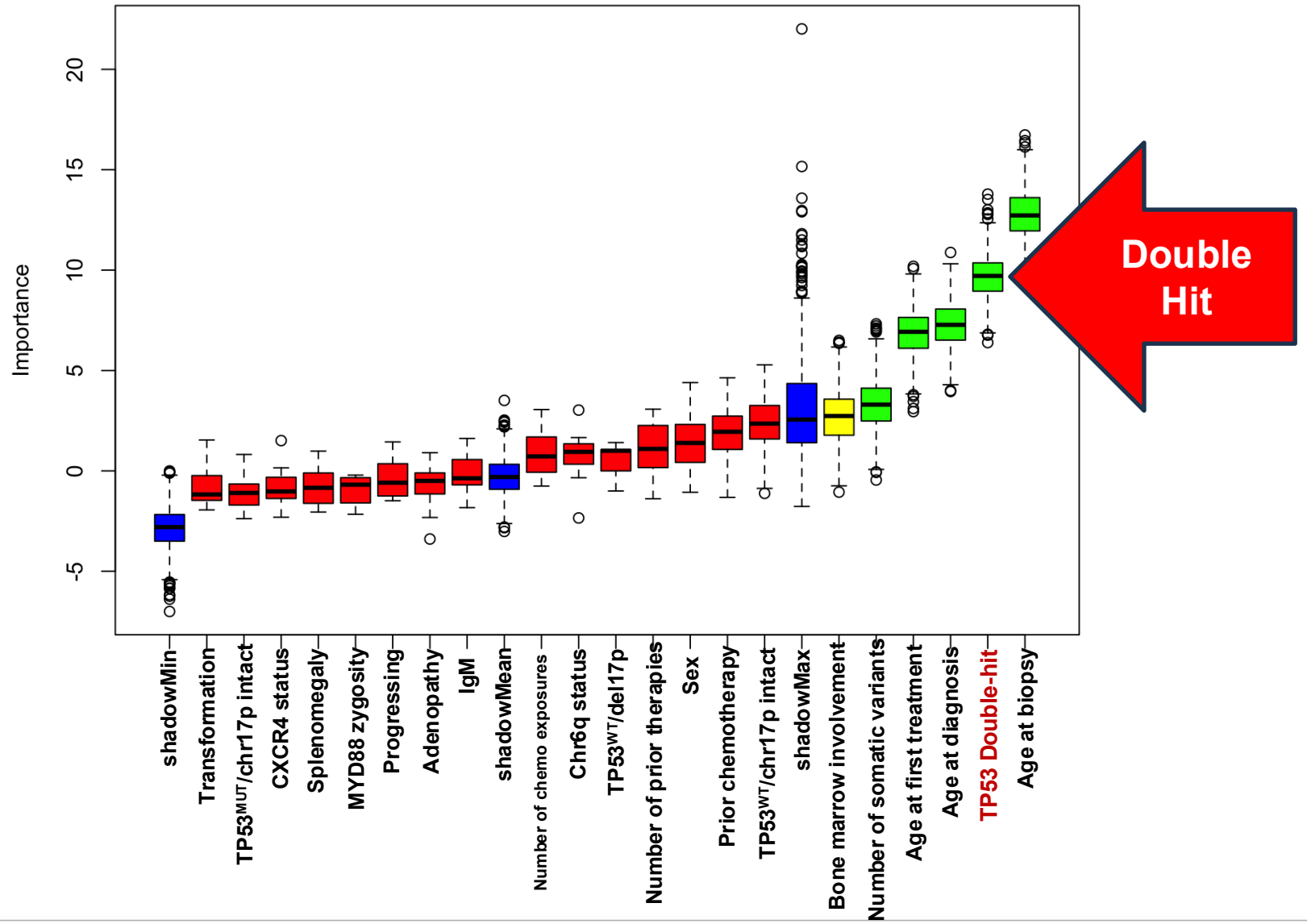
Multivariate Logistic Regression

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 $TP53^{ALT}$ were more common in patients who received both AA and NA (18.8%) versus either an AA or NA (6.1%) or no CT (3.6%); p=0.069 for three-way comparison.

Tsakmaklis N. et al, ASH 2025

Boruta Identifies TP53 Double-hit Status as One of the Most Relevant Predictors of OS



Cox proportional hazards model

Term	p-value	HR
Sex	0.022	2.14
Age at biopsy	<0.001	1.08
CXCR4 Mutated	0.389	1.30
TP53 Single-hit	0.737	0.78
TP53 Double-hit	0.001	3.85
>1 Prior Therapy	0.388	1.31

A Cox proportional hazards model adjusting for sex, age, CXCR4 status, amount of TP53 alterations, and number of prior therapies identified sex, age, and TP53 Double-hit as significantly impacting OS

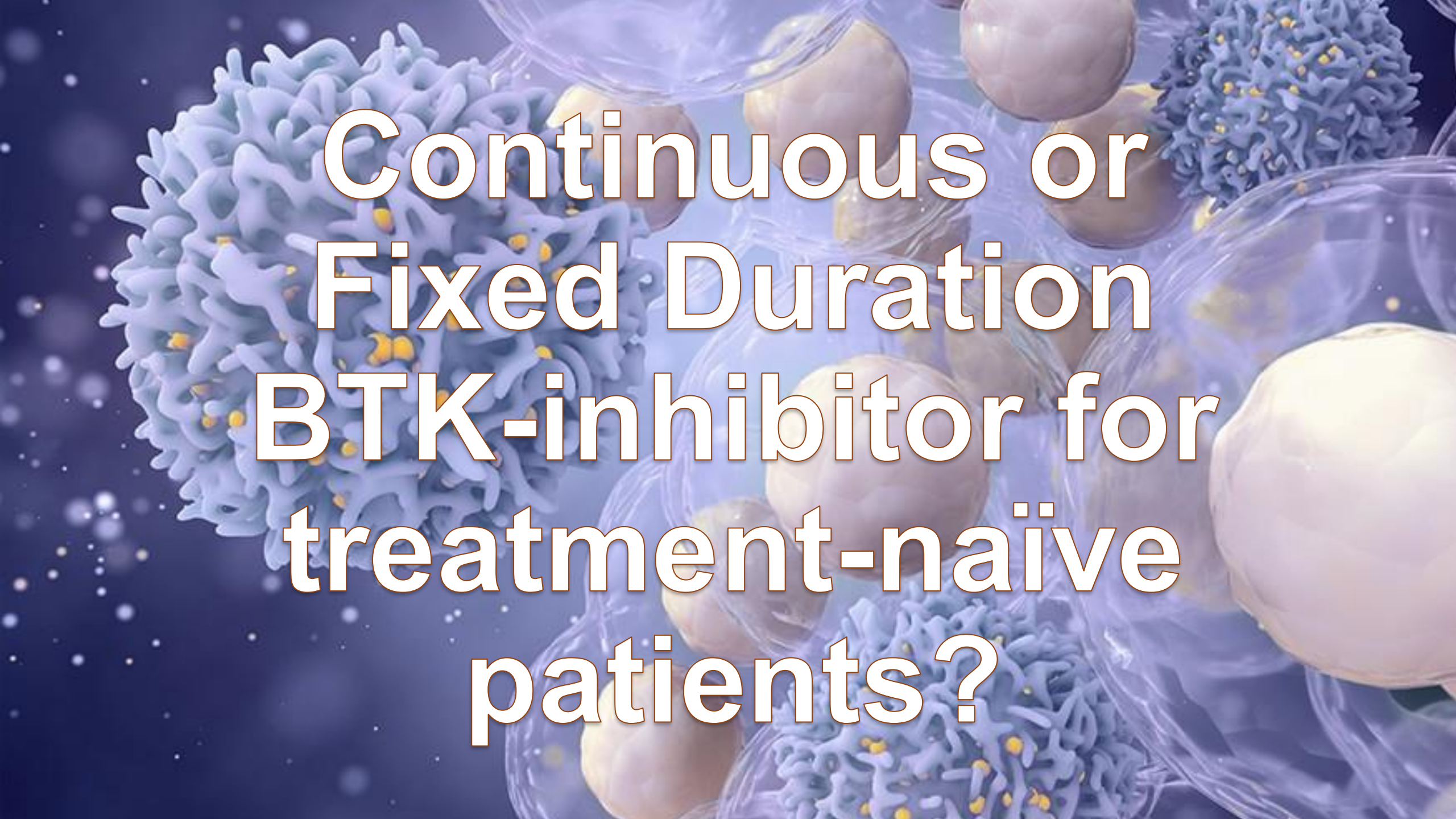
Treatment Algorithm for Symptomatic Treatment-Naïve WM

MYD88
CXCR4
TP53
Genotyping

- **MYD88^{Mut} CXCR4^{WT}** → **BTK-inhibitor (monotherapy)**
  Other options: Benda-R, PI based regimen
- **MYD88^{Mut} CXCR4^{Mut}** → **Rapid Response Required** → **Plasmapheresis for severe HV, CAGG, CRYOS, rapidly progressing IGM PN** → **Benda-R**
  Other options:
  PI based regimen,
  Zanubrutinib
- **MYD88^{Mut} CXCR4^{Mut}** → **Rapid Response Not Required** → **Zanubrutinib**
  Other options: Ibrutinib plus rituximab, Benda-R, PI based regimen
- **MYD88^{WT} CXCR4^{WT}** → **Zanubrutinib**
  Other options: Benda-R, or PI based regimen

[1]Zanubrutinib is recommended for those with MYD88^{WT}, CXCR4^{Mut} or TP53^{Alt}
[2]Bendamustine-R is recommended for those with bulky disease
[3]Bendamustine-R or Proteasome Inhibitors for symptomatic amyloid (with ASCT for eligible patients)
[4]BTK-inhibitor is recommended for BNS

Treon et al, Blood 2024


Continuous or
Fixed Duration
BTK-inhibitor for
treatment-naïve
patients?

Ibrutinib and Venetoclax (IVEN) for Treatment Naive WM

STUDY TERMINATED

Ibrutinib 420 mg (24 Months)

Venetoclax Ramp-up (1 Month), 400 mg (23 Months)

Median Time on Treatment: 10.2 months
Major RR 95%
VGPR 42% (29% $CXCR4^{Mut}$; 50% $CXCR4^{WT}$)
No CRs
3 yr PFS: 51%. Not impacted by CXCR4 status
V-fib (9%; 2 G5 events)

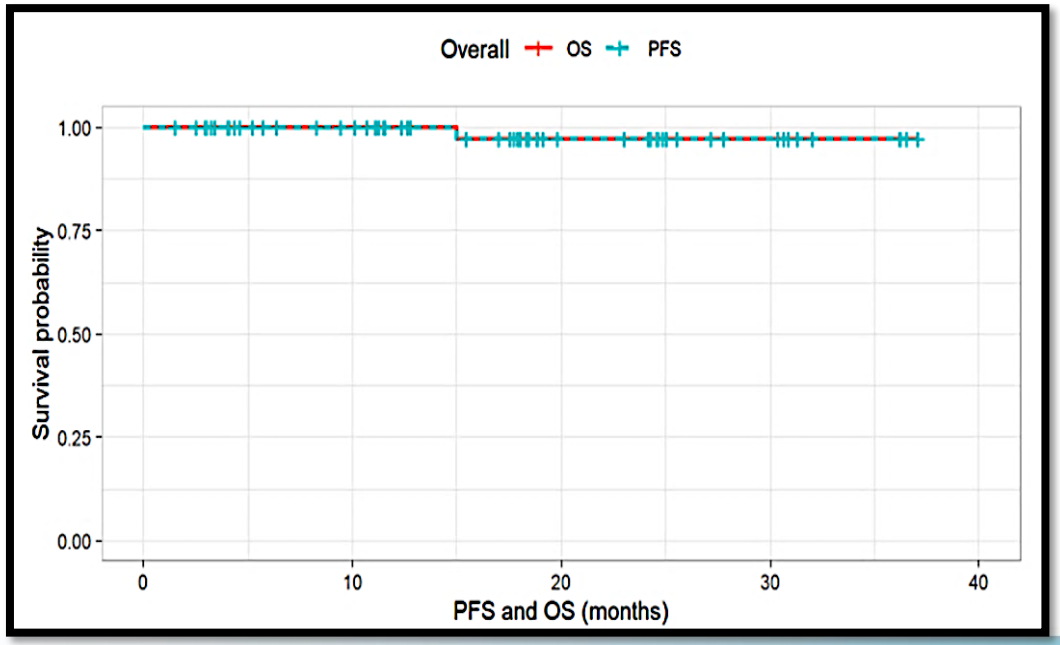
Castillo et al, IWWM-12, 2024

Bendamustine, Rituximab and Acalabrutinib (BRAWM) for Treatment Naïve WM

Acalabrutinib (12 Months)

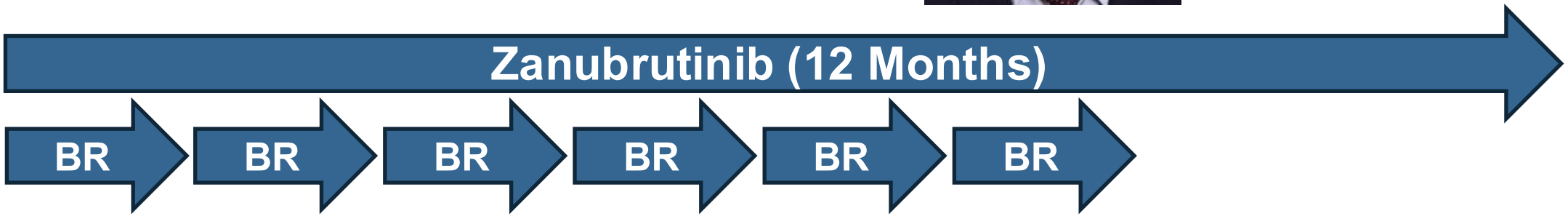
BR BR BR BR BR BR

Major RR 95%
VGPR 38%
CR 18%
MRD 23% (18 mos)

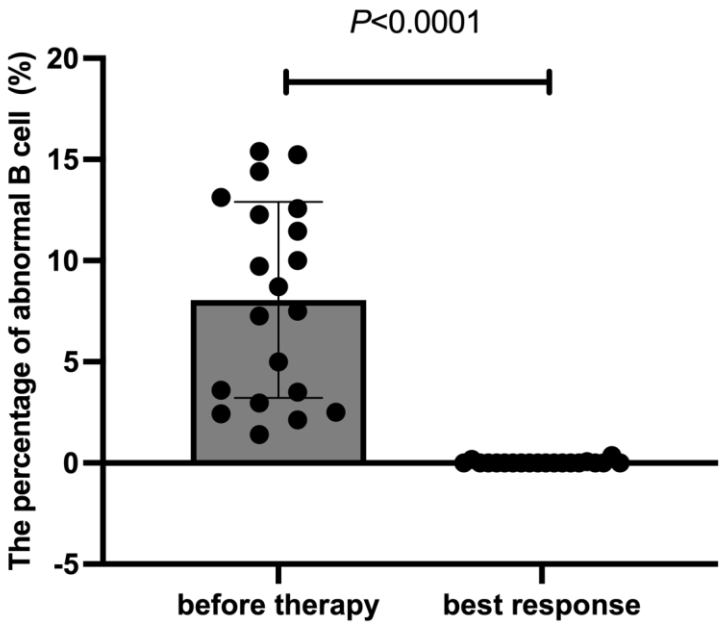


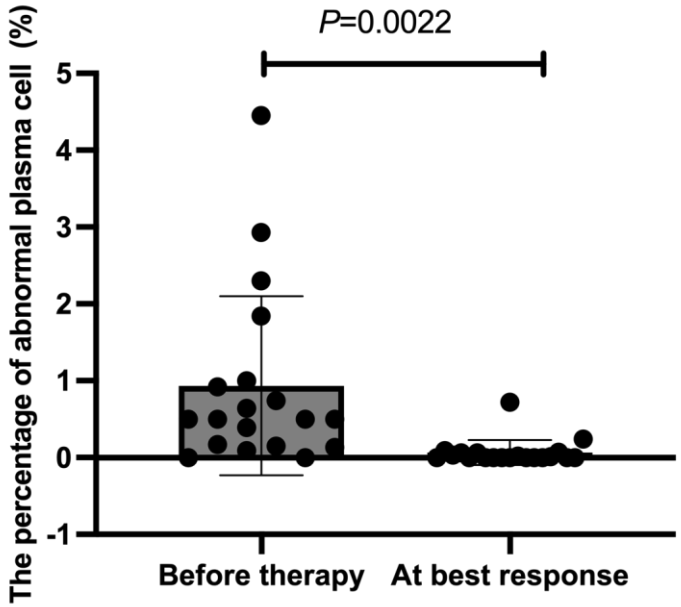
Berenstein et al, IWWM-12, 2024

Zanubrutinib, Bendamustine and Rituximab (ZBR) for Treatment Naïve WM



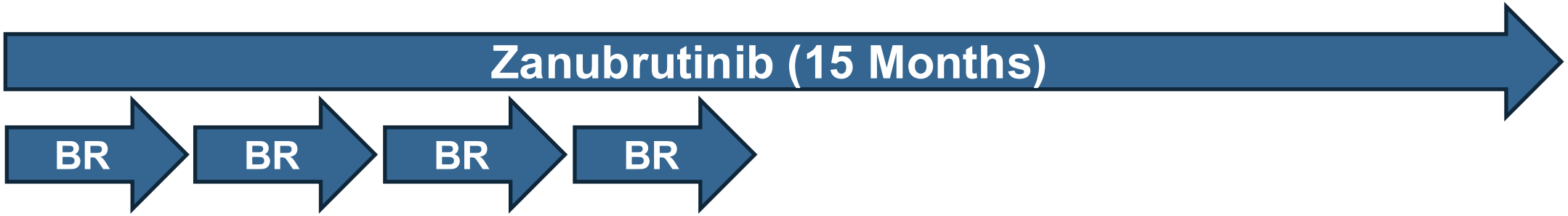
Major RR 95%
VGPR 65%
MRD (50% of evaluable patients)





Zanubrutinib, Bendamustine and Rituximab (ZeBRa) for Treatment Naïve WM

www.clinicaltrials.gov NCT06561347

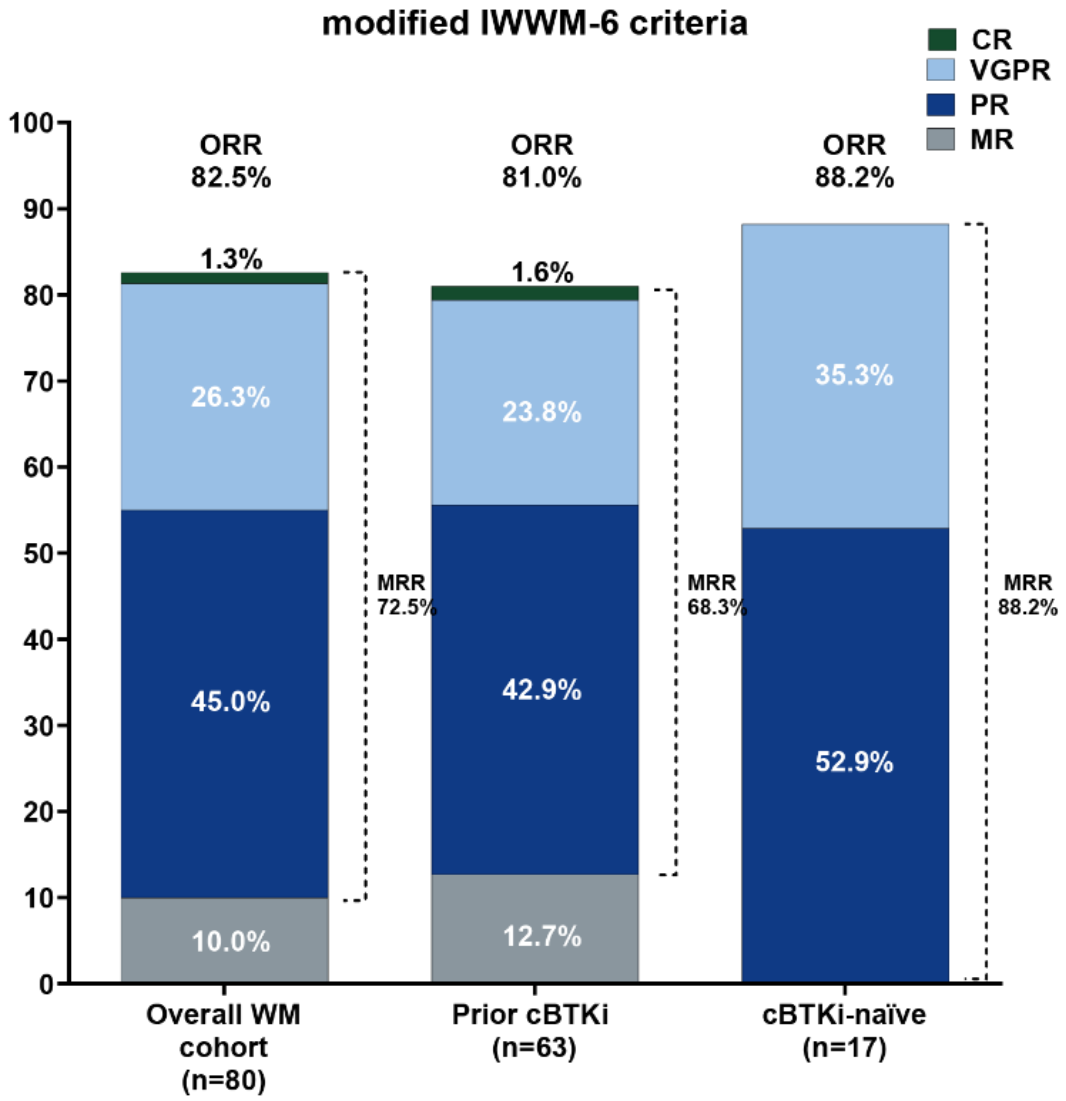


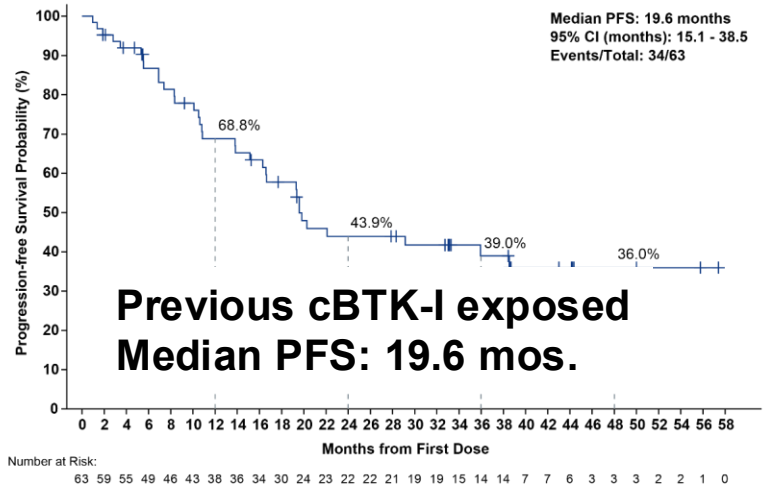
Inclusion Criteria:

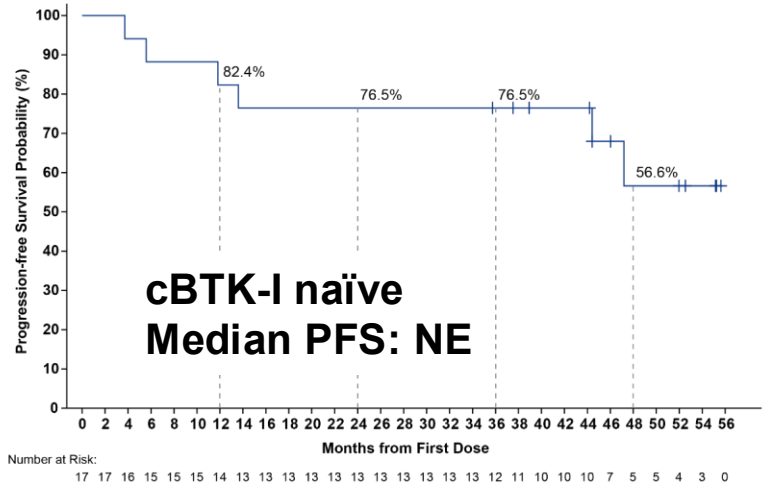
- Presence of any MYD88 and CXCR4 mutation status
- Meeting criteria for treatment per IWWM2 criteria.
- Participants must meet the following organ and marrow function as defined below:
  - ANC≥500/mcL believed to be caused by WM BM involvement.
  - Platelets ≥30,000/mcL believed to be caused by WM BM involvement. Hemoglobin ≥ 7 g/dL.
  - Total bilirubin ≤ 1.5 X institutional ULN
  - AST/ALT ≤2.5 × institutional ULN
  - Creatinine clearance ≥30 mL/min using the Cockcroft-Gault formula


How do we manage covalent BTK-inhibitor resistant disease?

Pirtobrutinib in Previously Treated WM



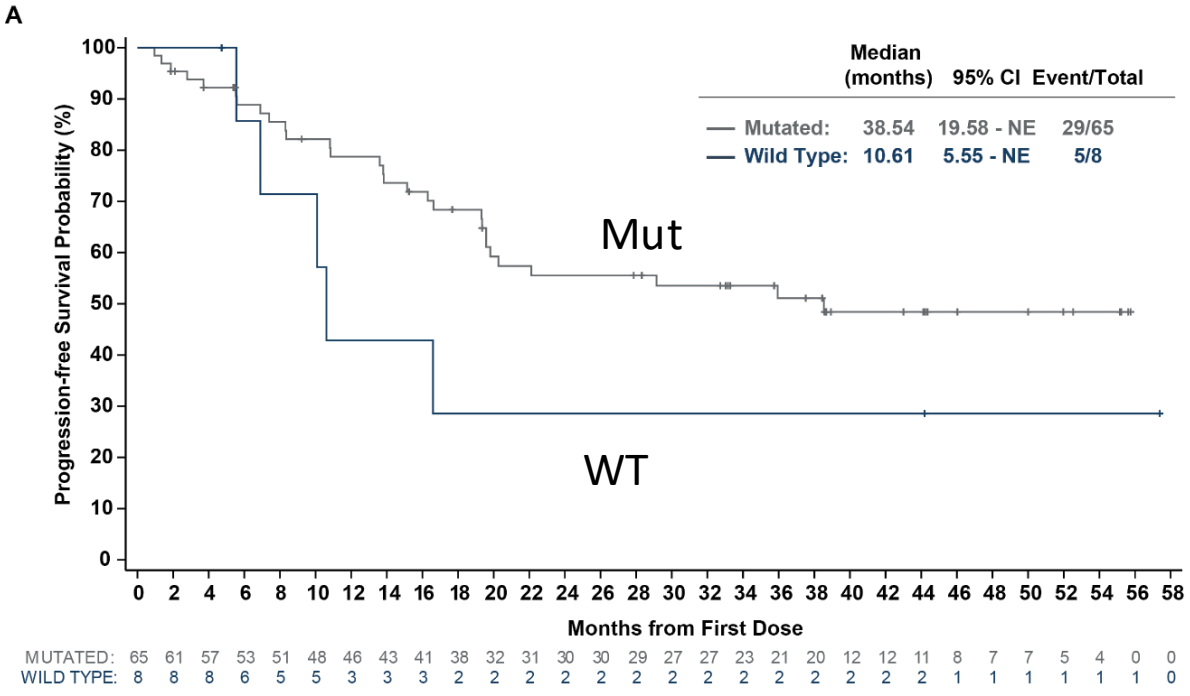




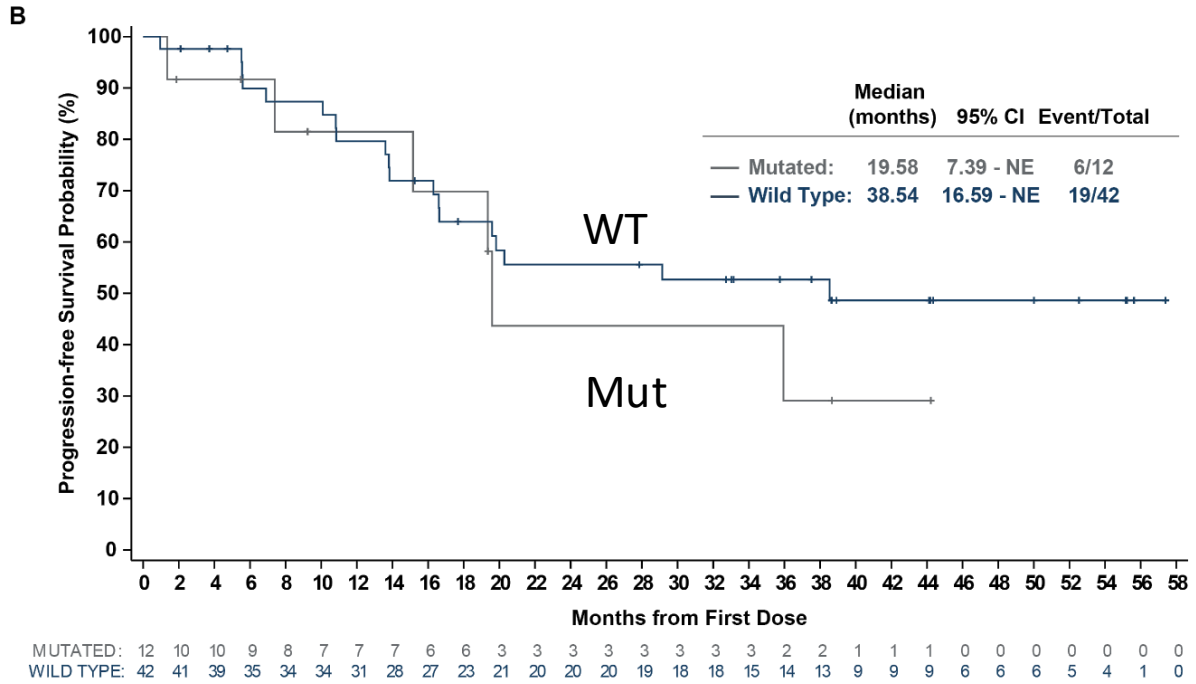
Palomba et al, Lancet Hematol. 2026 (accepted)

Progression-free survival for previously treated WM Patients treated with Pirtobrutinib by MYD88 and CXCR4 Mutation Status

MYD88 Status



CXCR4 Status

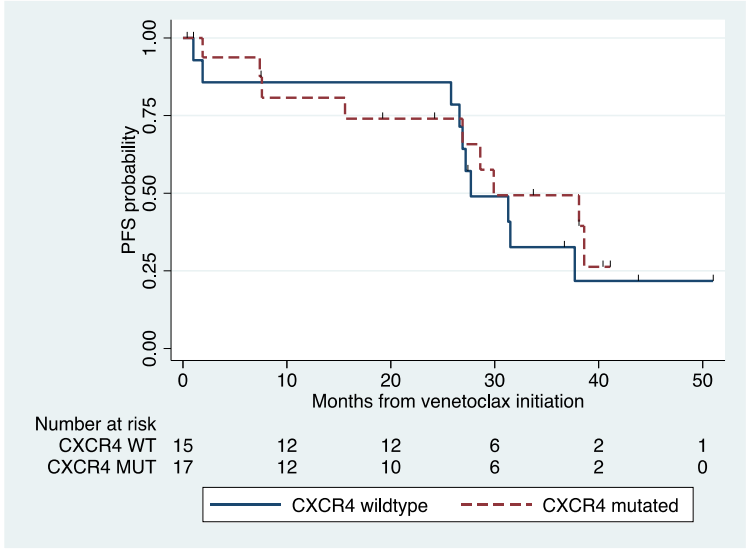


Palomba et al, Lancet Hematol. 2026 (accepted)

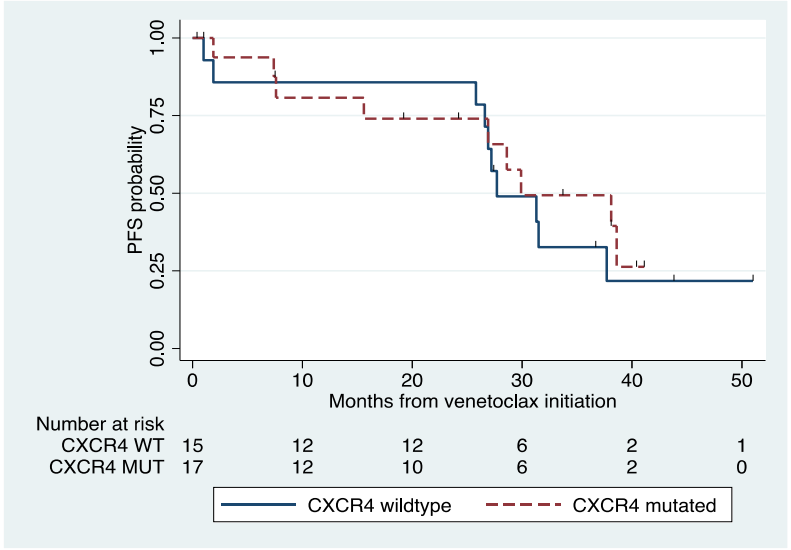
Venetoclax for Previously Treated WM

Dose escalation to 800 mg/day, 2 years treatment

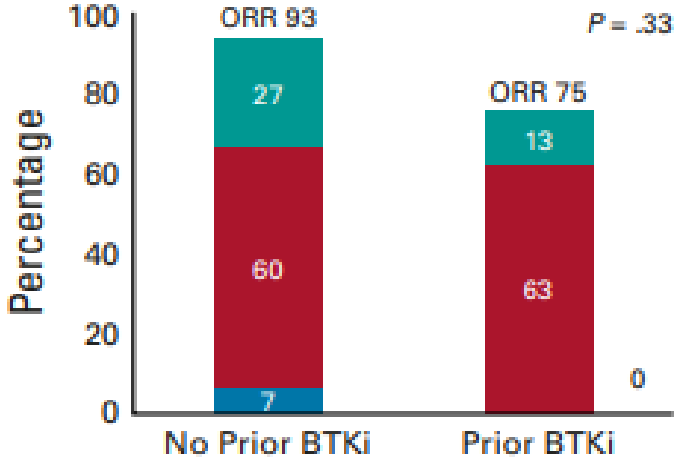
ORR 84%; Major RR 81%
Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

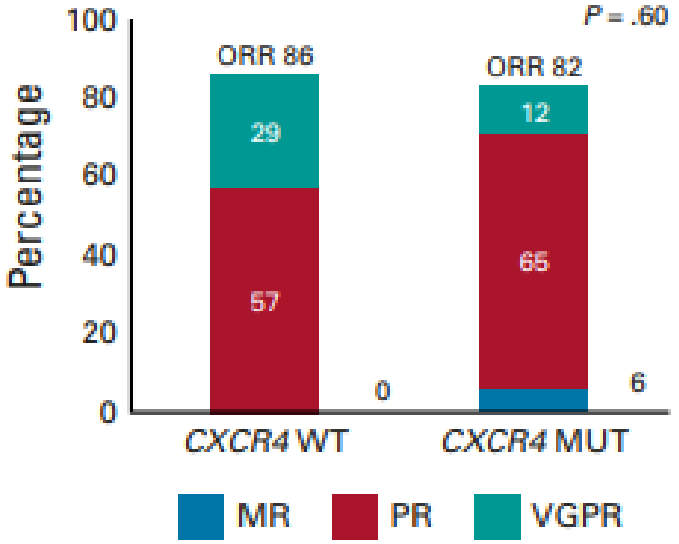


PFS for All Pts



PFS by CXCR4 Mut Status



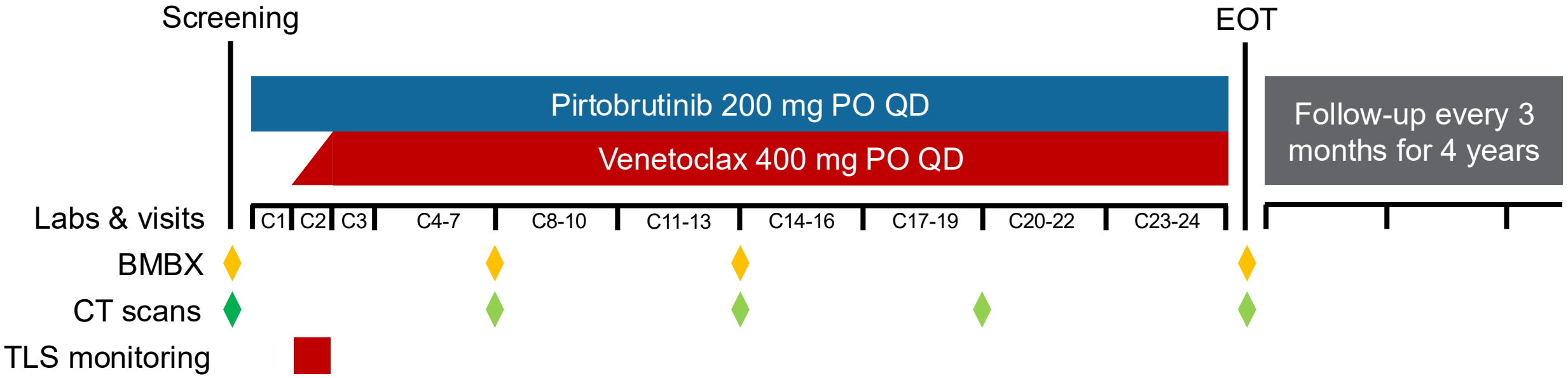


Castillo et al, JCO 2021

Pirtobrutinib and Venetoclax (PVEN) Treatment schema

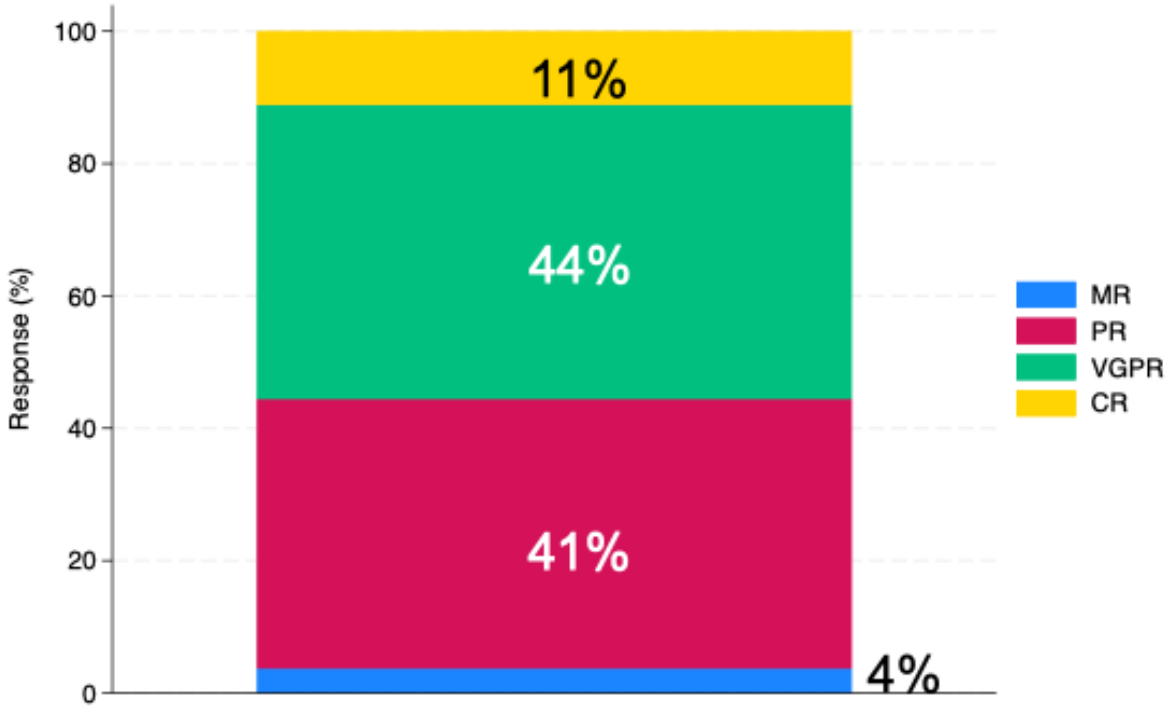
Key inclusion criteria
18+ years
Diagnosis and need for treatment per IWWM2
MYD88 L265P
1+ previous therapy

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

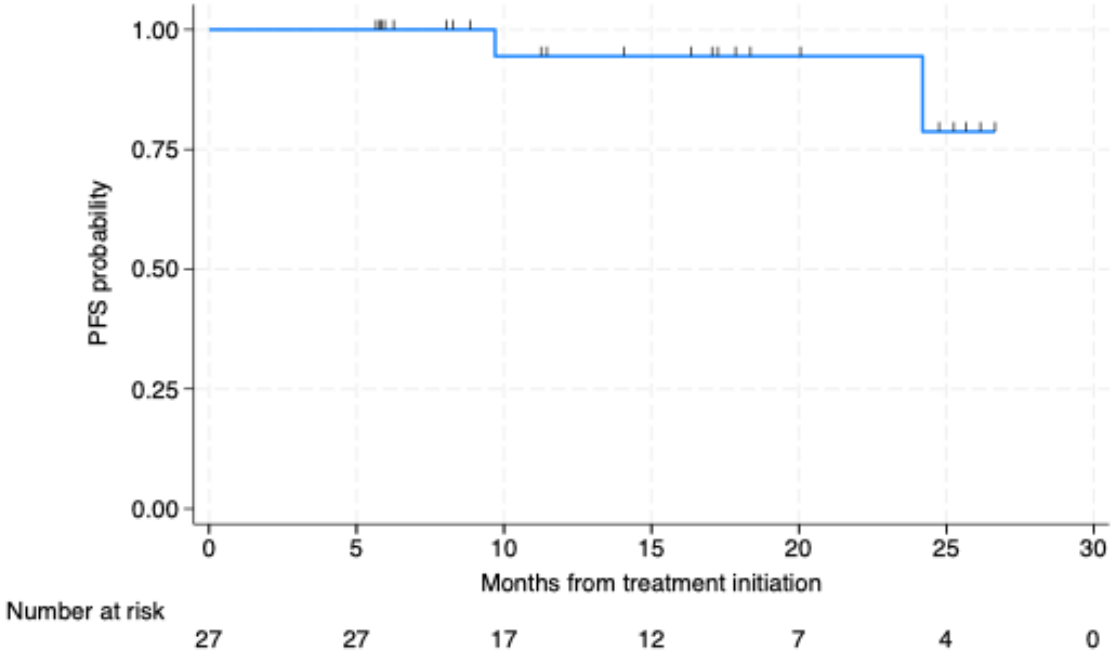


PVEN Responses

ORR 100%
Major RR 96%
VGPR/CR 11%



12 mo. PFS rate 94%
(95% CI 67-99%)



Median follow-up: 11 months (95% CI 8-18)

Castillo et al, ASH 2025

THE BTK DEGRADER BGB-16673 IS HIGHLY ACTIVE IN R/R WM

- Responses were observed at the lowest dose (100 mg; 7/9) and in patients with prior cBTK inhibitor (22/27) or ncBTK inhibitor (4/4)

	Total[a] (N=27)
Best overall response, n (%)	
VGPR	7 (25.9)
PR	13 (48.1)
MR	2 (7.4)
SD	3 (11.1)
Not evaluable	1 (3.7)
Discontinued prior to first assessment	1 (3.7)
ORR, n (%)[b]	**22 (81.5)**
Major response rate, n (%)[c]	**20 (74.1)**
DCR, n (%)[d]	25 (93.0)
Follow-up, median (range), months	5.0 (0.8-24.6)
Time to first response, median (range), months[e]	1.0 (0.9-3.7)

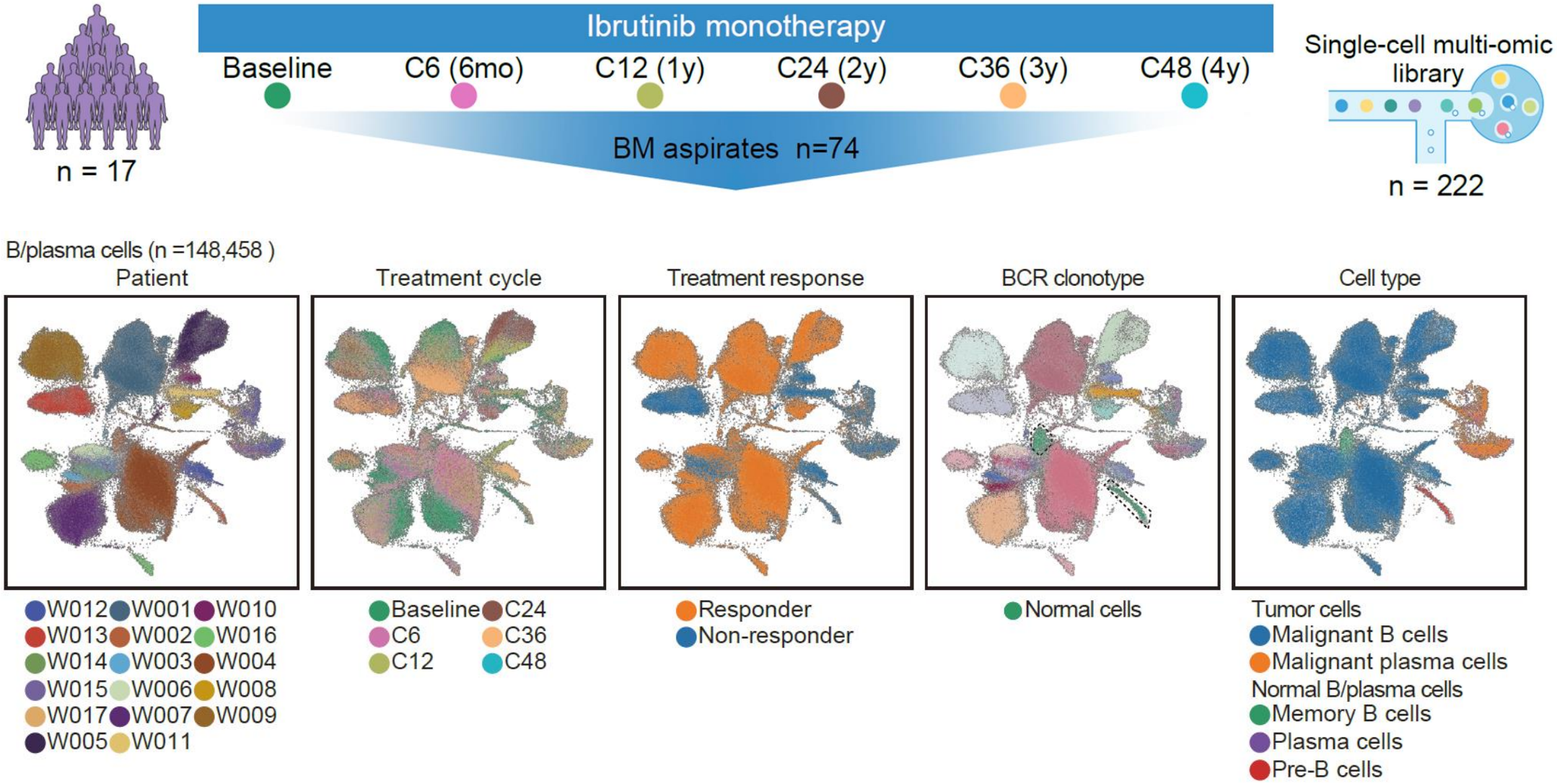
Mutation status, n/N tested (%)	Total[a] (N=27)
BTK	
Mutated	10/11 (90.9)
Unmutated	11/14 (78.6)
Unknown	1/2 (50.0)
MYD88	
Mutated	20/24 (83.3)
Unmutated	1/2 (50.0)
Unknown	1/1 (100)
CXCR4	
Mutated	11/12 (91.7)
Unmutated	10/13 (76.9)
Unknown	1/2 (50.0)
TP53	
Mutated	12/13 (92.3)
Unmutated	9/12 (75.0)
Unknown	1/2 (50.0)

a
e
best overall response of SD or better.

cBTK, covalent BTK; DCR, disease control rate; MR, minor response; ncBTK, noncovalent BTK; VGPR, very good partial response.

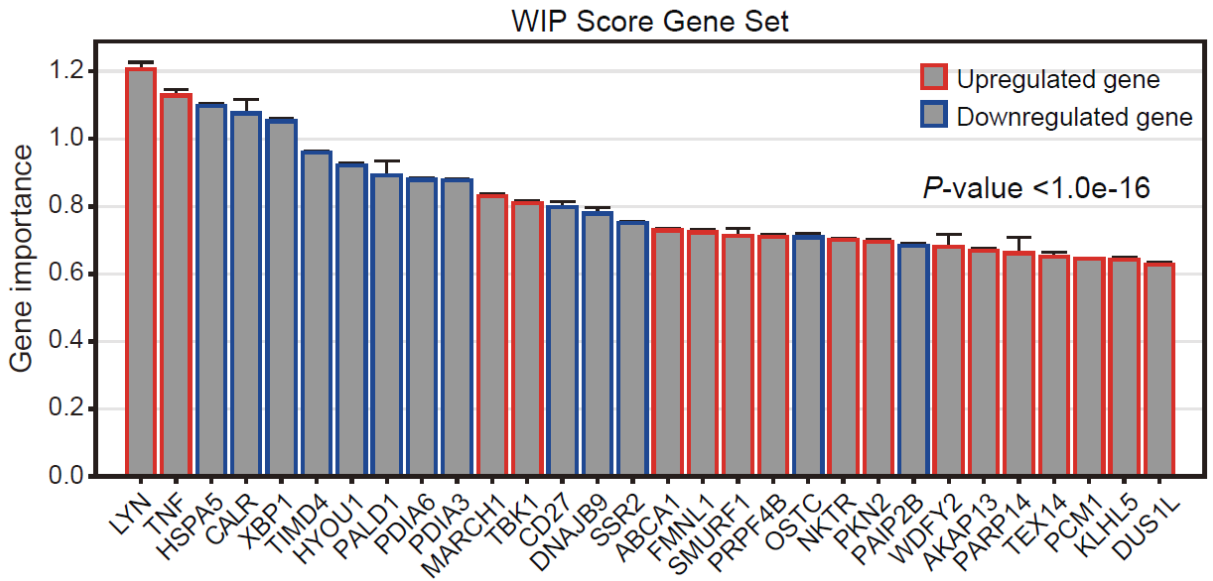
Seymour et al, IWWM-12, 2024

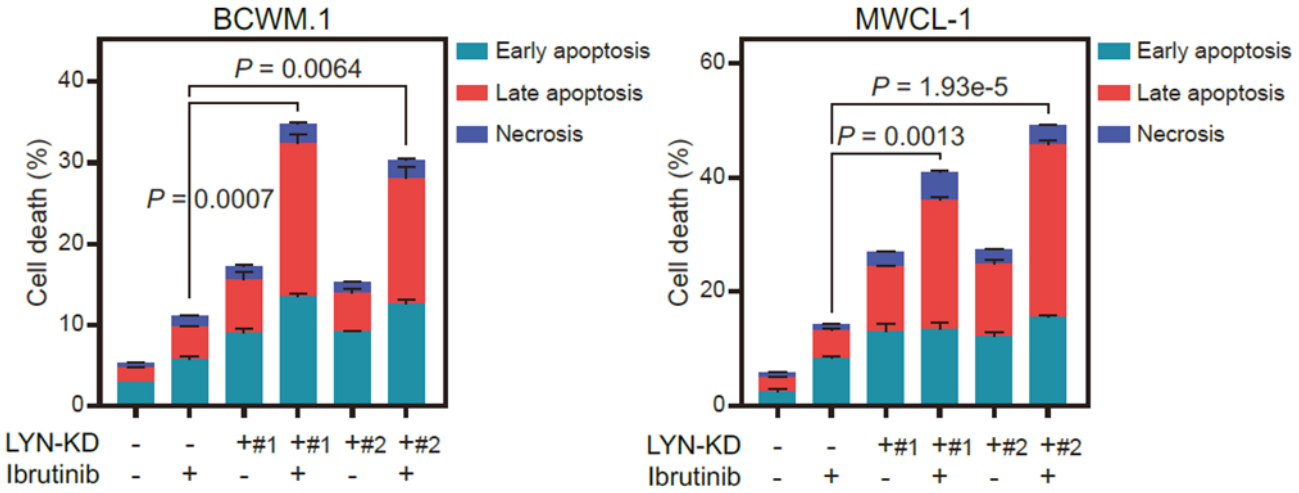
Single-cell sequencing of longitudinal BM aspirates from WM patients treated with ibrutinib monotherapy with serial 5-year tumor collection and follow-up.

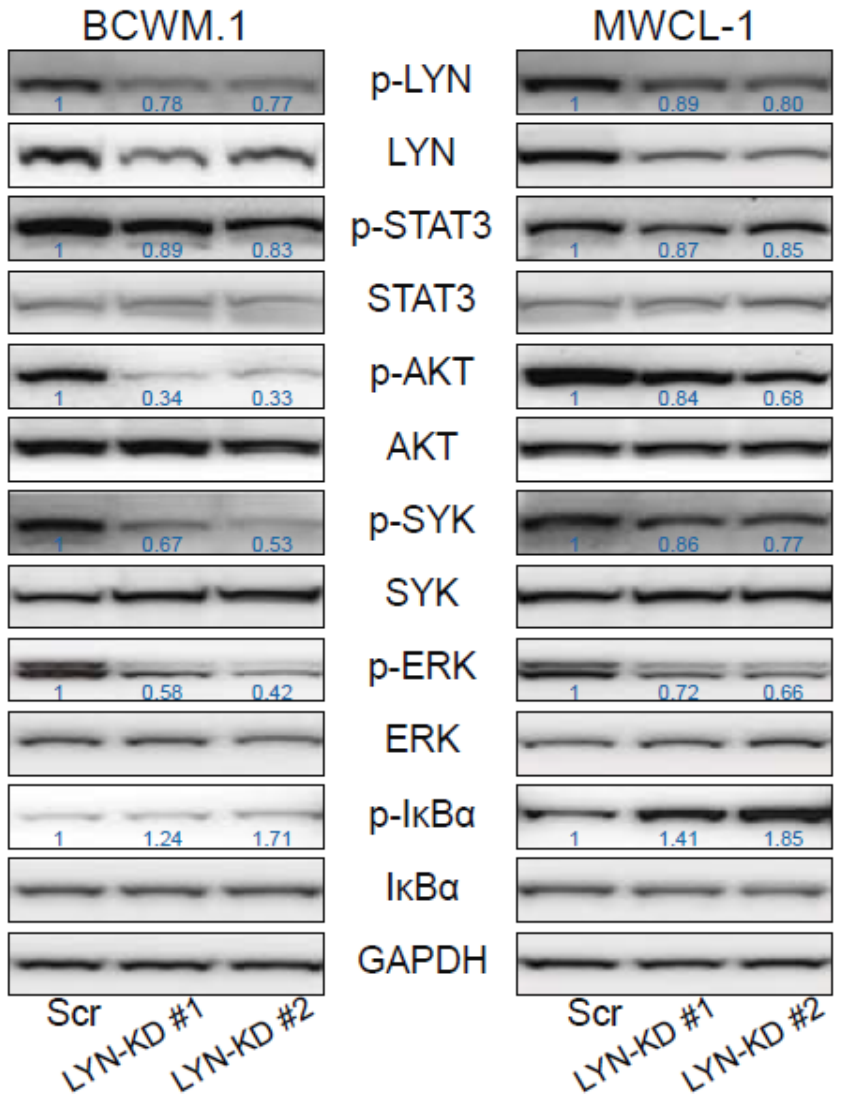


Sun et al, Blood. 2026 Feb 11:blood.2025032268.

The SRC family member LYN emerged as a top gene in ibrutinib-resistant WM disease, and LYN knockdown decreased pro-survival signaling and increased ibrutinib sensitivity.







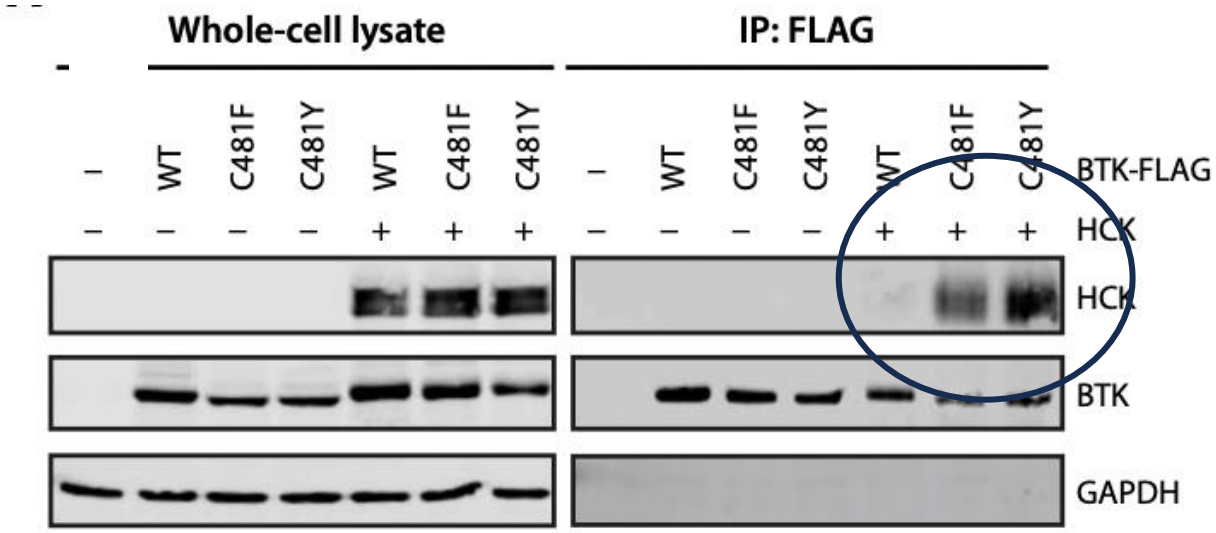
Sun et al, Blood. 2026 Feb 11:blood.2025032268.

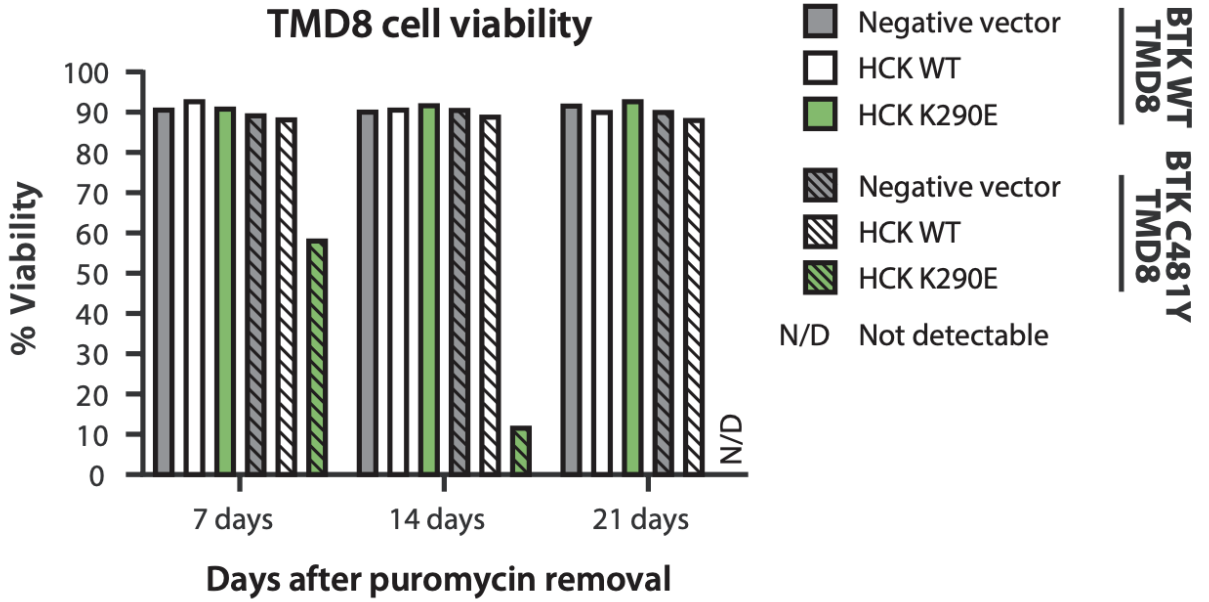
CANCER

Kinase-deficient BTK mutants confer ibrutinib resistance through activation of the kinase HCK

Kamaldeep Dhami[1], Anirban Chakraborty[1], Tarikere L. Gururaja[1], Leo W.-K. Cheung[1,2], Chaohong Sun[2], Felix DeAnda[1], XiaoDong Huang[1]*

BTK^{Cys481Phe}
BTK^{Cys481Tyr}

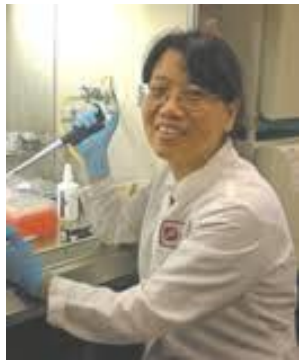


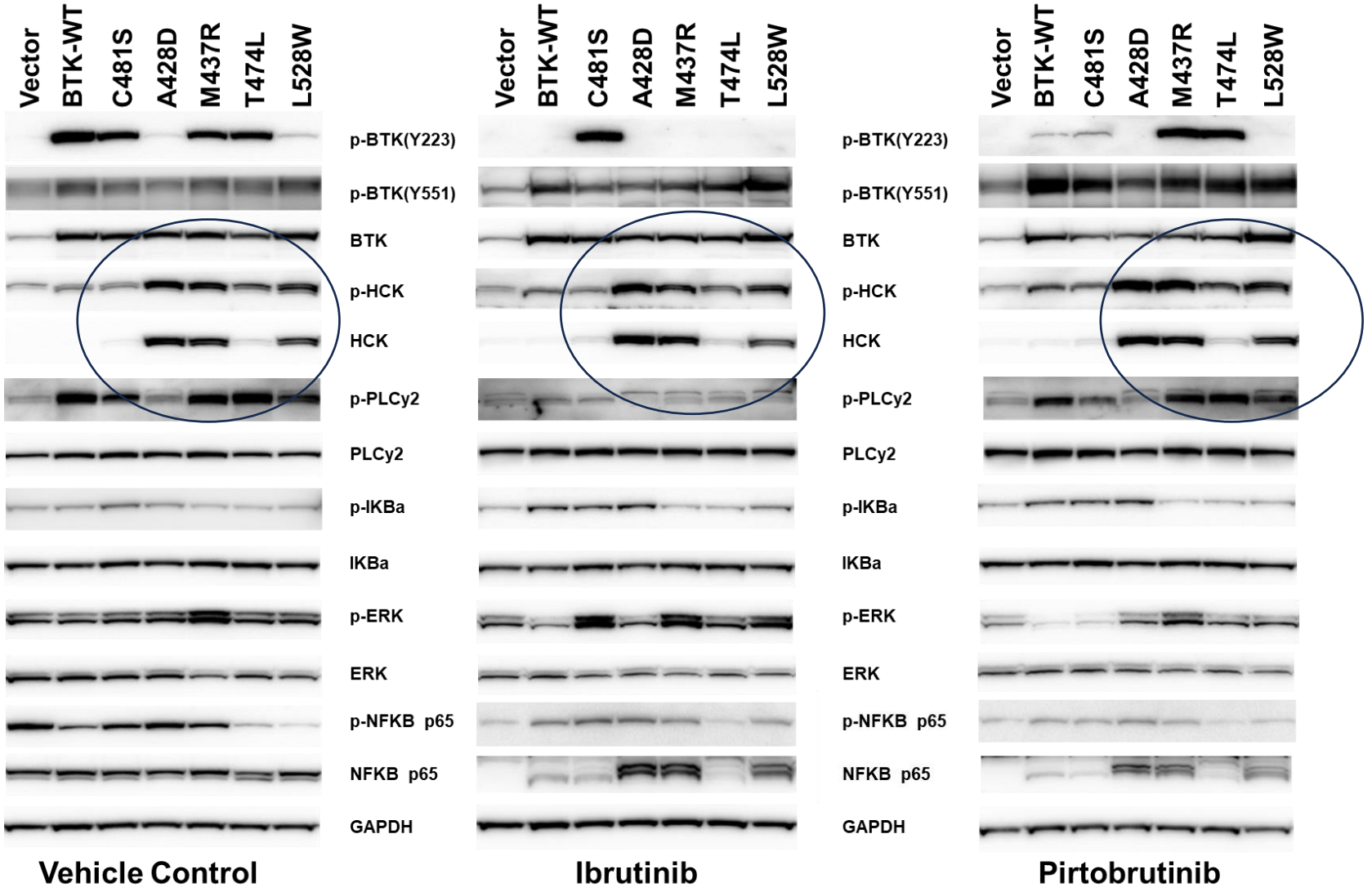


Acquired BTK mutations related to BTK-inhibitor resistance for agents used to treat WM

	BTK-Inhibitor Class		
BTK Mutation	Covalent	Non-Covalent	PROTAC
$BTK^{Cys481Ser}$	●		
$BTK^{Cys481Arg}$	●		
$BTK^{Cys481Tyr}$	●		
$BTK^{Val416Leu}$		●	
$BTK^{Ala428Asp}$	●	●	●
$BTK^{Thr474Leu}$		●	
$BTK^{Leu528Trp}$	●	●	
$BTK^{Met437Arg}$		●	

HCK is activated in BCWM.1 WM Cells expressing BTK mutations associated with BTK non-covalent kinase inhibitors and PROTACS





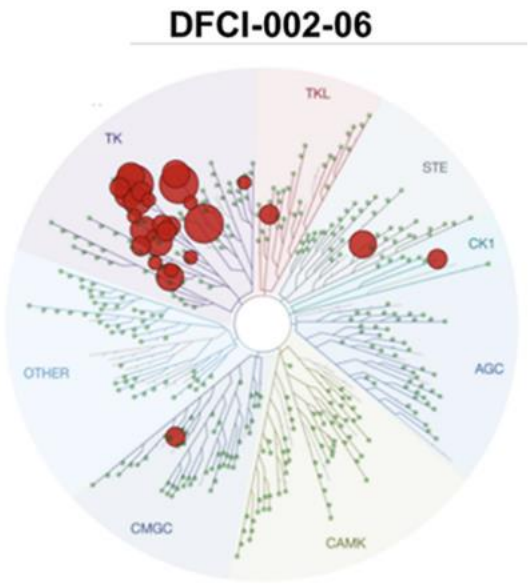
Liu et al, ASH 2025

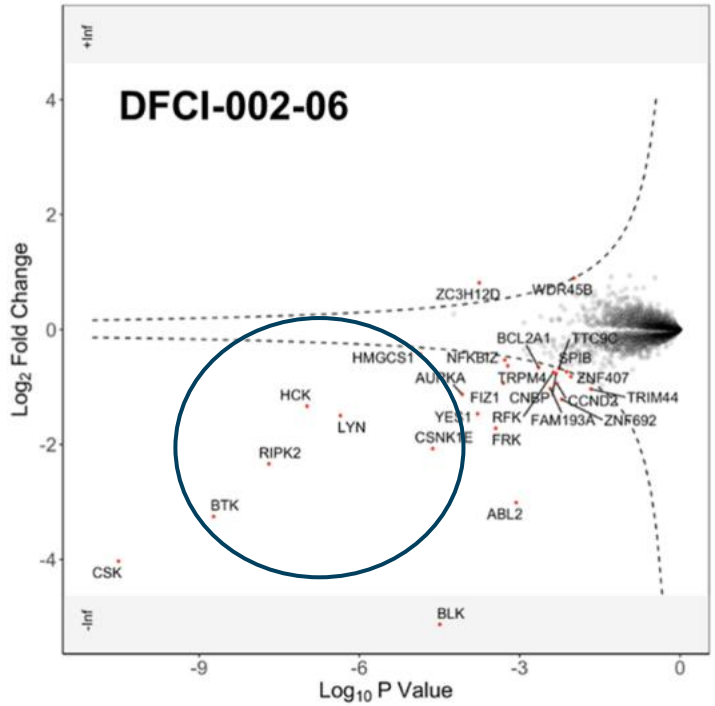
Journal of Medicinal Chemistry

pubs.acs.org/jmc Article

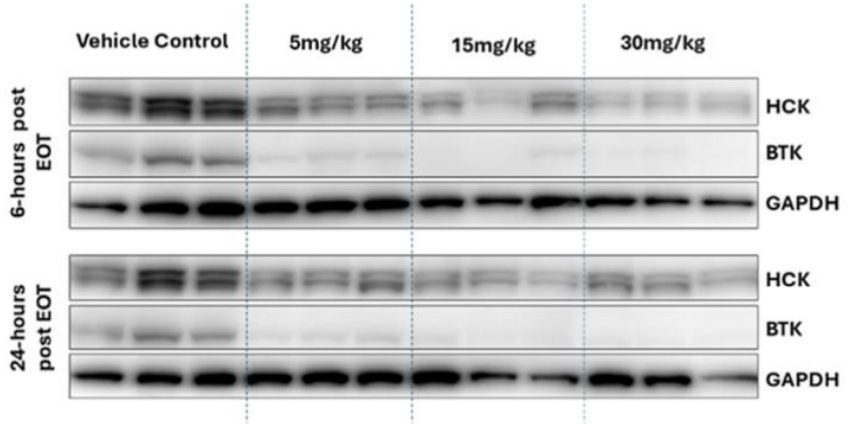
Discovery and Characterization of a First-In-Class HCK/BTK PROTAC DFCI-002-06 for the Treatment of MYD88 Mutated B Cell Malignancies

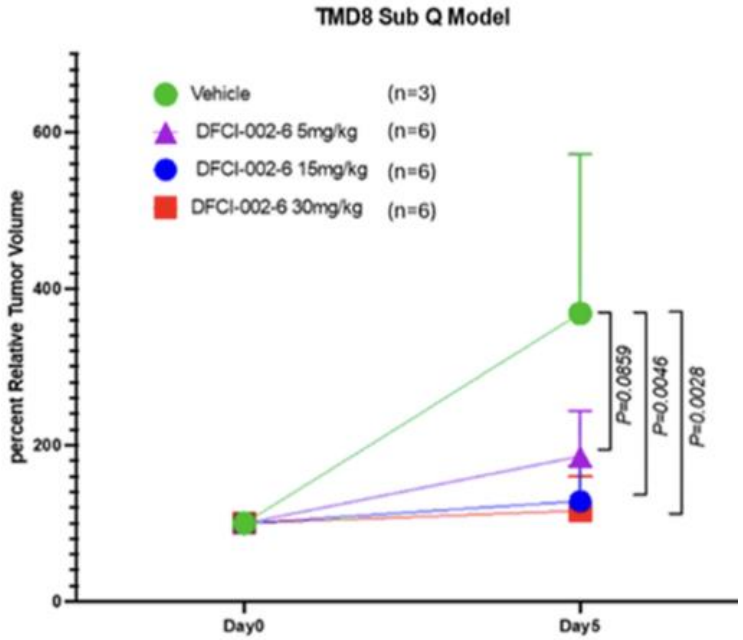
John M. Hatcher,[⊥] Shirong Liu,[⊥] Amanda Kofides, Alexa Canning, Dominic Pizzarella, Xia Liu, Nickolas Tsakmaklis, Maria Guerrera, Christopher Patterson, Alberto Guijosa, Prafulla Gokhale, Zachary Hunter, Shayna Sarosiek, Jorge Castillo, Jinhua Wang, Sara J. Buhrlage, and Steven P. Treon*



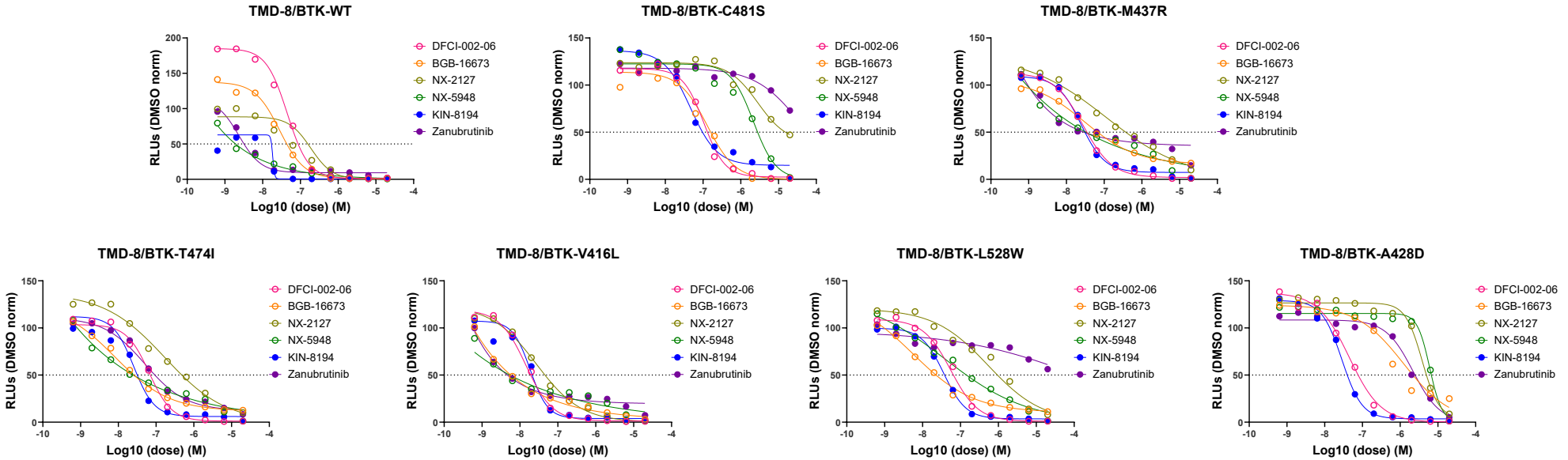


TMD8 Xenograft Model



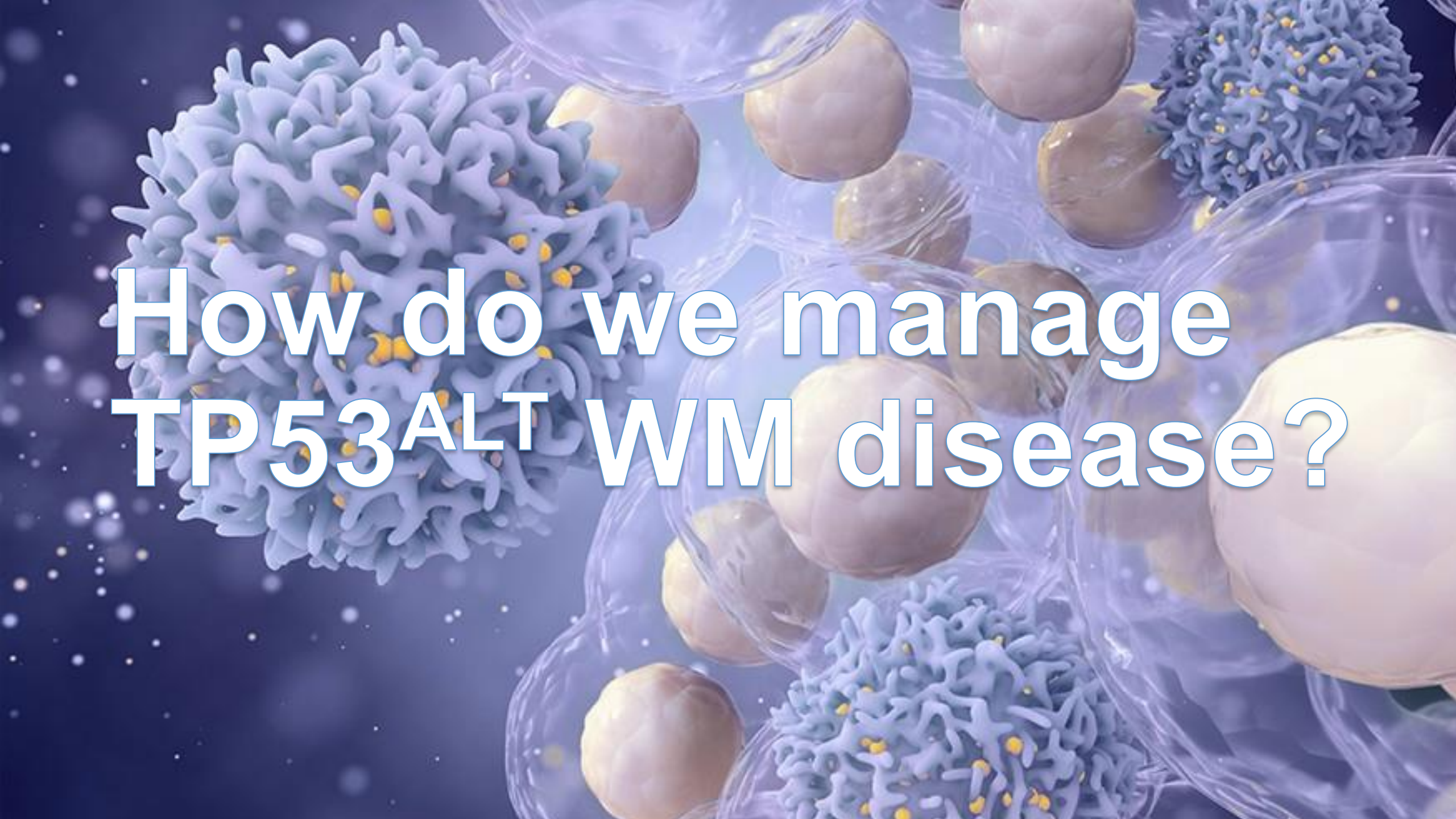


Dose-Response Curves for BTK and HCK Targeting Compounds in MYD88 mutated TMD-8 cells expressing mutated BTK



	BTK-WT	BTK-C481S	BTK-V416L	BTK-A428D	BTK-M437R	BTK-T474I	BTK-L528W
DFCI-002-06	**4.5E-08**	1.05E-07	**1.45E-08**	**4.49E-08**	**2.76E-08**	**6.59E-08**	**5.57E-08**
BGB-16673	**2.82E-08**	1.3E-07	**6.29E-25**	3.08E-07	**3.05E-08**	**8.19E-09**	**5.6E-09**
NX-2127	1.87E-07	2.82E-06	**2.7E-08**	3.84E-06	1.14E-07	1.72E-07	5.39E-07
NX-5948	**2E-15**	2.17E-06	**3.24E-33**	6.07E-06	**2.76E-30**	**1.9E-26**	**3.82E-08**
KIN-8194	**1.85E-08**	**4.66E-08**	1.87E-08	**2.86E-08**	**2.44E-08**	**2.56E-08**	**3.64E-08**
Zanubrutinib	**2.34E-09**	3.93E-05	2.24E-20	2.18E-06	-	**5.09E-08**	0.000149

Liu et al, ASH 2025


How do we manage
TP53ALT WM disease?

Phase II Study of the CD19-ADC Loncastuximab in Previously Treated WM

Shayna Sarosiek, PI. NCT05190705

	N (range or %)
Median age, y	71 (53-78)
Male sex	9 (64%)
Median previous therapies	4 (2-10)
Median serum IgM, mg/dL	2146 (723-5955)
Median hemoglobin, g/dL	9.5 (8.5-12.6)
Median BM involvement, %	53 (4-90)
MYD88 MUT	12 (86%)
CXCR4 MUT (n=13)	8 (62%)
TP53 MUT	**8 (54%)**
LN ≥1.5 cm or EMD	3 (21%)
Splenomegaly ≥15 cm	1 (7%)

	MYD88^{Mut}	CXCR4^{Mut}	TP53^{ALT}	RESPONSE
WM-1	YES	YES	NO	VGPR
WM-2	YES	YES	NO	PD
WM-3	YES	NO	NO	PR
WM-4	YES	NO	NO	VGPR
WM-5	NO	NO	NO	VGPR
WM-6	NO	NO	NO	MR
WM-7	YES	YES	YES	CR
WM-8	YES	YES	YES	VGPR
WM-9	YES	YES	YES	VGPR
WM-10	YES	NO	YES	VGPR
WM-11	YES	YES	YES	VGPR
WM-12	YES	YES	YES	VGPR
WM-13	YES	UNK	YES	VGPR
WM-14	YES	YES	YES	PR

Prospective Cellular Therapies Trials for WM

Agent	Target	Investigator	Response Activity	Trial Status
Epcoritimab	CD20	Von Keudell (Harvard)	NA	In progress
Epcoritamab	CD20	Vos (Amsterdam)	NA	In progress
Surovatamig	CD19	Sarosiek Mouhaddiene (Harvard)	NA	In progress
MB106 CAR T	CD20	Shadman (Fred Hutch)	MRR 67% CR 33% (N=6)	Enrollment stopped for lack of sponsor funding

13th International Workshop on WM

October 13-17, 2026

Ranjana Advani, Steve Ansell, Prashant Kapoor, Steve Treon

Co-Organizers

Palm Springs, California

http://waldenstromsworkshop.org