Waldenstrom's Macroglobulinemia: How I Treat in 2024

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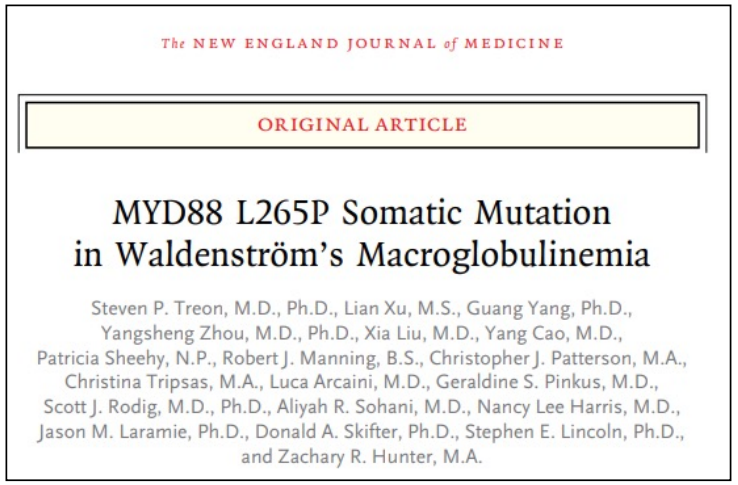
MYD88 Directed Pro-survival Signaling in WM



The NEW ENGLAND JOURNAL of MEDICINE

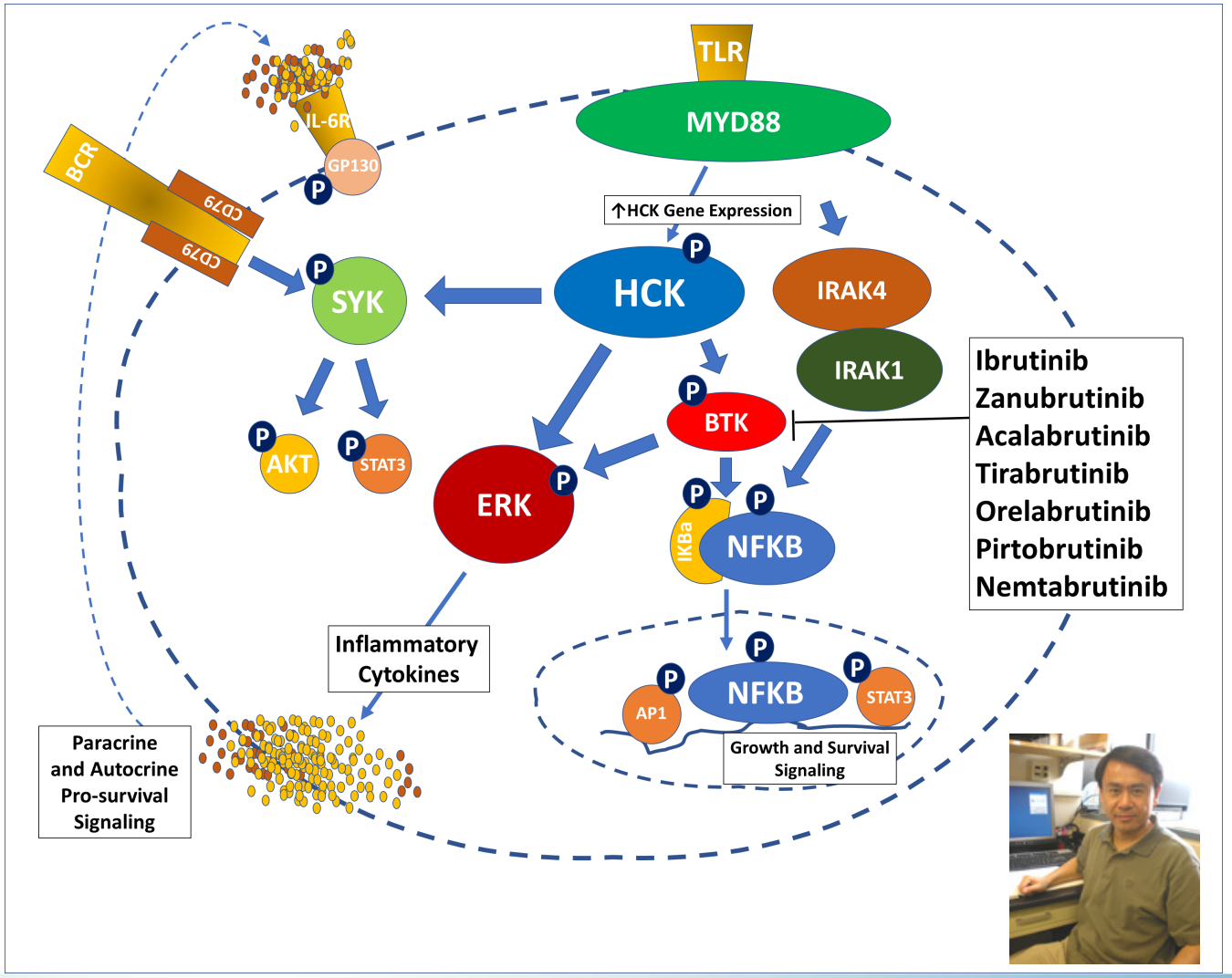
ORIGINAL ARTICLE

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	TN, R/R	Ibrutinib	150	3 mo.	92% / 76%	31%	68% @ 54 mo.
ASPEN-2 (MYD88^{WT})	TN, R/R	Zanubrutinib	28	3 mo.	78% / 63%	27%	84% @ 42 mo.
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%	24% (prior cBTKi) 29%	57% @ 18 mo. (for prior cBTKi) N/A for cBTKi naïve.

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

Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

Plenary Paper

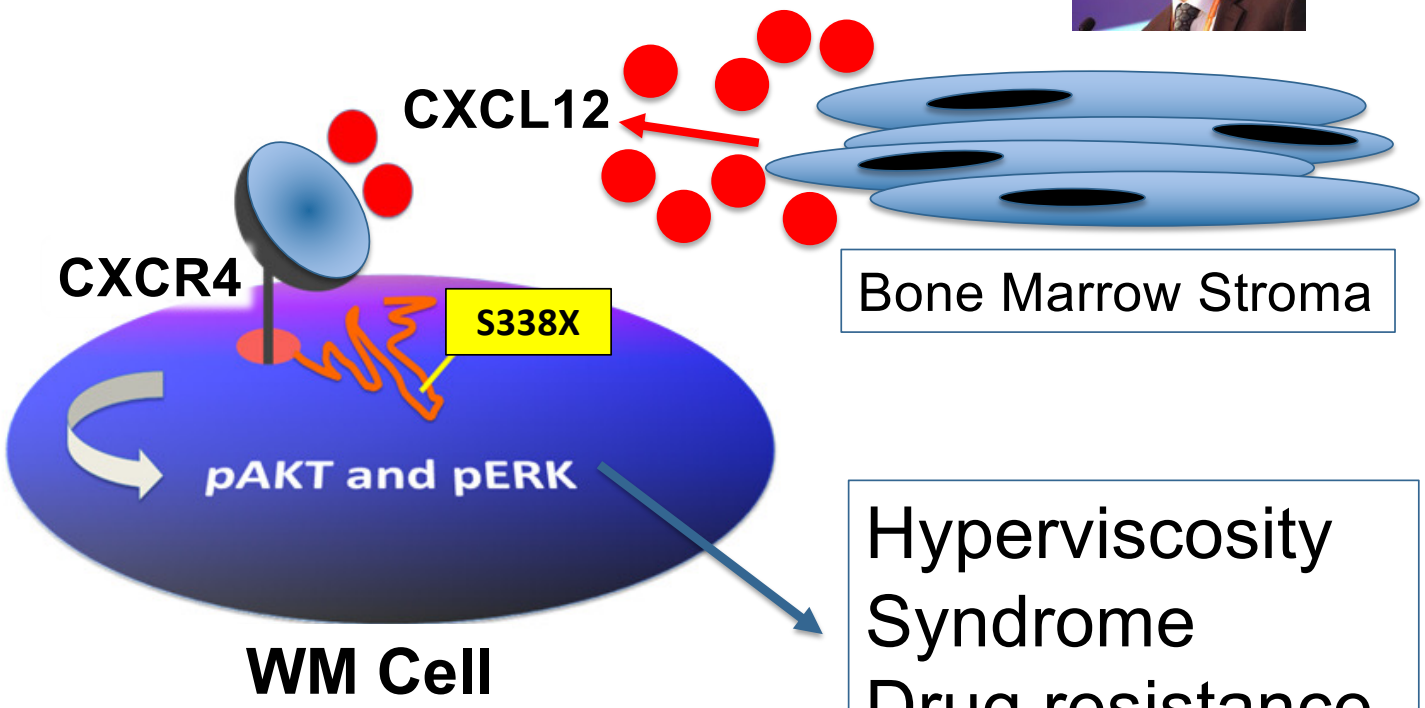
LYMPHOID NEOPLASIA

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 have CXCR4 mutations**
- **>40 different CXCR4 mutations, most common is S338X.**



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

Impact of CXCR4 Mutation Status in BTK-Inhibitor Studies 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 Study	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 $CXCR4^{WT}$

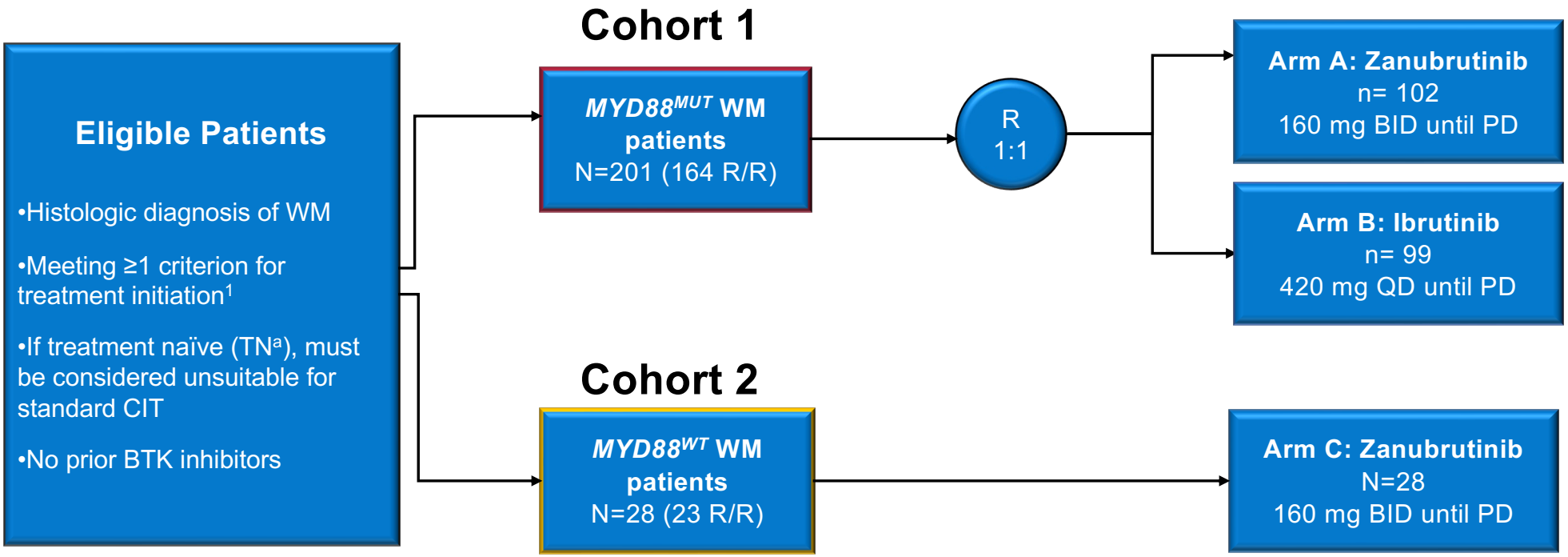
Median Time to Major Response: (4.2 vs. 1.9 mos)

Median Major RR: 71% vs. 87%

Median ≥VGPR: 14% vs. 41%

PFS: 59% vs. 75% @4 years

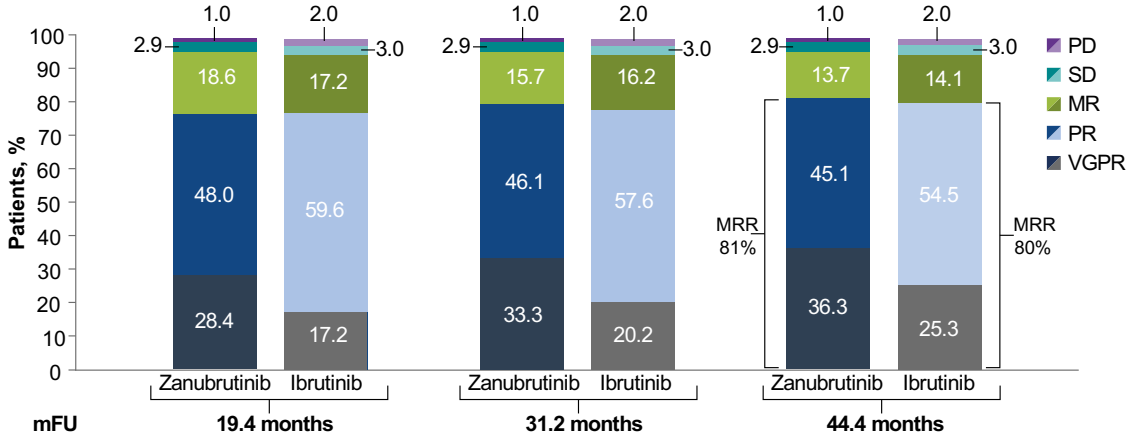
Phase 3 ASPEN Study
Zanubrutinib vs. Ibrutinib in WM



NCT03053440

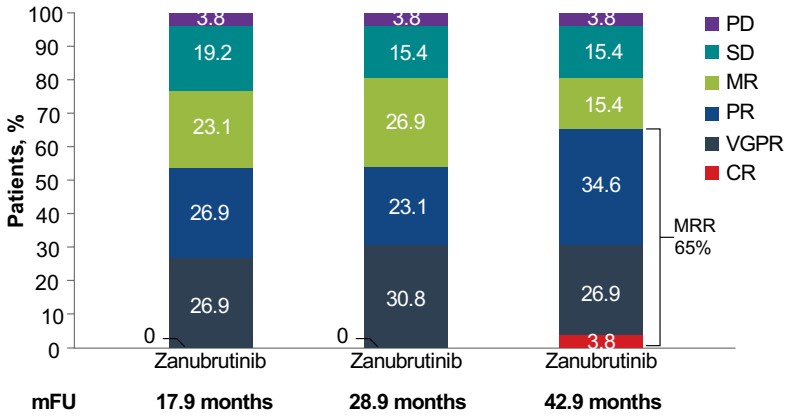
ASPEN: Best Overall Response and PFS by Investigator Assessment

Responses Over Time in Patients With *MYD88^MUT^*



- At 44.4 months event free rates for PFS were 78.3% and 69.7% for zanubrutinib and ibrutinib, respectively. For OS, 87.5% and 85.2%, respectively.

Responses Over Time Observed in *MYD88^WT^*



- At 42.9 months event-free rates for PFS and OS were 53.8% and 83.9%, respectively.

Dimopoulos MA et al, JCO 2023

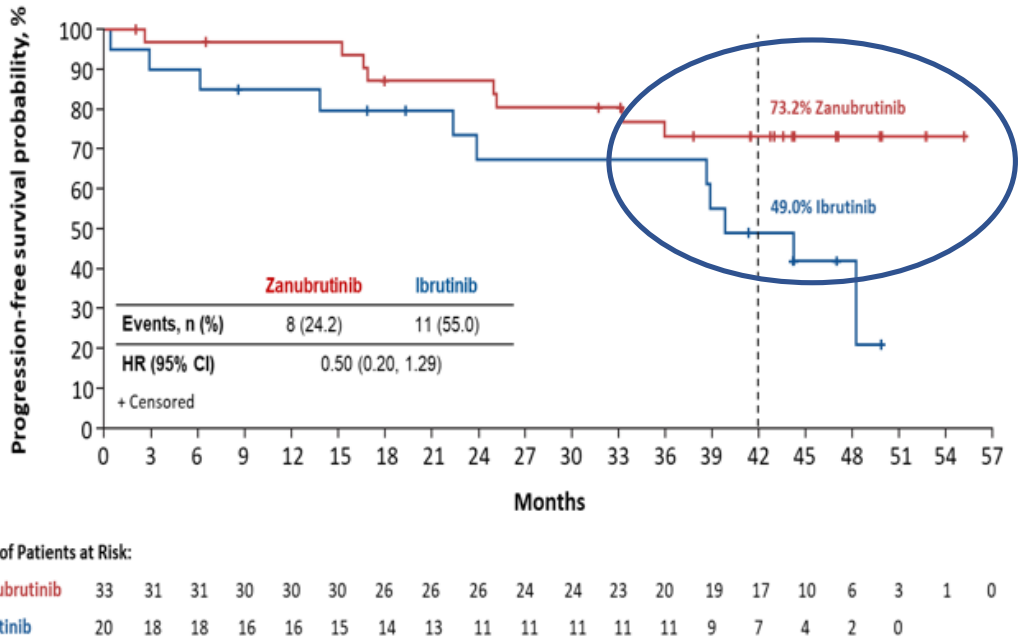
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

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)
Time to MR, median (months)	6.6	3.4	2.8	2.8
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}

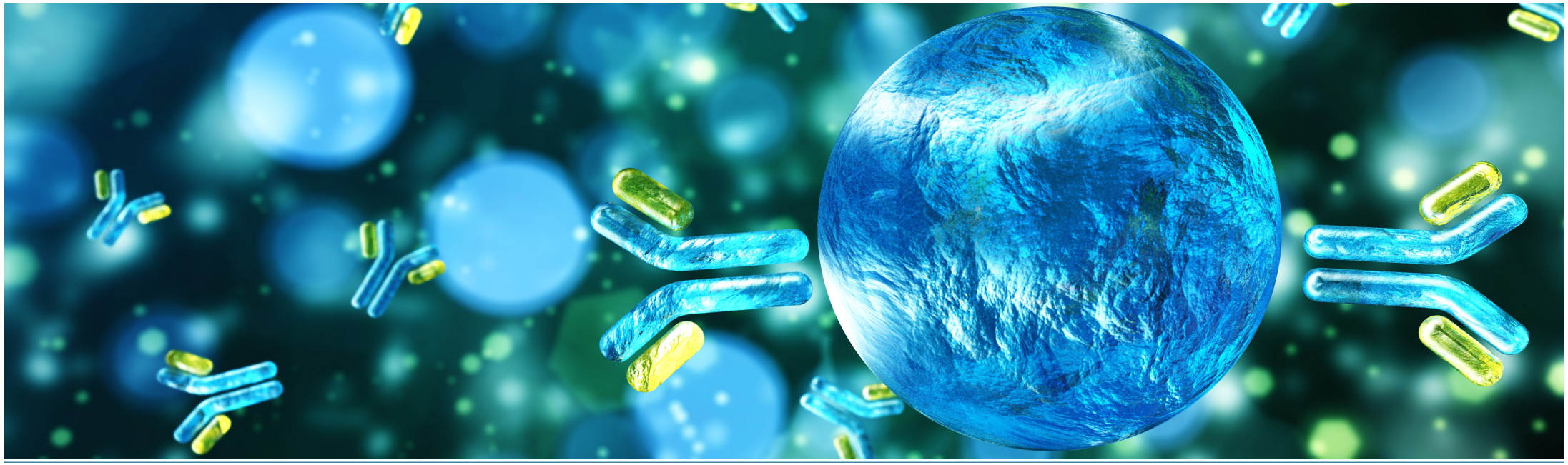


Tam et al, Blood Adv. 2024; Dimopoulos et al JCO 2023

ASPEN STUDY Adverse Events of Interest (Cohort 1)

AEs,[a] n (%)	Any grade		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)

Dimopoulos et al, JCO 2023



Do we give BTK-inhibitors or chemoimmunotherapy to treatment-naïve patients?

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

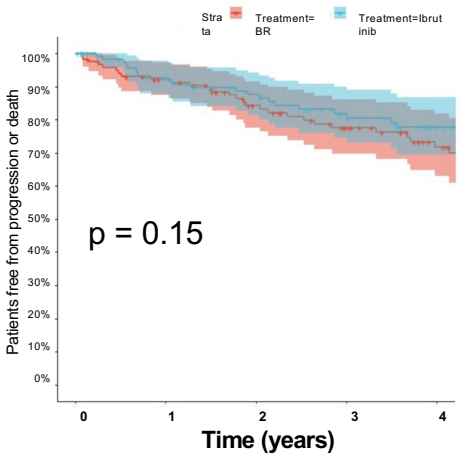
Jithma P. Abeykoon[1], Shaji Kumar[1], Jorge J. Castillo[2], Shirley D'sa[3], Efstathios Kastritis[4], Eric Durot[5], Encarl Uppal[3], Morel Pierre[6], Jonas Paludo[1], Reema Tawfiq[1], Shayna R Sarosiek[7], Olabisi Ogunbiyi[8], Pascale Cornillet-Lefebvre[9], Robert A. Kyle[1], Alain Delmer[10], Morie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

MAYO CLINIC

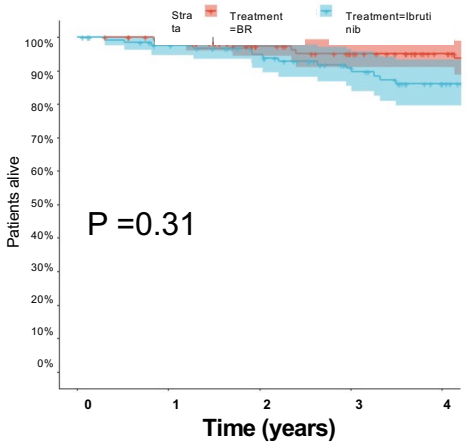
CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

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

Progression-free survival



Overall survival



- Bivariate analysis of age matched patients who received either Benda-R or Ibrutinib (N=246)
- 77% of Benda-R patients received 6 cycles
- MYD88 WT patients excluded
- Median Follow-Up: 4.2 years

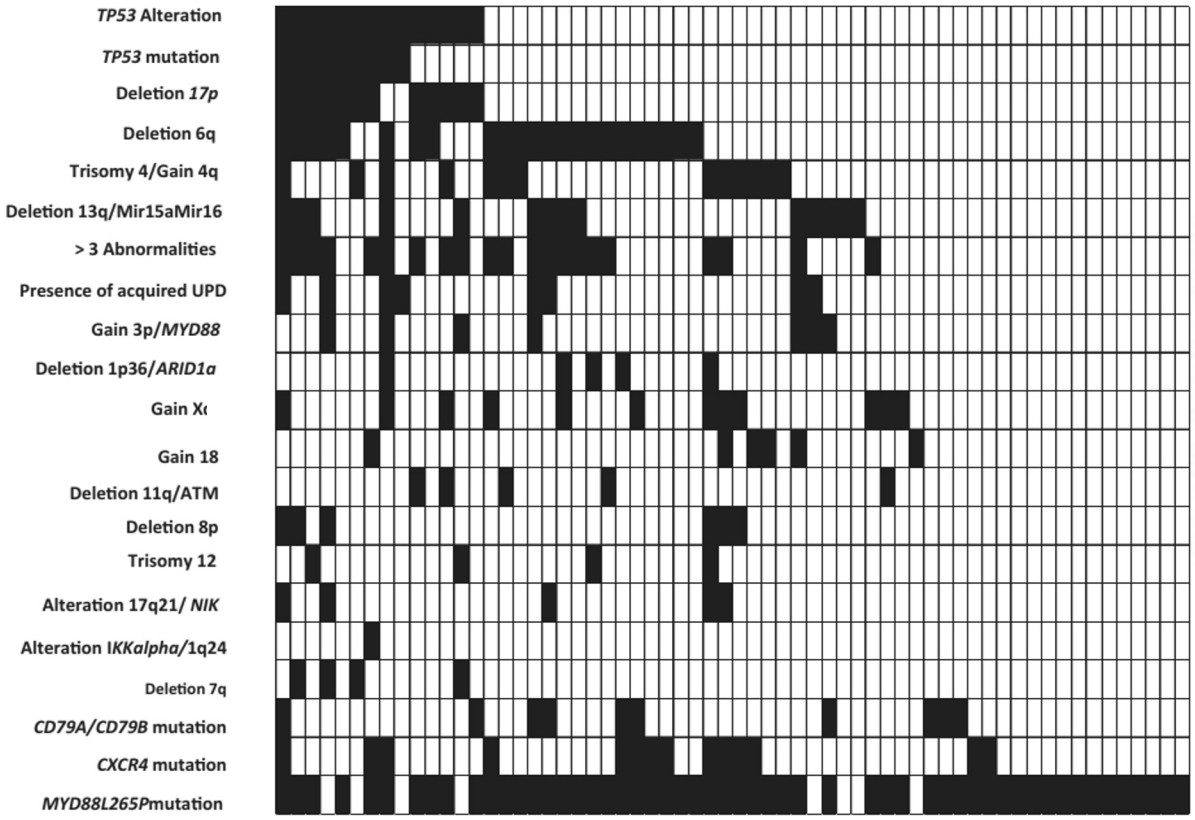
Abeykoon et al, Updated IWWM-11, 2022.

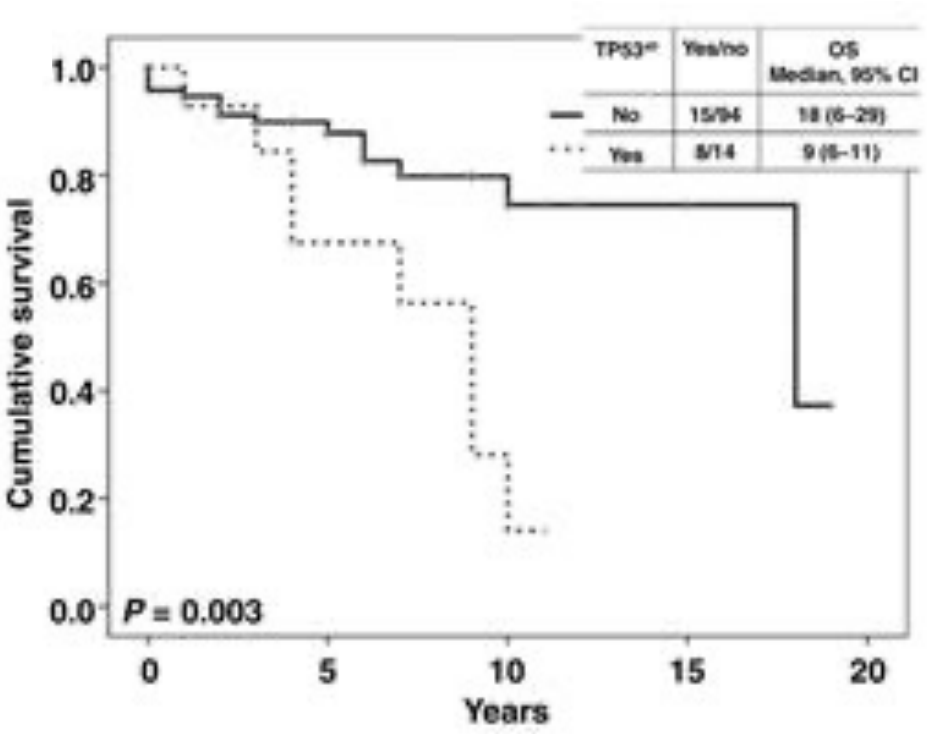
TP53 Alterations in Biomarker Analysis of ASPEN Study

	N=	Total $TP53^{Mut}$	Treatment Naïve $TP53^{Mut}$	Previously Treated $TP53^{Mut}$
All Patients	210	52/210 (24.8%)	7/41 (17.1%)	46/169 (27.2%)
$MYD88^{Mut}$	190	48/190 (25.2%)	6/36 (16.6%)	42/154 (27.3%)
$MYD88^{WT}$	20	5/20 (25%)	1/5 (20%)	4/15 (26.7%)

Tam et al, Blood Adv. 2024

Impact of TP53 Alterations on Survival in Waldenstrom's Macroglobulinemia





Poulain et al, CCR 2017

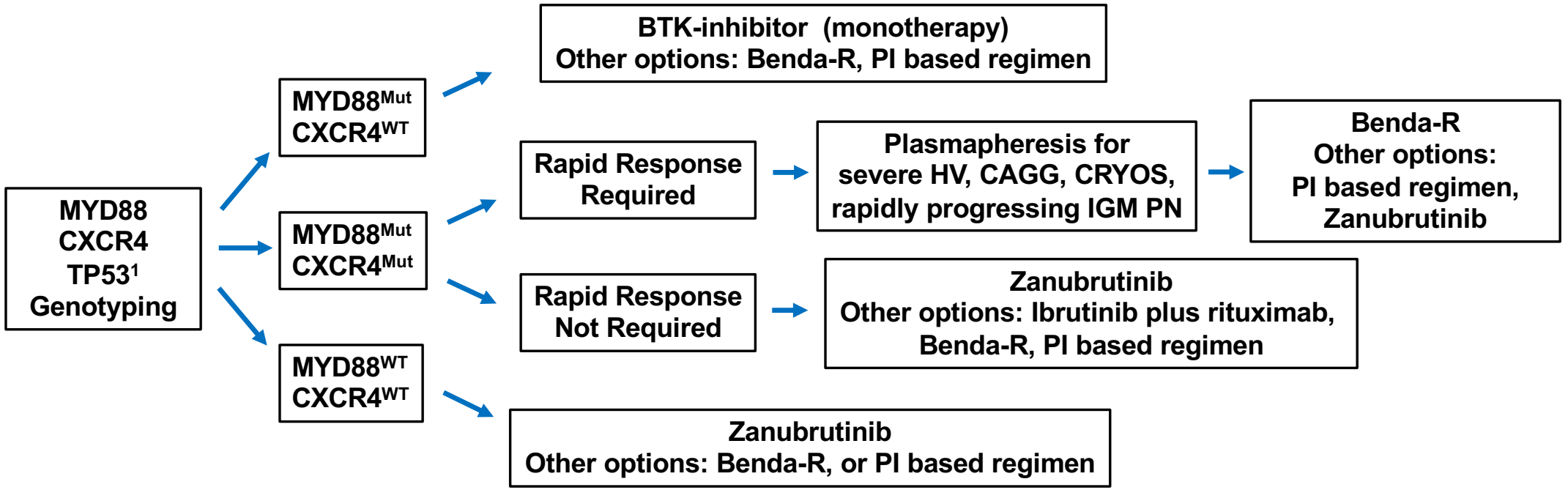
Outcomes in ASPEN Study for TP53 Wild-Type vs. TP53 Mutated Patients

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)†
Major Response, 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 Major Response (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				
Event-free rate at 42 months, %	72.1	**57.9**	84.6	**62.0**
P value[b]	-	**0.027**	-	0.120

- Compared to ibrutinib, zanubrutinib demonstrated a more favorable VGPR+CR rate (*P* value[c] < 0.05) and trend for major response rate (*P* value[c] = 0.11) in *TP53*^{MUT}

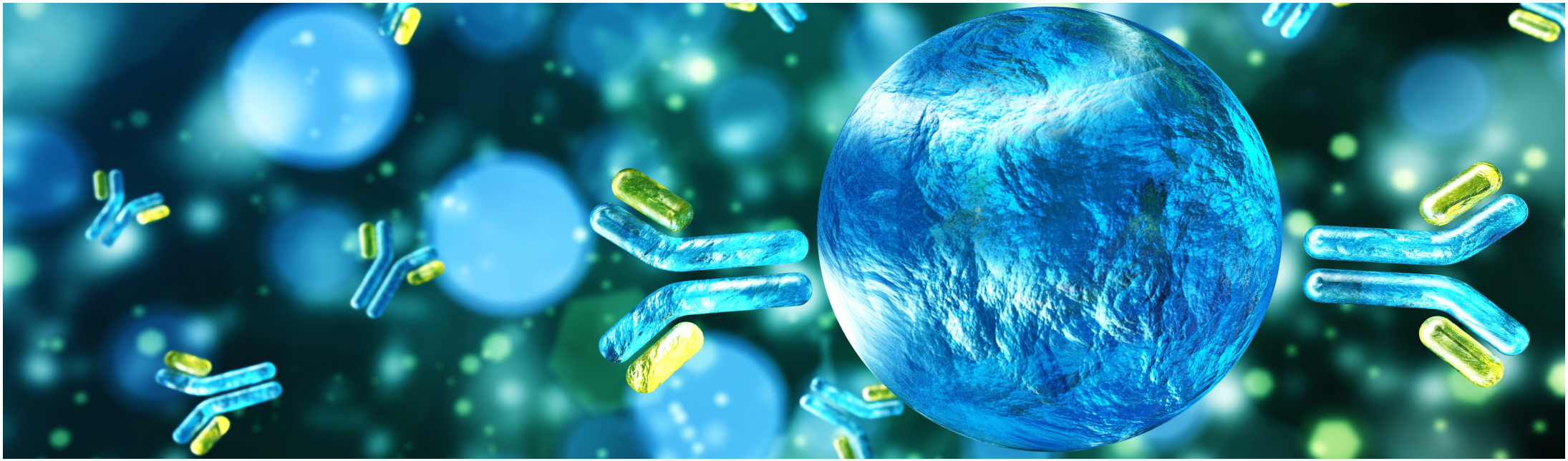
Tam et al, Blood Adv. 2024

Treatment Algorithm for Symptomatic Treatment-Naïve Waldenstrom Macroglobulinemia



1. Zanubrutinib is recommended for TP53 Alt WM Patients

Treon et al, How I Treat WM, Blood 2024



How do we manage BTK-inhibitor intolerant or resistant disease?

N=385

Dose Reductions Related to Adverse Effects in Ibrutinib Treated WM Patients

- **95/358 (25%) required at least 1 dose reduction for intolerance**

  -Median time to 1st dose reduction 7.3 (0.5-75 months)

  -26/95 (27%) continued to be symptomatic after dose-reduction

  -10/26 of dose-reduced patients required second dose-reduction at a median of 23 (3-75 months)

  -Median age 71 vs 66 years for dose reduced patients

- **Hematological responses were maintained or improved in 73% and 21% of dose reduced patients within 1 year of follow-up.**

Sarosiek et al, BJH 2023

Zanubrutinib in Previously Treated B-Cell Malignancies Intolerant to Ibrutinib/Acalabrutinib

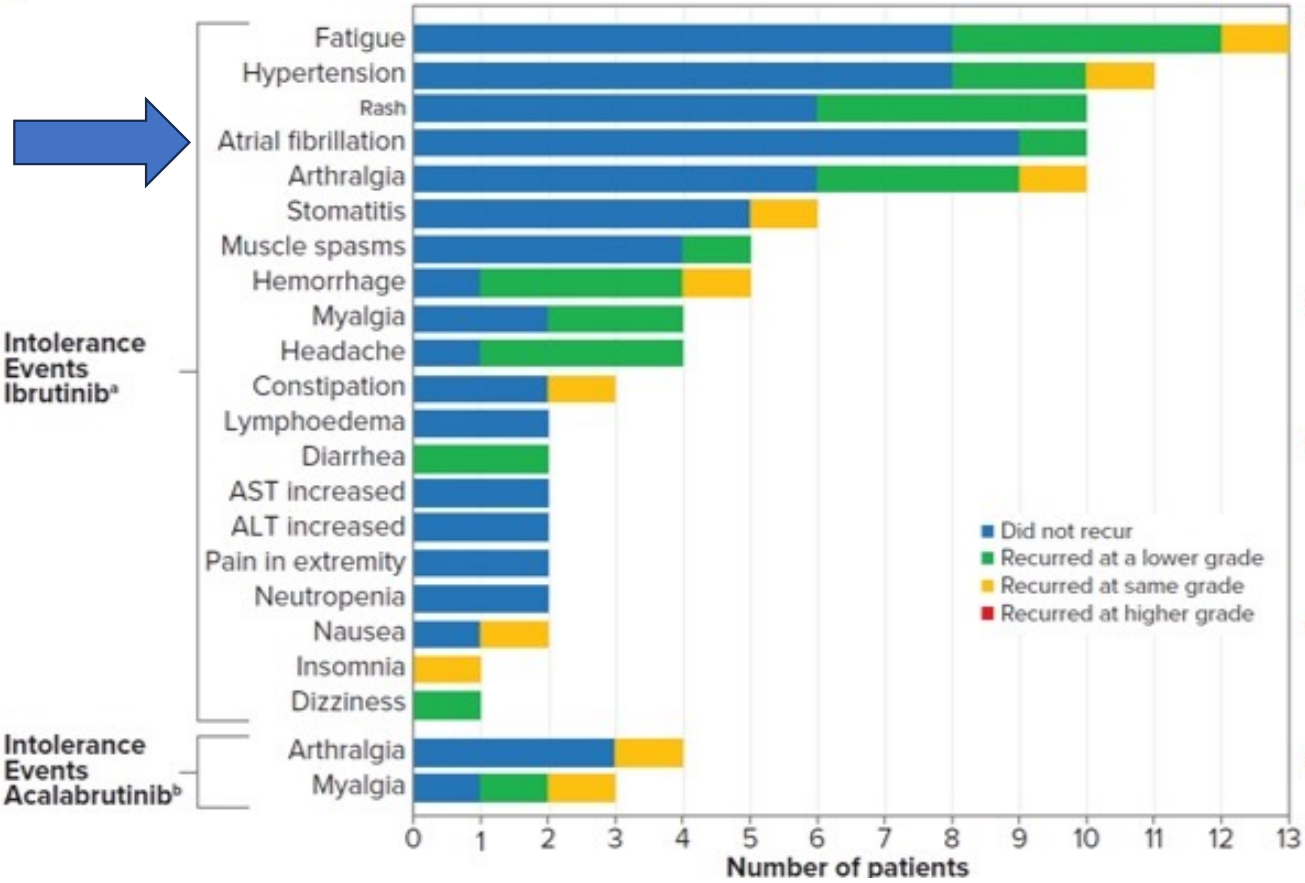
Shadman et al, Lacet Haematol. 2023

Characteristics	Cohort 1 (prior ibrutinib) (n=57)	Cohort 2 (prior acalabrutinib +/- ibrutinib) (n=10)	Total (N=67)
Indication, n (%)			
CLL	38 (66.7)	5 (50.0)	43 (64.2)
WM	9 (15.8)	2 (20.0)	11 (16.4)
SLL	6 (10.5)	1 (10.0	7 (10.4)
MCL	2 (3.5)	1 (10.0)	3 (4.5)
MZL	2 (3.5)	1 (10.0)	3 (4.5)
Age, median (range), year	71.0 (49-91)	73.5 (65-83)	71.0 (49-91)
Male, n (%)	30 (52.6)	6 (60.0)	36 (53.7)
ECOG PS 0, n (%)	33 (57.9)	4 (40.0)	37 (55.2)
No. of prior therapy regimens, median (range)	1.0 (1-12)	2.5 (1-5)	1.0 (1-12)
Prior BTKi, n (%)	57 (100)	10 (100)	67 (100)
Ibrutinib monotherapy	49 (86.0)	6 (60.0)[a]	55 (82.1)
Ibrutinib combination therapy	9 (15.8)[b]	0	9 (13.4)
Acalabrutinib monotherapy	0	10 (100)	10 (14.9)
Time on prior BTKi,[c] median (range), months	10.61 (1.1-73.7)	3.33 (0.5-26.9)	—
On-study zanubrutinib dosing regimen			
160 mg bid	35 (61.4)	7 (70.0)	42 (62.7)
320 mg qd	22 (38.6)	3 (30.0)	25 (37.3)

Data Cutoff: 8 September 2021

a. Six patients had both prior ibrutinib and acalabrutinib therapies. b. One patient received ibrutinib combination therapy followed by ibrutinib monotherapy. c. Cumulative ibrutinib exposure for cohort 1 and acalabrutinib for cohort 2.

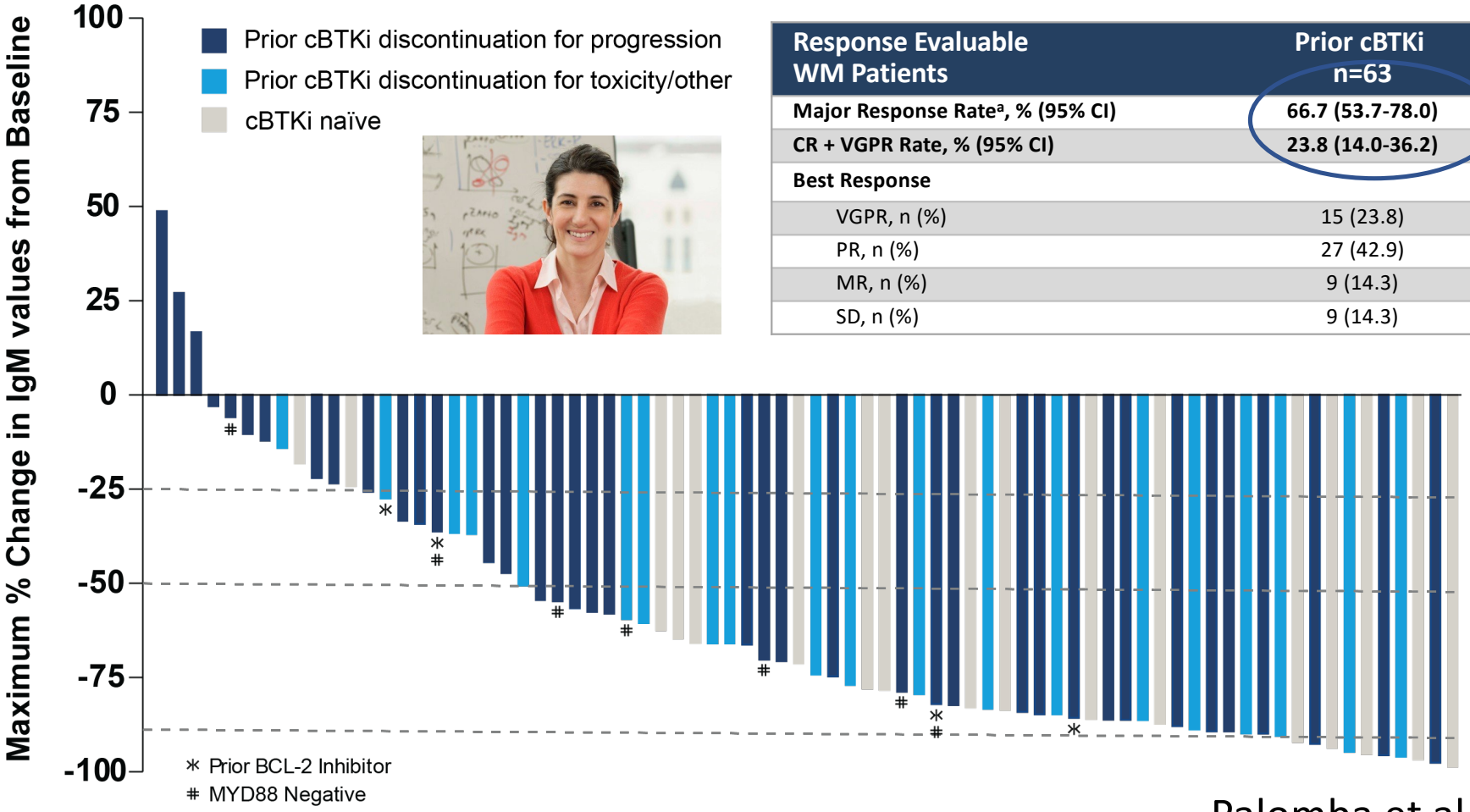
Recurrence of Adverse Events following Switchover to Zanubrutinib



- 34/57 (59.6%) of patients who took ibrutinib and 7/10 (70.0%) of patients who took acalabrutinib did not have recurrence of any intolerance event
- No ibrutinib or acalabrutinib intolerance events recurred at a higher severity
- 81/115 (70.4%) ibrutinib intolerance events and 15/18 (83.3%) acalabrutinib intolerance events did not recur
- 25/38 (65.8%) grade 3 ibrutinib intolerance events and 3/4 (75.0%) grade 3 acalabrutinib intolerance events did not recur while on zanubrutinib
- All grade 4 intolerance events (neutropenia [n=2], ALT increase [n=1], AST increase [n=1]) did not recur on zanubrutinib
- 1 patient (1.5%) discontinued zanubrutinib due to recurrence of a prior intolerant event (myalgia; acalabrutinib)

Shadman et al, Lancet Haematol 2023

Non-covalent BTK-I Pirtobrutinib Efficacy in WM Patients



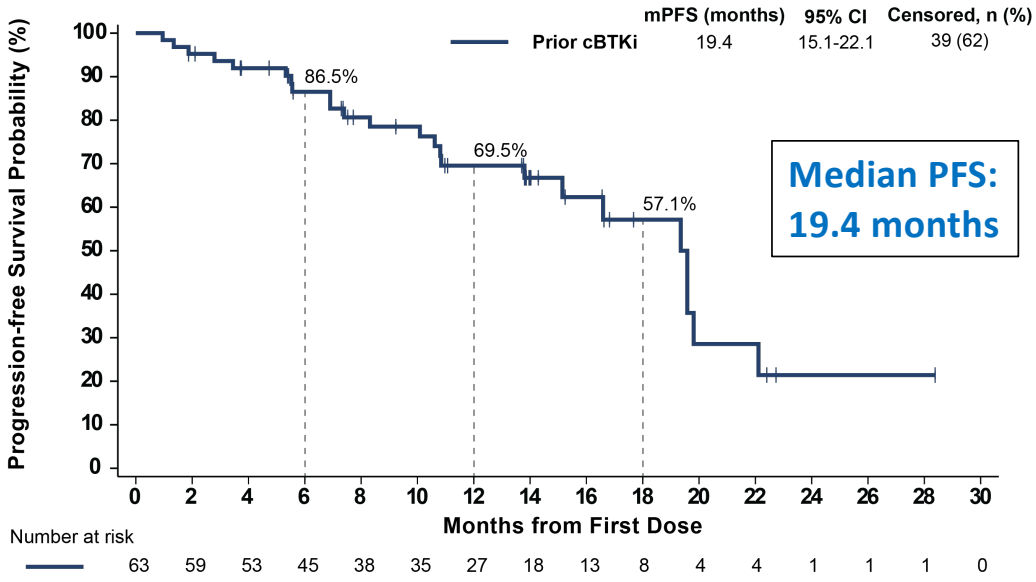
Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	**66.7 (53.7-78.0)**	**88.2 (63.6-98.5)**
CR + VGPR Rate, % (95% CI)	**23.8 (14.0-36.2)**	**29.4 (10.3-56.0)**
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)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

Palomba et al, ASH 2022

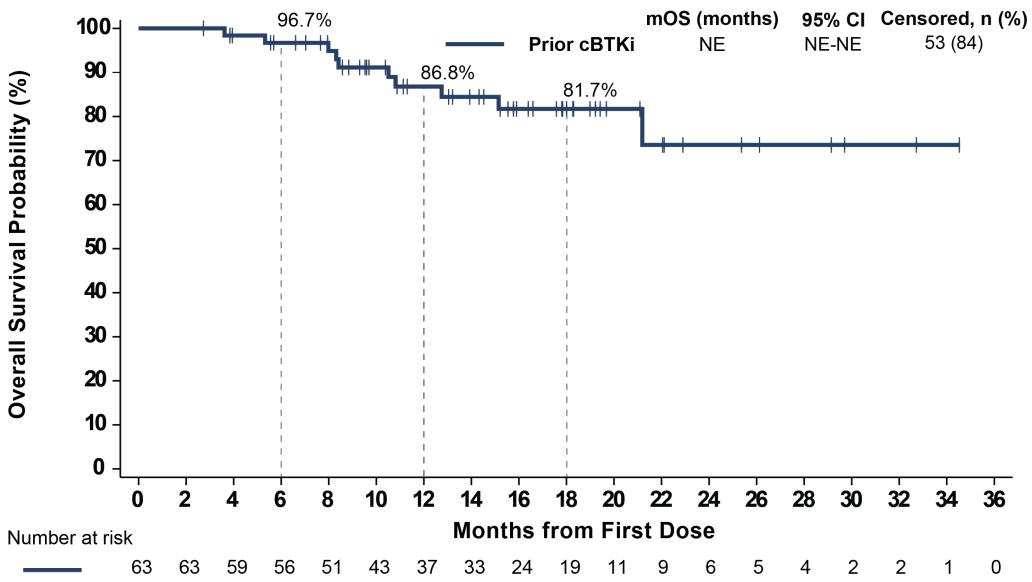
Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding IgM is in normal range or has at least 90% reduction from baseline. [a]Major response includes subjects with a best response of CR, VGPR, or PR. Total % may be different than the sum of the individual components due to rounding.

Pirtobrutinib in WM: PFS and Overall Survival in Prior cBTKi Patients

Progression-Free Survival



Overall Survival



- **Median follow-up for PFS and OS in patients receiving prior cBTKi was 14 and 16 mos, respectively.**
- **55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib.**

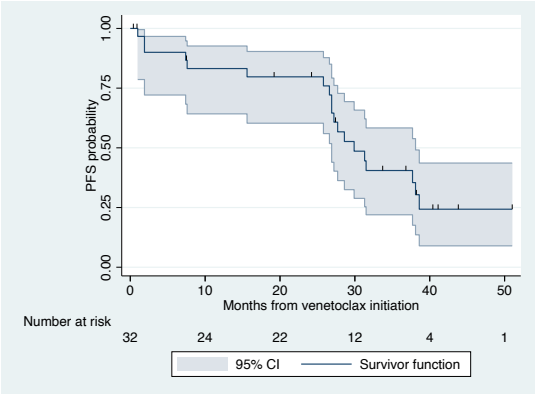
Palomba et al, ASH 2022

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

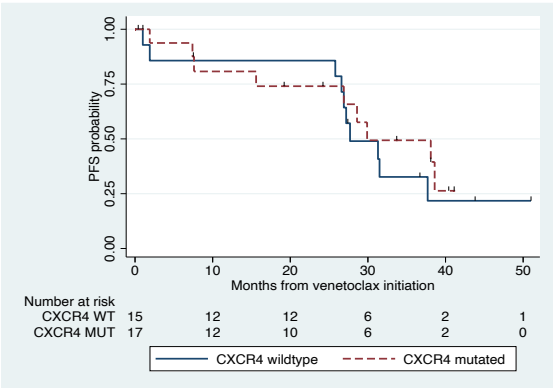
Venetoclax for Previously Treated WM

Dose escalation to 800 mg/day, 2 years treatment

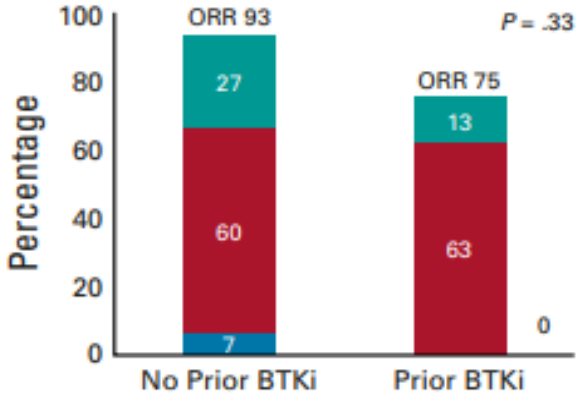
ORR 84%; Major RR 81%
Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

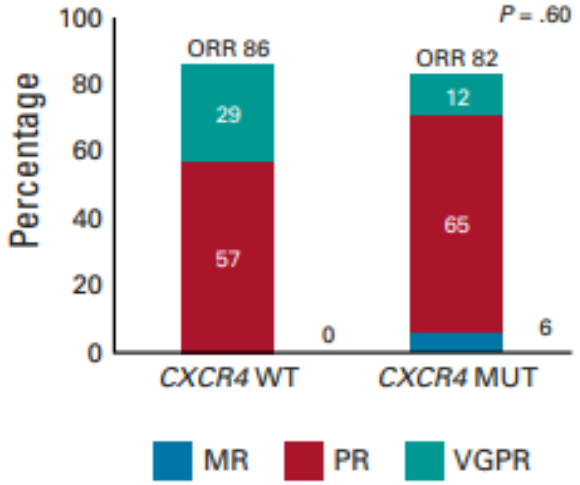


PFS for All Pts



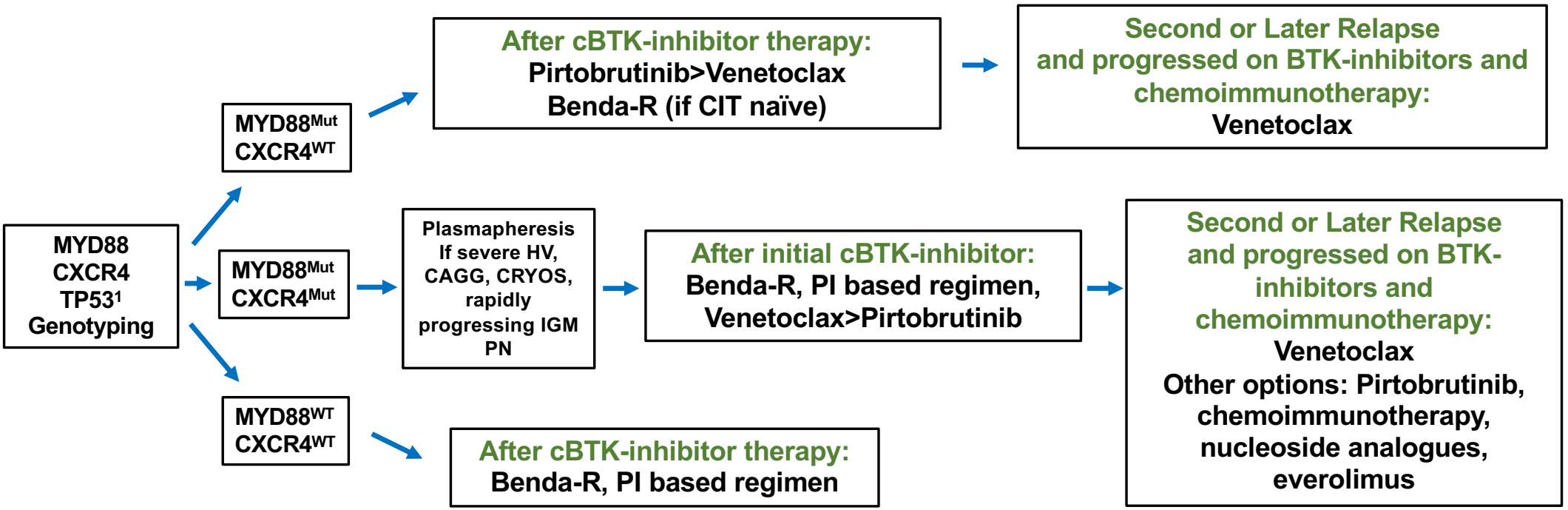
PFS by CXCR4 Mut Status





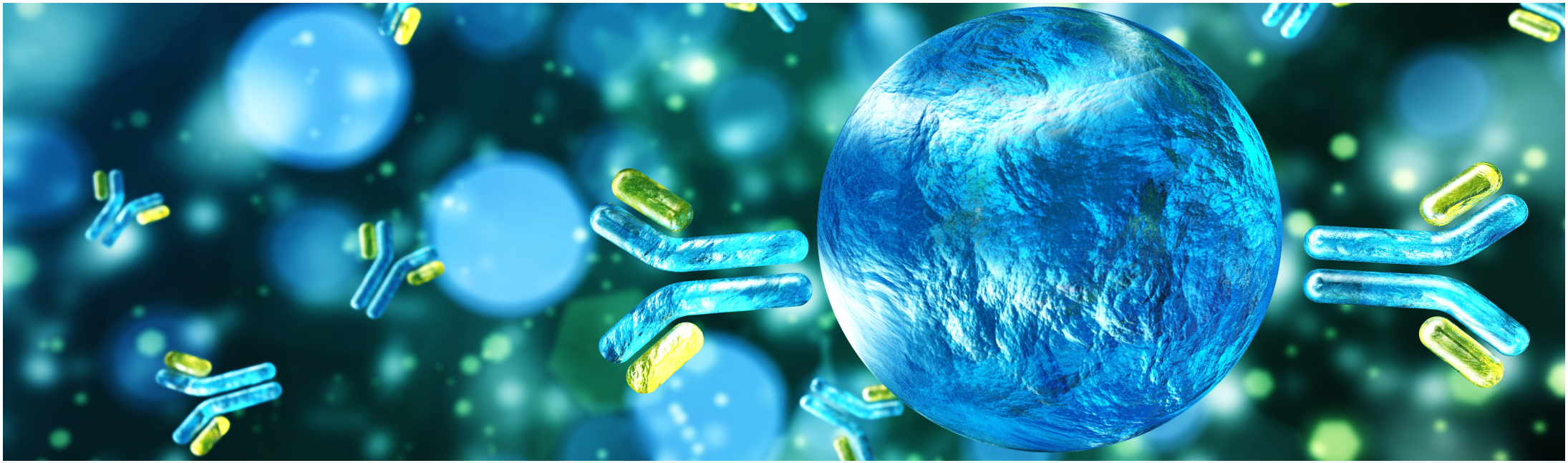
Castillo et al, JCO 2021

Treatment Algorithm for Symptomatic Previously Treated Waldenstrom Macroglobulinemia



1. Zanubrutinib is recommended for TP53 Alt WM Patients

Adapted from Treon et al, Blood 2024



What does the future hold for WM therapy?

A Multi-Center, Open-Label, Single-Arm Phase II Trial of Bendamustine, Rituximab and Acalabrutinib in Treatment Naïve WM - BRAWM

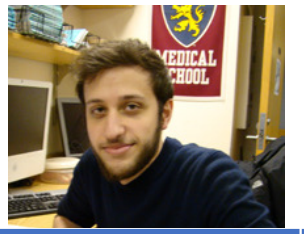
- N=38 (May 2023).
- Major Response Rate 100%; VGPR 67% for 24 pts who reached cycle 7.
- 14/38 patients (37%) experienced grade 3/4 toxicities during combination treatment, 3 febrile neutropenias; 9 non-febrile neutropenias.

BRAWM

Berinstein et al, ICML 2023

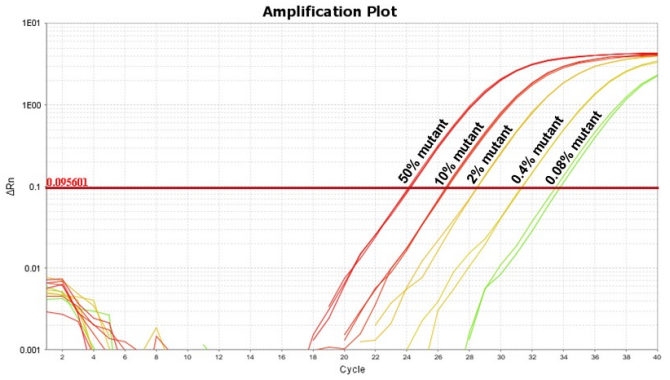
Sunnybrook RESEARCH INSTITUTE

CLINICAL TRIALS FOR QUANTITATIVE MYD88^{L265P} RESPONSE ASSESSMENT



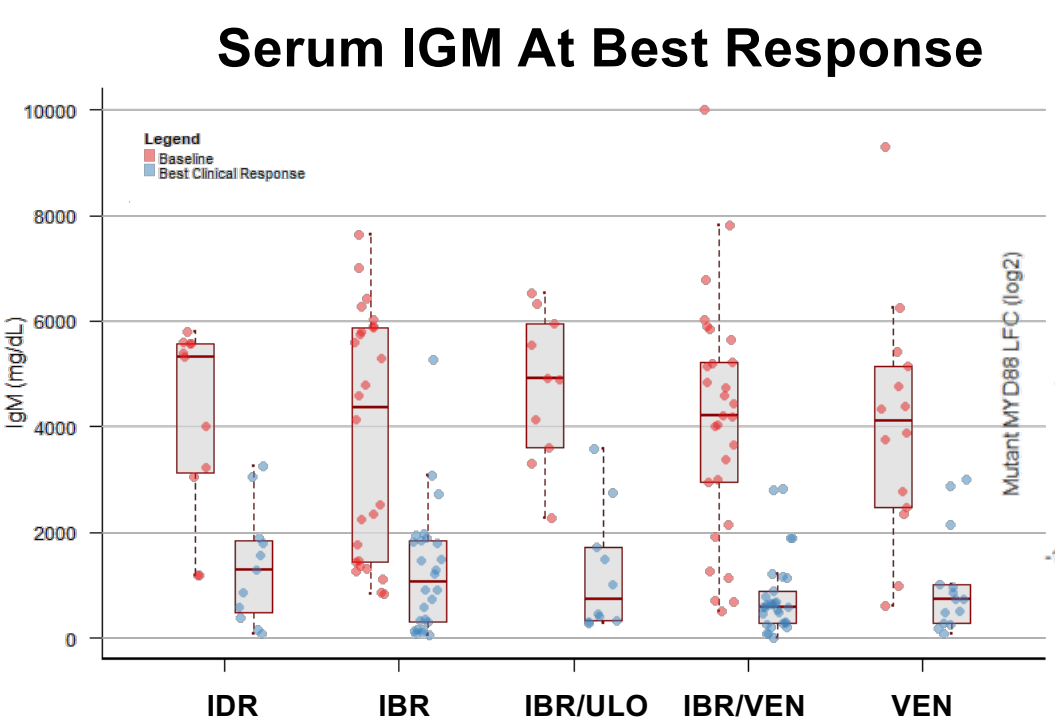
Trial	Therapy	Mechanism	Cohort	N=
NCT02300437	Ixazomib, Dex, Rituximab (IDR)	Proteasome Inhibitor and CD20 MoAb	Untreated	15
NCT02604511	Ibrutinib (IBR)	BTK Inhibitor	Untreated	26
NCT02677324	Venetoclax (VEN)	BCL2 Inhibitor	Previously Treated	14
NCT03225716	Ibrutinib, Ulocuplumab	BTK Inhibitor and CXCR4 MoAb	Untreated	10
NCT04273139	Ibrutinib, Venetoclax	BTK Inhibitor and BCL2 Inhibitor	Untreated	31

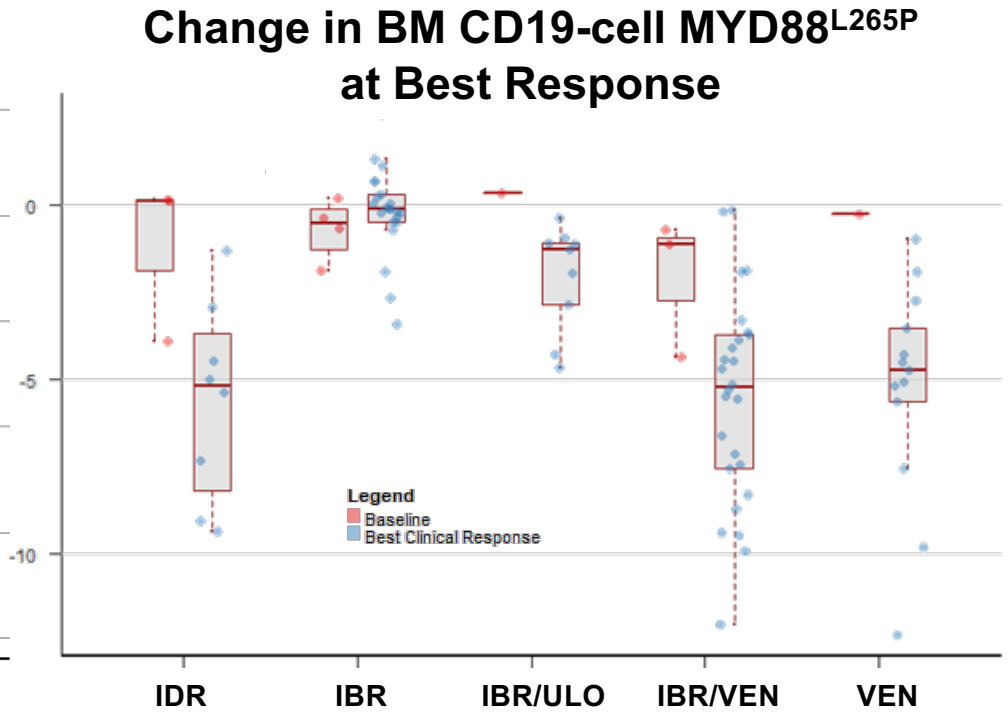
- ***Available*** **bone marrow and matched peripheral blood DNA from CD19-selected cells from 96 WM patients who participated in 5 clinical trials.**
- **Samples were taken at baseline, 6 and 12 months, and best response.**
- **A standard curve was made by serially diluting DNA from heterozygous MYD88 L265P mutated BCWM.1 WM cells with DNA from MYD88 wild-type OCI-Ly19 cells.**
- ***Standard curve was used to convert dCT values to percentage of MYD88 L265P for each sample. Assay sensitivity was 0.08%***



Tsakmaklis et al, ASH 2023

RESPONSE BY SERIAL SERUM IGM and qMYD88 ASSESSMENTS AT BEST RESPONSE





IDR, Ixazomib, Dex, Rit; IBR, Ibrutinib; ULO, Ulocuplumab; VEN, Venetoclax

Castillo et al, Blood Adv 2020; Treon et al, Blood 2021; Castillo et al, Leukemia 2022; Castillo et al, JCO 2022; Castillo et al, Blood 2023.

Efficacy of Sonrotoclax as Monotherapy and Zanubrutinib

BGB-11417-101 – NHL or WM

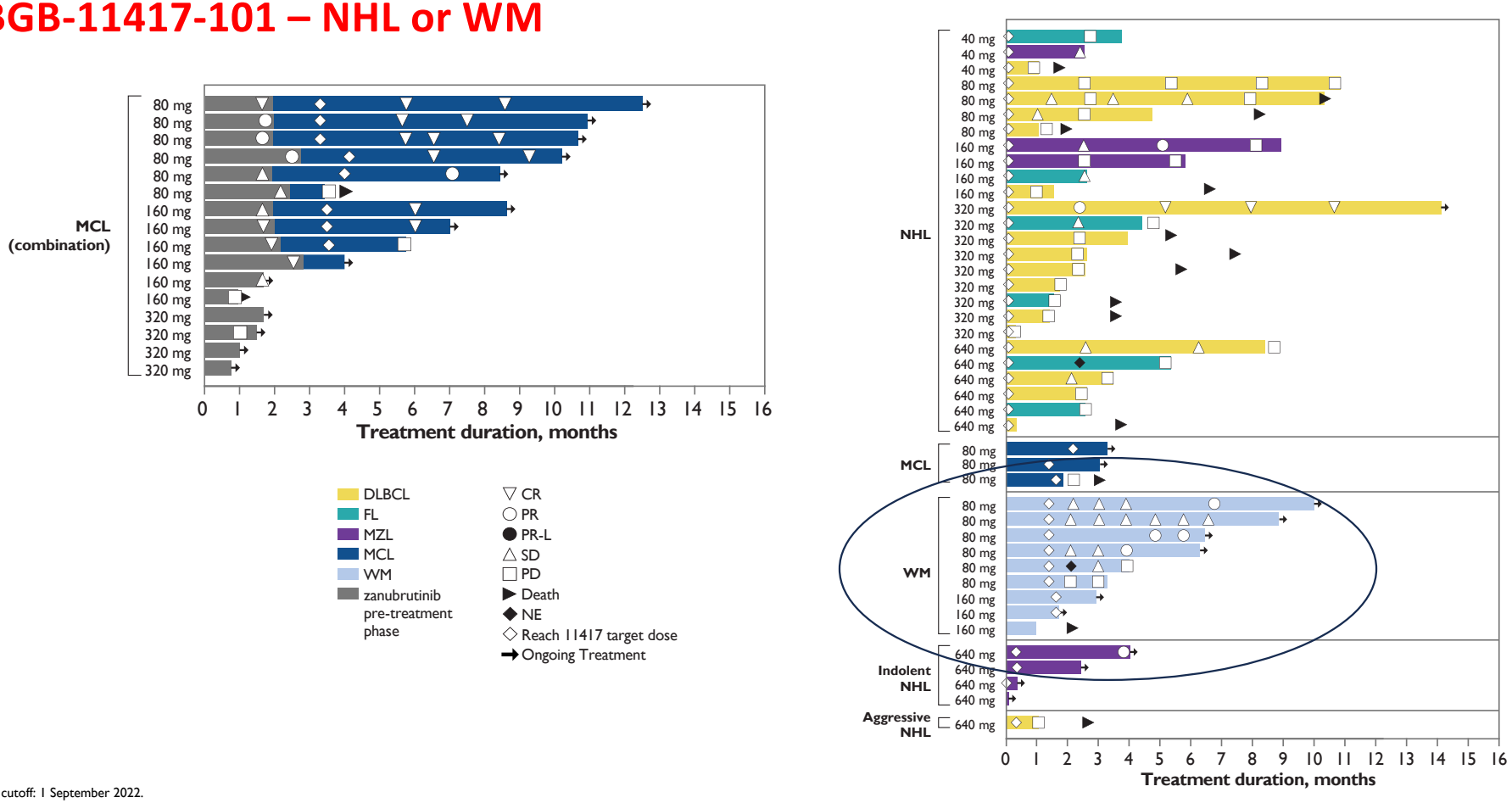
Response, n (%)	BGB-11417 monotherapy (N=43)		BGB-11417 + zanubrutinib combination (N=16)
	R/R NHL, DLBCL, MZL, FL, tFL, MCL (N=34)[a]	R/R WM (N=9)[b]	R/R MCL (N=16)[c]
Treated with BGB-11417	34	9	10
Efficacy evaluable	29[d]	7	9
Best overall response[e]	3 (10)	3 (43)	7 (78)
CR	1 (3)	0	6 (67)
PR	2 (7)	3 (43)	1 (14)
SD	7 (24)	2 (29)	0
PD	18 (62)	1 (14)	2 (22)
Discontinued before assessment	1 (3)	1 (14)	0
Follow-up, months (range)	7 (0.1-29)	6 (2-10)	5 (1-13)

Major RR 86%

Data cutoff: 1 September 2022.
aAt 40 mg: n=3; 80 mg: n=7; 160 mg: n=4; 320 mg: n=9; 640 mg: n=11. bAt 80mg: n=6; 160 mg: n=3. cAt 80 mg: n=12; 160 mg: n=4. dOne patient with MCL on monotherapy MCL was efficacy evaluable. ePR or better.
CR=complete response, DLBCL=diffuse large B-cell lymphoma, FL=follicular lymphoma, MCL=mantle cell lymphoma, NHL=non-Hodgkin's lymphoma, PD=progressive disease, PR=partial response, R/R=relapsed/refractory, SD=stable disease, tFL=transformed follicular lymphoma,
Soumerai J et al. Poster presented at ASH 2022 Abstract 4201

Sonrotoclax: Duration of Treatment and Best Response[a]

BGB-11417-101 – NHL or WM



Data cutoff: 1 September 2022.
aSafety analysis set.
All received treatments were monotherapy except patients in part 3B, which were combo MCL
CR=complete response, DLBCL=diffuse large B-cell lymphoma, FL=follicular lymphoma, MCL=mantle cell lymphoma, MZL=marginal zone lymphoma, NHL=non-Hodgkin's lymphoma, PD=progressive disease, PR=partial response, PR-L=partial response with lymphocytosis, SD=stable disease, WM=Waldenström's macroglobulinemia,
Soumerai J et al. Poster presented at ASH 2022 Abstract 4201

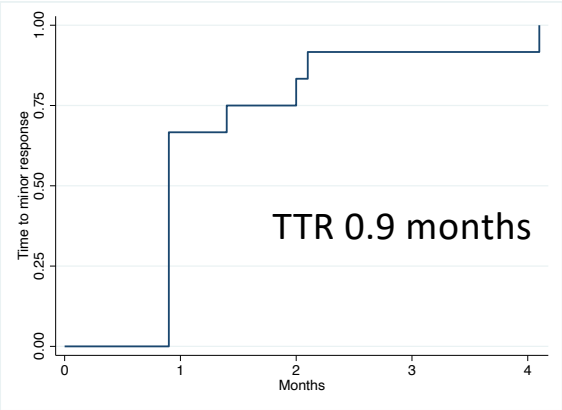
Pirtobrutinib and Venetoclax Study in Relapsed/Refractory WM

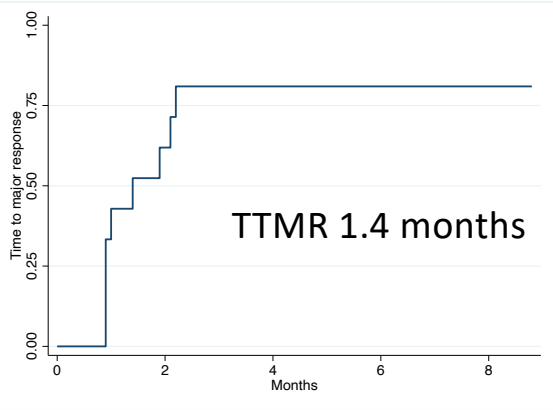
Characteristic	Number/Median	Percentage/Range
Median age	66	57-75
Female sex	7	50%
N previous lines	2	1-3
Previous R-regimens	11	79%
Previous BTKi	7	50%
Previous R-reg + BTKi	4	29%
Median IgM	2234	551-7249
Median hemoglobin	9	6.6-11.5
Median platelet count	187	60-279
MYD88 L265P	12	86%
CXCR4 MUT	5	36%
TP53 MUT	1	7%
Median BM involvement	80%	20-90%

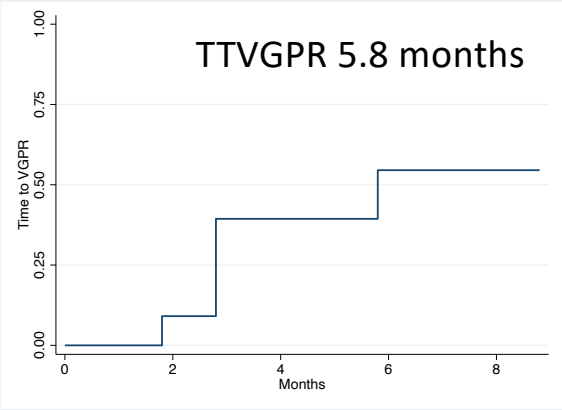
NCT05734495

Pirtobrutinib and Venetoclax Study in Relapsed/Refractory WM

Responses	
ORR	100%
Major RR	75%
VGPR	42%







Data for 12 Evaluable Patients; Median follow-up 8.4 months

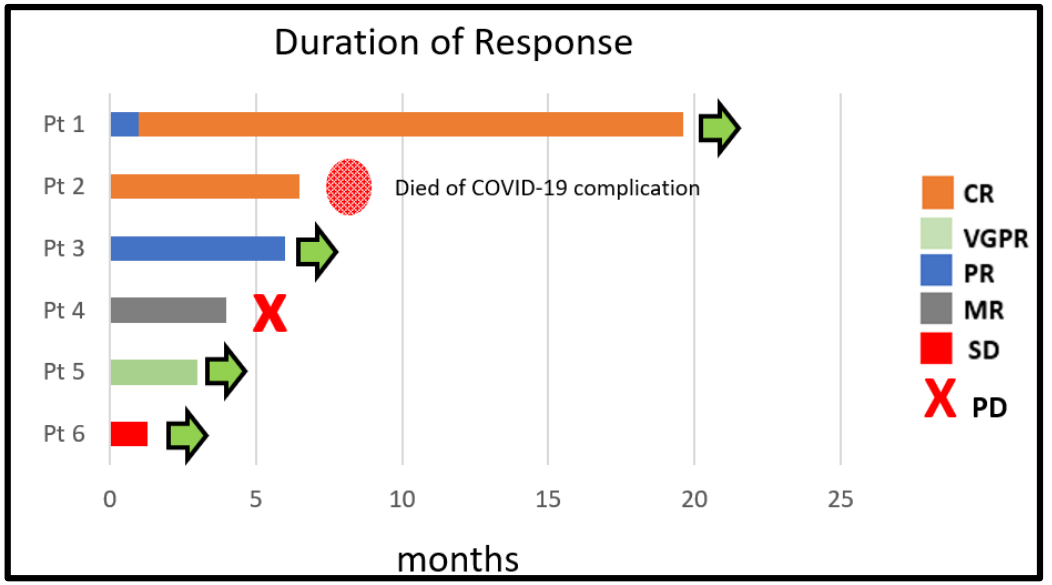
CD20 CAR-T Cell Therapy

Mazyar Shadman

Patient characteristics (N=6)	
Age, median (range)	69 (51-79)
Female, n (%)	2 (33%)
Prior lines of therapy, median (range)	7.5 (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%



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

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

†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.

Targeting HCK Signaling in WM

LEUKEMIA & LYMPHOMA SOCIETY®

IWMF International Waldenstrom's Macroglobulinemia Foundation

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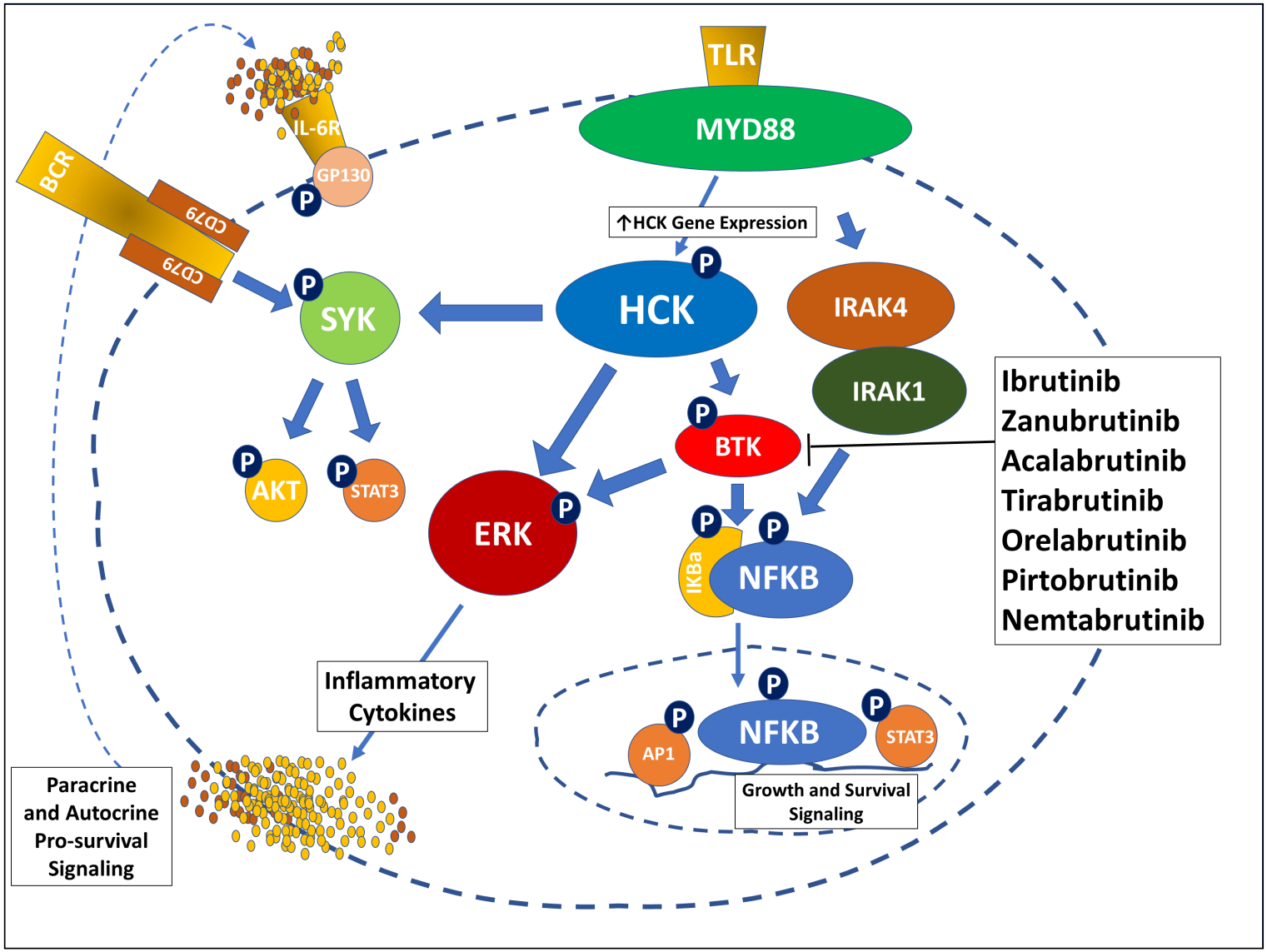


KIN-8194 is a highly potent HCK/BTK Kinase Inhibitor

blood Regular Article

LYMPHOID NEOPLASIA

The HCK/BTK inhibitor KIN-8194 is active in MYD88-driven lymphomas and overcomes mutated BTK^{Cys481} ibrutinib resistance

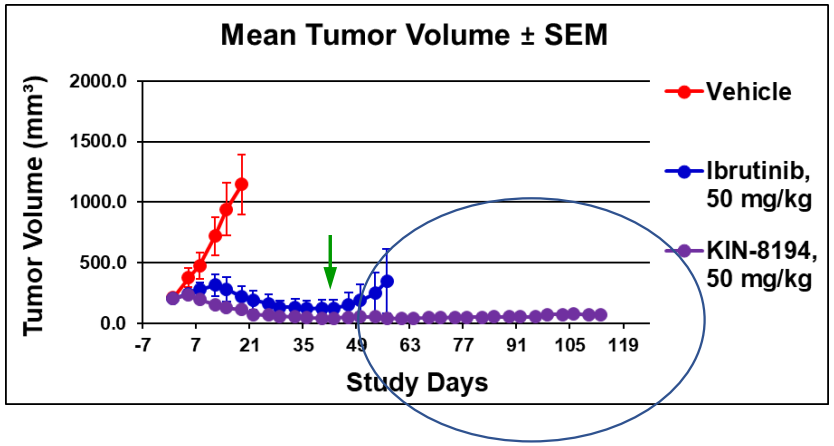
Guang Yang,[1,2] Jinhua Wang,[3] Li Tan,[3] Manit Munshi,[1] Xia Liu,[1] Amanda Kofides,[1] Jiaji G. Chen,[1] Nicholas Tsakmaklis,[1] Maria G. Demos,[1] Maria Luisa Guerrera,[1] Lian Xu,[1] Zachary R. Hunter,[1,2] Jinwei Che,[3] Christopher J. Patterson,[1] Kirsten Meid,[1] Jorge J. Castillo,[1,2] Nikhil C. Munshi,[2,4] Kenneth C. Anderson,[2,4] Michael Cameron,[5] Sara J. Buhrlage,[3] Nathanael S. Gray,[3] and Steven P. Treon[1,2]

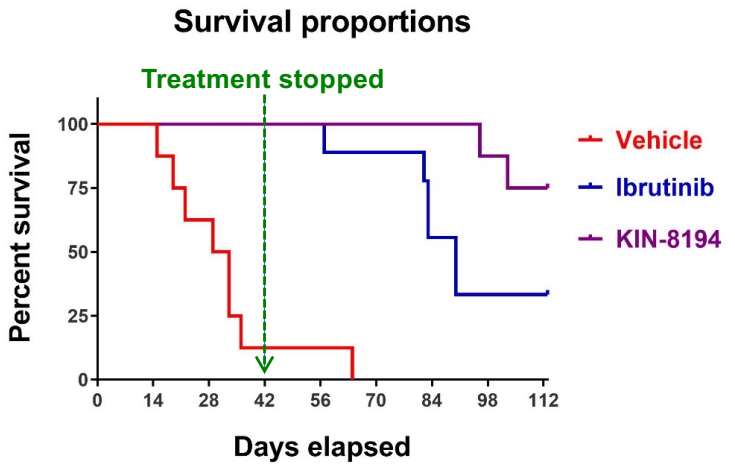
[1]Bing Center for Waldenstrom's Macroglobulinemia; [2]Department of Medical Oncology, Dana-Farber Cancer Institute and Harvard Medical School, Boston, MA; [3]Department of Cancer Biology, Dana-Farber Cancer Institute, and Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA; [4]Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Boston, MA; and [5]Department of Molecular Medicine, Scripps Research, La Jolla, CA

KEY POINTS

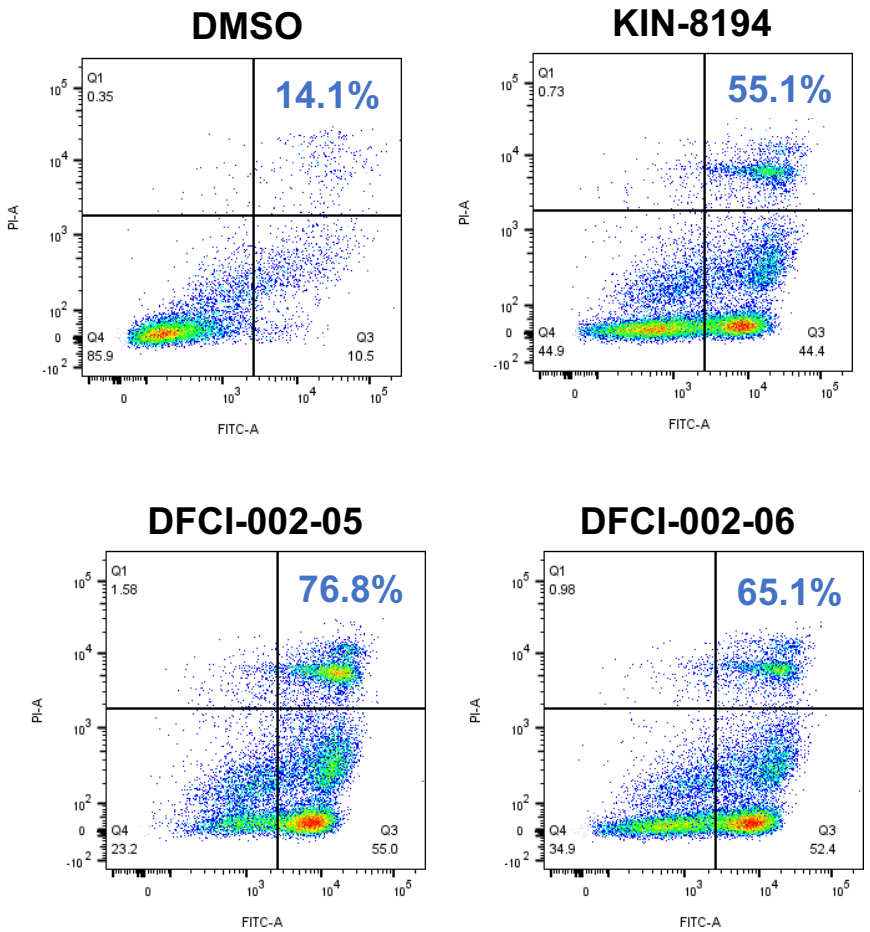
- KIN-8194 is a highly potent dual HCK and BTK inhibitor with superior antitumor activity over ibrutinib in MYD88-mutated B-cell lymphomas.
- KIN-8194 overcomes ibrutinib resistance with a survival benefit in TMD-8 ABC DLBCL xenografted mice and synergizes with venetoclax.

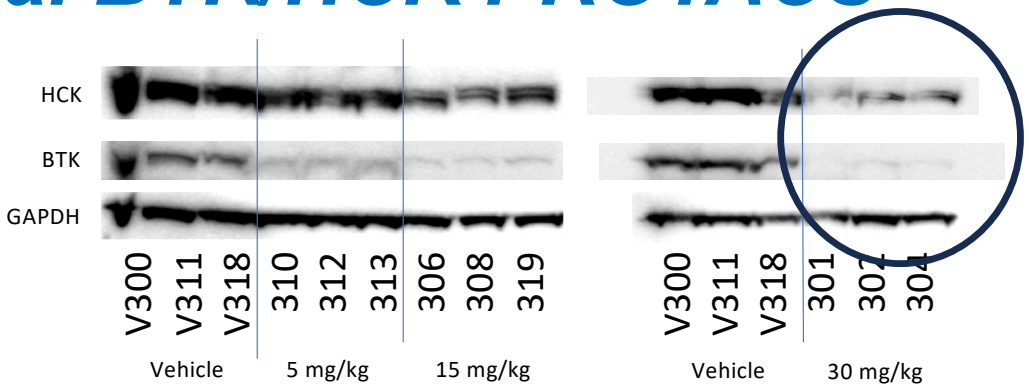
Activating mutations in MYD88 promote malignant cell growth and survival through hematopoietic cell kinase (HCK)–mediated activation of Bruton tyrosine kinase (BTK). Ibrutinib binds to BTK^{Cys481} and is active in B-cell malignancies driven by mutated MYD88. Mutations in BTK^{Cys481}, particularly BTK^{Cys481Ser}, are common in patients with acquired ibrutinib resistance. We therefore performed an extensive medicinal chemistry campaign and identified KIN-8194 as a novel dual inhibitor of HCK and BTK. KIN-8194 showed potent and selective in vitro killing of MYD88-mutated lymphoma cells, including ibrutinib-resistant BTK^{Cys481Ser}-expressing cells. KIN-8194 demonstrated excellent bioavailability and pharmacokinetic parameters, with good tolerance in rodent models at pharmacologically achievable and active doses. Pharmacodynamic studies showed sustained inhibition of HCK and BTK for 24 hours after single oral administration of KIN-8194 in an MYD88-mutated TMD-8 activated B-cell diffuse large B-cell lymphoma (ABC DLBCL) and BCWM.1 Waldenström macroglobulinemia (WM) xenografted mice with wild-type BTK (BTK^{WT})– or BTK^{Cys481Ser}-expressing tumors. KIN-8194 showed superior survival benefit over ibrutinib in both BTK^{WT}- and BTK^{Cys481Ser}-expressing TMD-8 DLBCL xenografted mice, including sustained complete responses of >12 weeks off treatment in mice with BTK^{WT}-expressing TMD-8 tumors. The BCL_2 inhibitor venetoclax enhanced the antitumor activity of KIN-8194 in BTK^{WT}- and BTK^{Cys481Ser}-expressing MYD88-mutated lymphoma cells and markedly reduced tumor growth and prolonged survival in mice with BTK^{Cys481Ser}-expressing TMD-8 tumors treated with both drugs. The findings highlight the feasibility of targeting HCK, a key driver of mutated MYD88 pro-survival signaling, and provide a framework for the advancement of KIN-8194 for human studies in B-cell malignancies driven by HCK and BTK.

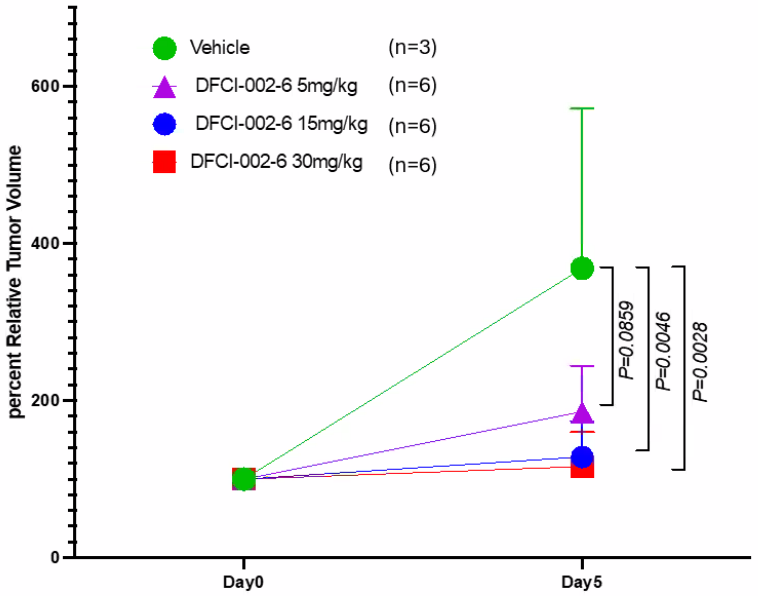




Development of Highly Potent and Bioavailable dual Bifunctional BTK/HCK PROTACS







Liu et al, ASH 2023

12th International Workshop on Waldenstrom's Macroglobulinemia

Prague, Czech Republic - October 17-19, 2024

www.waldenstromsworkshop.org


Thank you, Dr. Bruce Cheson for organizing IWWM-1 that fostered a growing global community devoted to finding a cure for WM!
INTERNATIONAL WORKSHOP ON WALDENSTRÖM'S MACROGLOBULINEMIA
Madrid
IWWM-11
2022
Closing Ceremonies of the 11th International Workshop on Waldenstrom's Macroglobulinemia
Madrid, Spain 2022