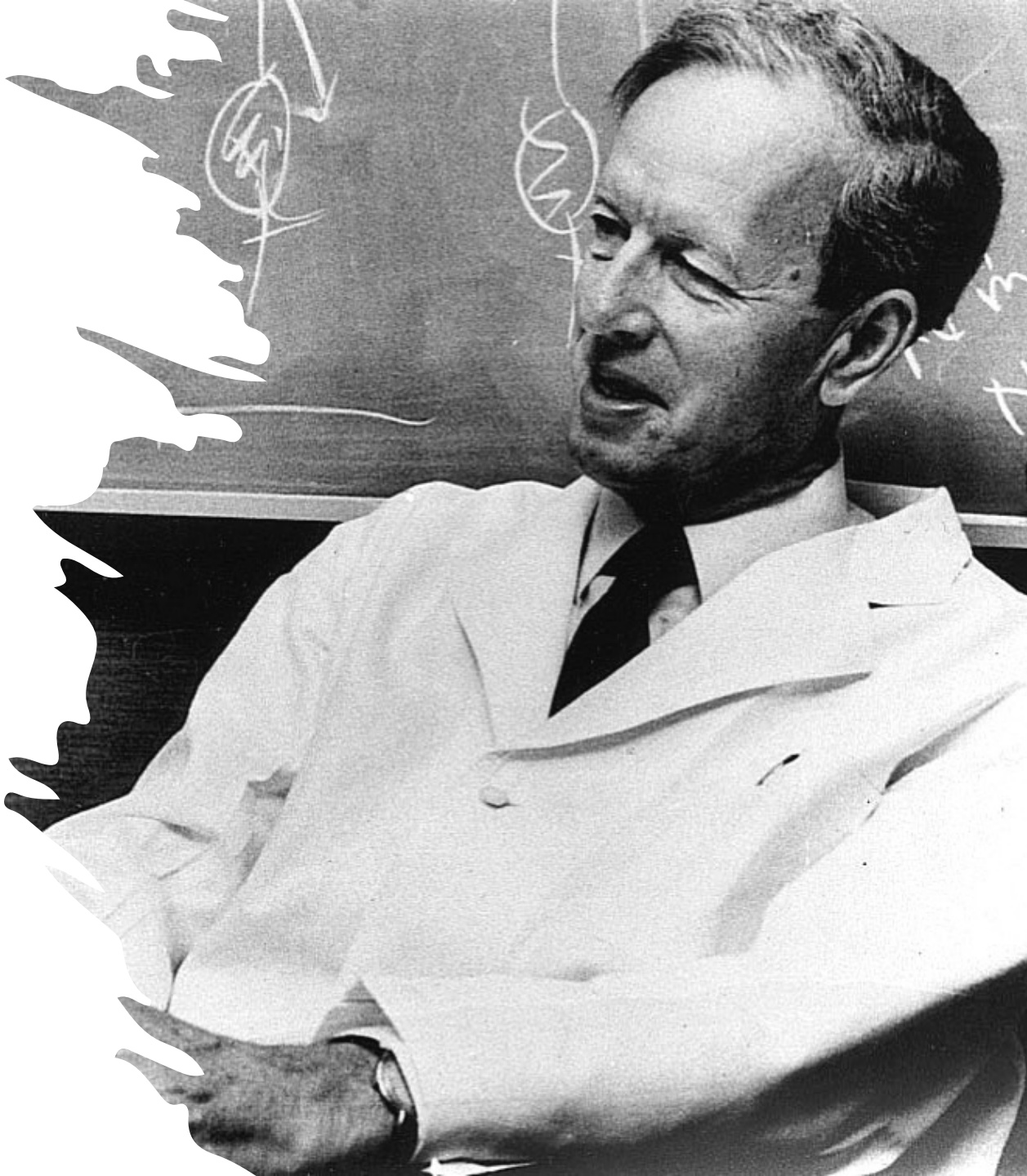
Treatment Advances in Waldenstrom's Macroglobulinemia

Steven P. Treon MD, PhD, FRCP, FACP

Harvard Medical School

Bing Center for Waldenstrom's Macroglobulinemia

Dana Farber Cancer Center, Boston MA



MYD88 Directed Pro-survival Signaling in WM

The NEW ENGLAND JOURNAL of MEDICINE

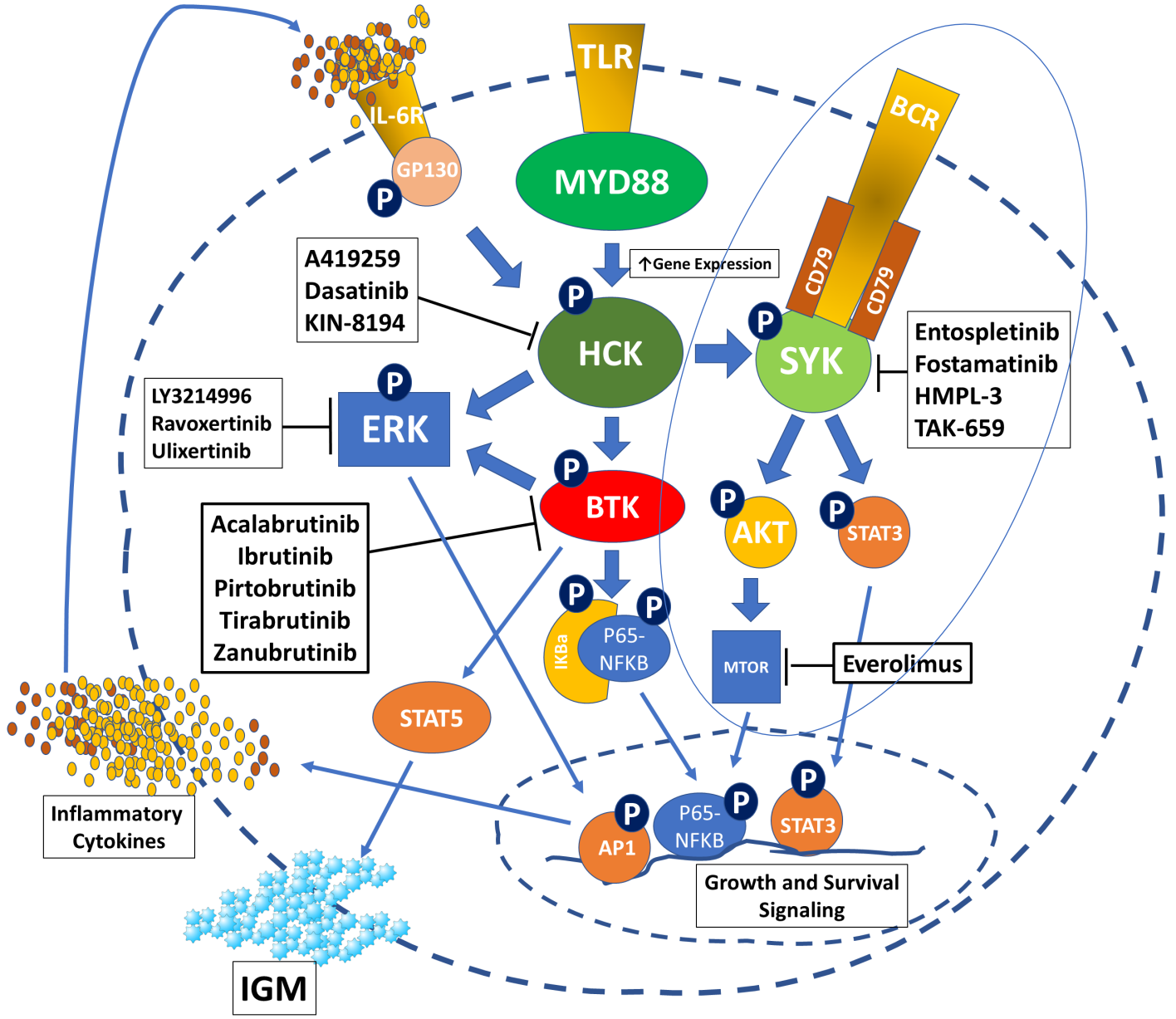
ORIGINAL ARTICLE

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.



CXCR4 Receptor (WHIM-like) Mutations Are Common in WM

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

Regular Article

CLINICAL TRIALS AND OBSERVATIONS

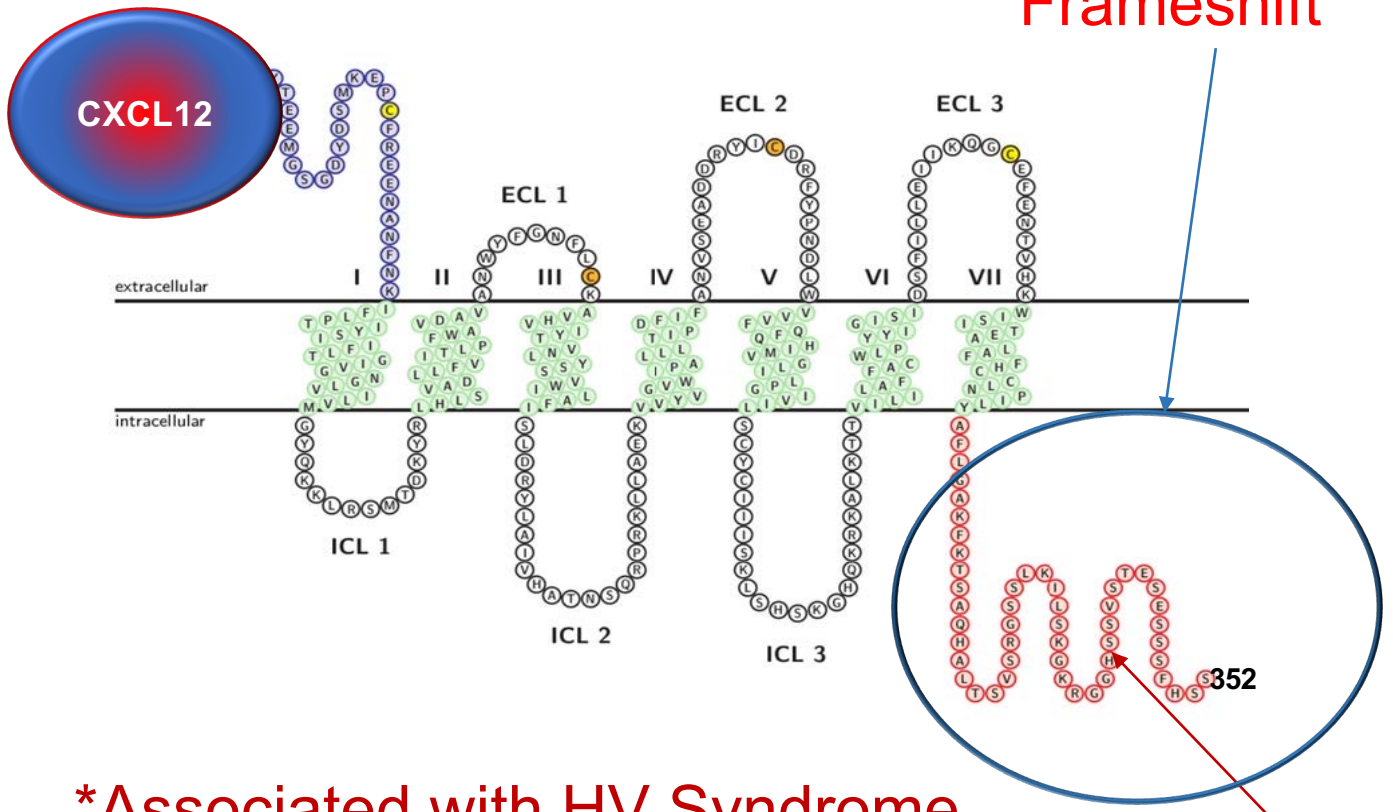
Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenström macroglobulinemia

Steven P. Treon,[1,2] Yang Cao,[1,2] Lian Xu,[1,2] Guang Yang,[1,2] Xia Liu,[1,2] and Zachary R. Hunter[1,3]

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

30-40% of WM patients have CXCR4 mutations

CXCR4 mutations
Non-sense (S338X)*
Frameshift



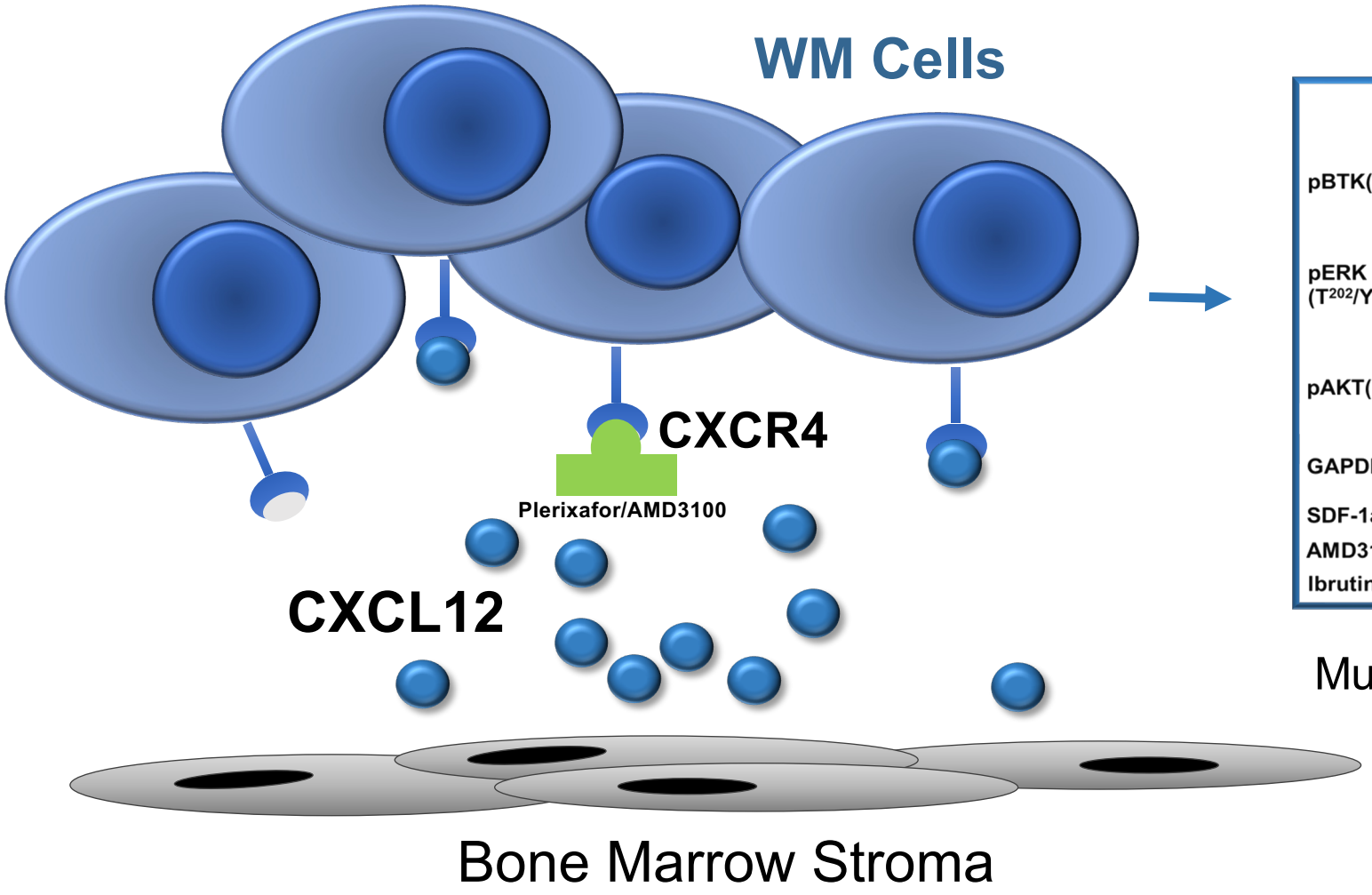
*Associated with HV Syndrome

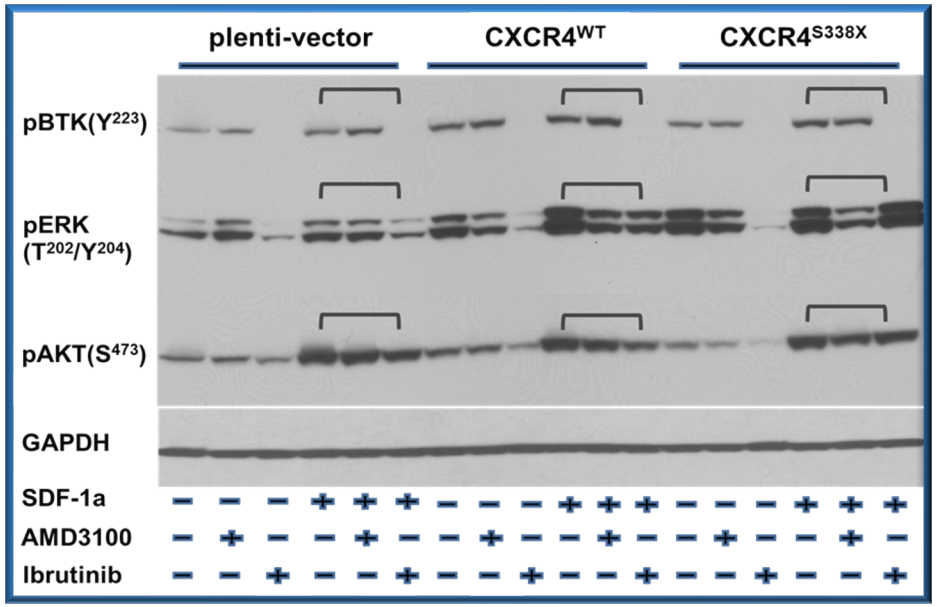
S338X

Adapted from Kahler et al. *AIMS Biophysics.* 2016, 3(2): 211-231.

Hunter et al *Blood*. 2014;123(11):1637-1646.; Treon et al, *Blood.* 2014;123(18):2791-2796; Poulain, et al. *Clin Cancer Res*. 2016;22(6):1480-1488.

Mutated CXCR4 Triggers AKT- and ERK- Mediated Resistance to Ibrutinib





Mutated CXCR4 turns on AKT and ERK leading to Ibrutinib resistance

Cao Y, et al. *Leukemia*. 2015;29(1):169-176.

Ibrutinib monotherapy in previously-treated WM: Pivotal Trial

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib in Previously Treated Waldenström's Macroglobulinemia

Steven P. Treon, M.D., Ph.D, Christina K. Tripsas, M.A., Kirsten Meid, M.P.H., Diane Warren, B.S., Gaurav Varma, M.S.P.H., Rebecca Green, B.S., Kimon V. Argyropoulos, M.D., Guang Yang, Ph.D., Yang Cao, M.D., Lian Xu, M.S., Christopher J. Patterson, M.S., Scott Rodig, M.D., Ph.D., James L. Zehnder, M.D., Jon C. Aster, M.D., Ph.D., Nancy Lee Harris, M.D., Sandra Kanan, M.S., Irene Ghobrial, M.D., Jorge J. Castillo, M.D., Jacob P. Laubach, M.D., Zachary R. Hunter, Ph.D., Zeena Salman, B.A., Jianling Li, M.S., Mei Cheng, Ph.D., Fong Clow, Sc.D., Thorsten Graef, M.D., M. Lia Palomba, M.D., and Ranjana H. Advani, M.D.

N=63	Median	Range
Age (yrs)	63	44-86
Prior therapies	2	1-9
Refractory to prior therapy	25 (40%)	N/A
Hemoglobin (mg/dL)	10.5	8.2-13.8
Serum IgM (mg/dL)	3,520	724-8,390
B_2M (mg/dL)	3.9	1.3-14.2
BM Involvement (%)	60	3-95
Adenopathy >1.5 cm	37 (59%)	N/A
Splenomegaly >15 cm	7 (11%)	N/A

Treon et al, NEJM 2015

Ibrutinib Activity in Previously Treated WM: *Update of the Pivotal Trial (median f/u 59 mos)*

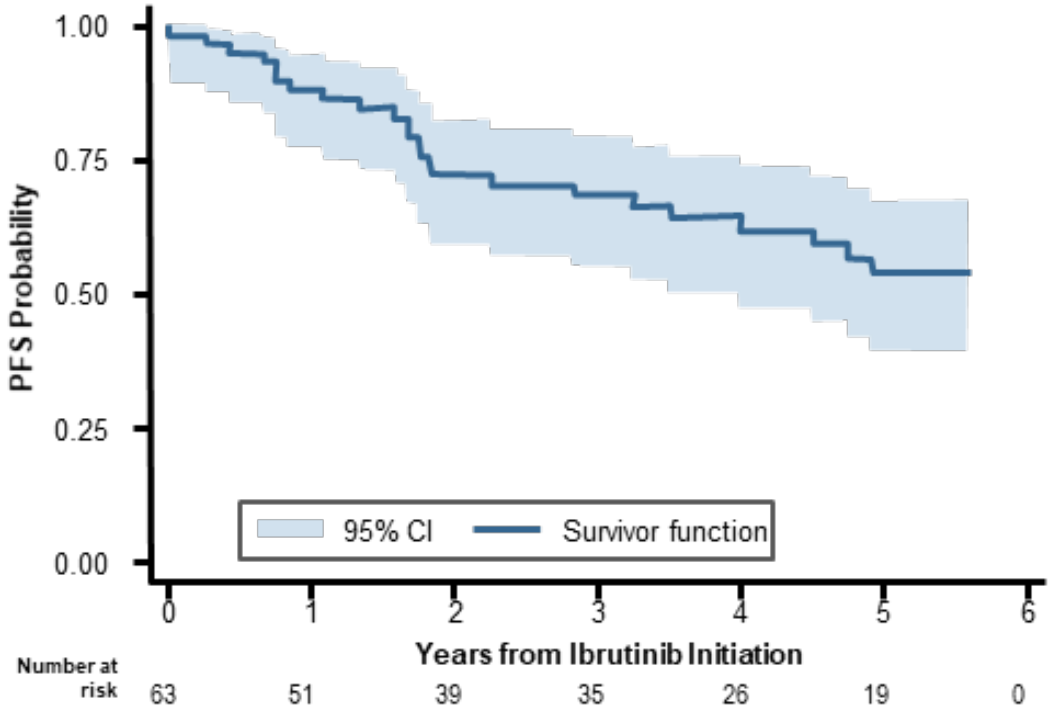
	All Patients	MYD88^{MUT} CXCR4^{WT}	MYD88^{MUT} CXCR4^{MUT}	MYD88^{WT} CXCR4^{WT}	P-value
N	63	36	22	4	N/A
Overall Response Rate-no. (%)	90.5%	100%	86.4%	50%	<0.01
Major Response Rate-no. (%)	**79.4%**	**97.2%**	**68.2%**	**0%**	**<0.0001**
Categorical responses					
Minor responses-no. (%)	11.1%	2.8%	18.2%	50%	<0.01
Partial responses-no. (%)	49.2%	50%	59.1%	0%	0.03
Very good partial responses-no. (%)	**30.2%**	**47.2%**	**9.1%**	**0%**	**<0.01**
Median time to response (months)					
Minor response (≥Minor response)	0.9	0.9	0.9	0.9	0.38
Major response (≥Partial response)	**1.8**	**1.8**	**4.7**	**N/A**	**0.02**

***One patient had MYD88 mutation, but no CXCR4 determination and had SD.**

Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

Ibrutinib Activity in Previously Treated WM: *Updated PFS of the Pivotal Trial (median f/u 59 mos)*

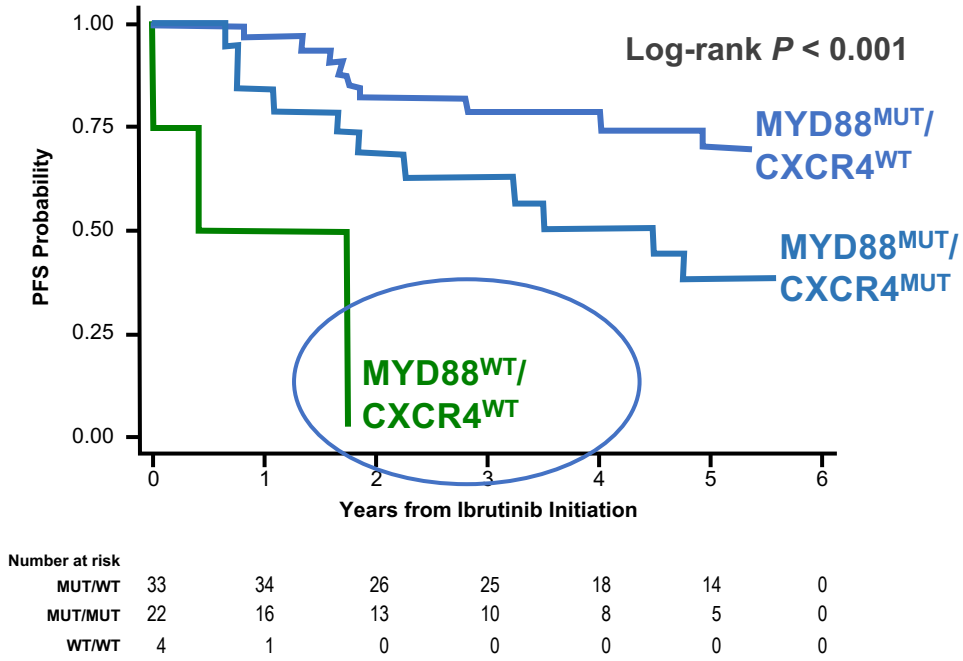
All patients



5-year PFS: 54%

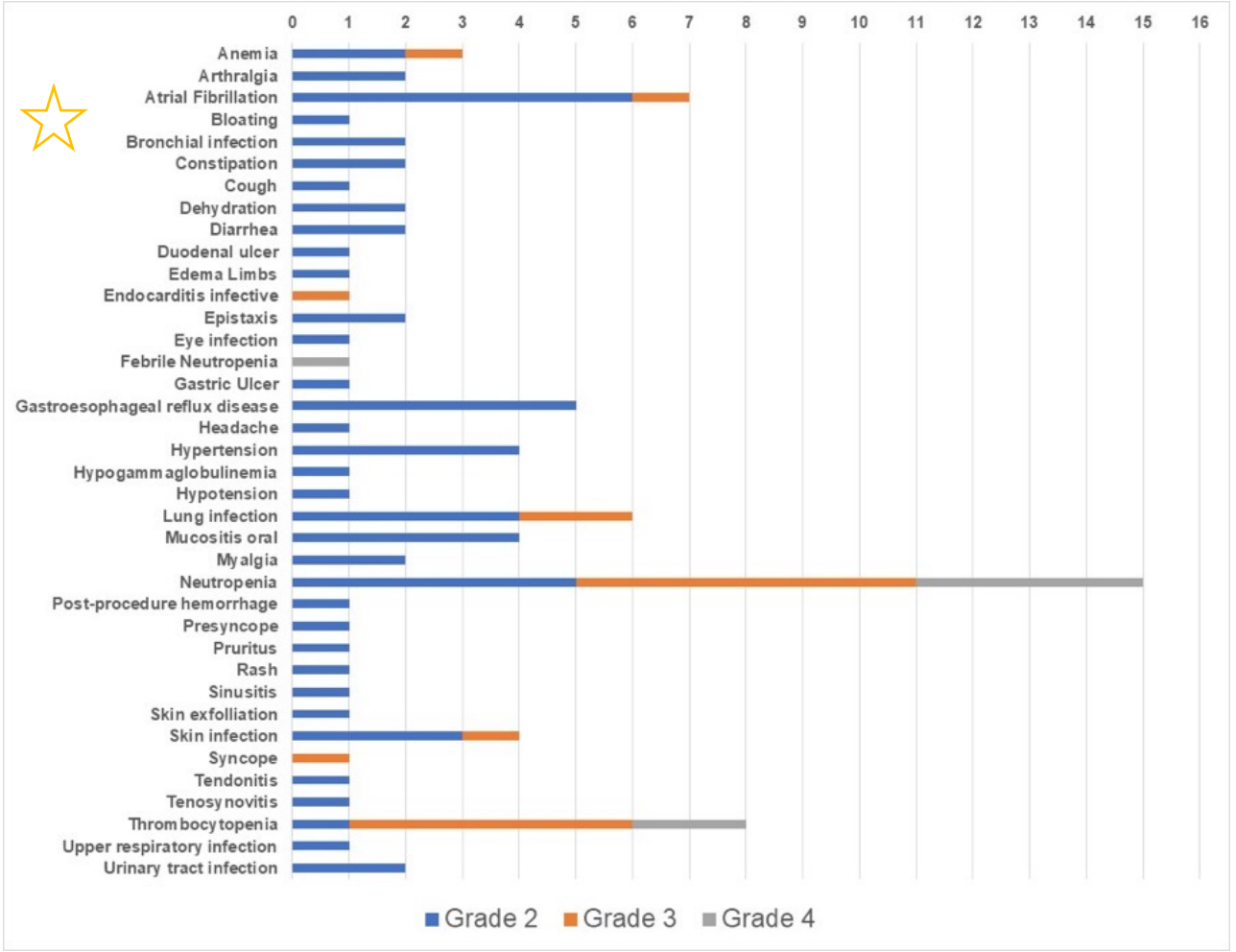
5-year OS: 87%

MYD88 and CXCR4 Mutation Status



Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

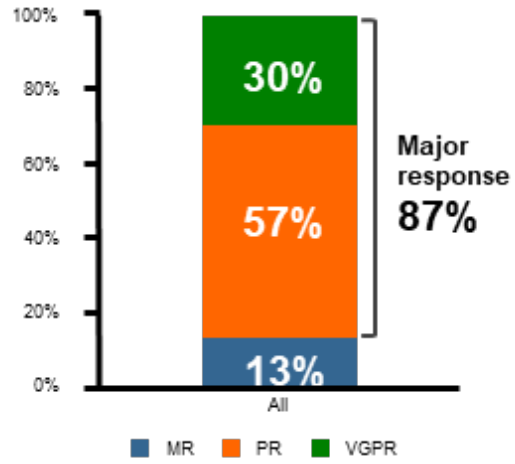
Ibrutinib Activity in Previously Treated WM:
Long Term Toxicity Findings (grade ≥2) of the Pivotal Trial

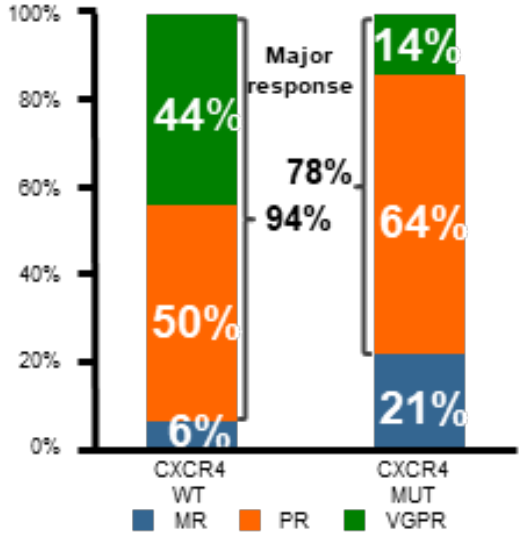


☆ Increased since original report; 8 patients (12.7%) with Afib, including grade 1; 7 continued ibrutinib with medical management.

Treon, et al. *N Engl J Med*. 2015;372(15):1430-1440.; Updated in Treon, et al. *J Clin Oncol*. 2021;39(6):565-575.

Update of Ibrutinib Monotherapy: Treatment-Naïve WM Patients





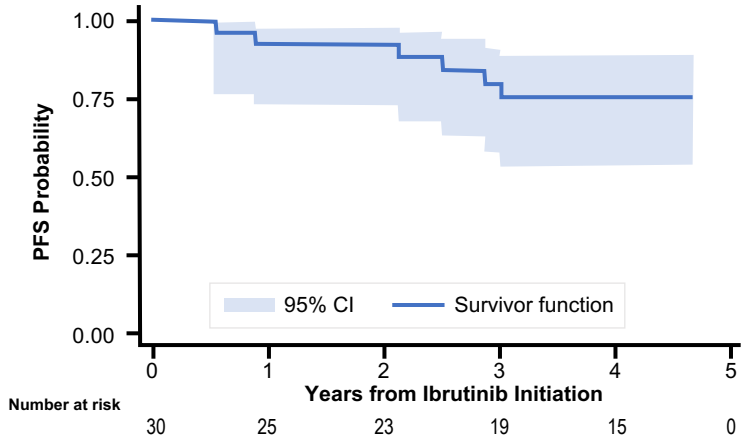
Median time to Response

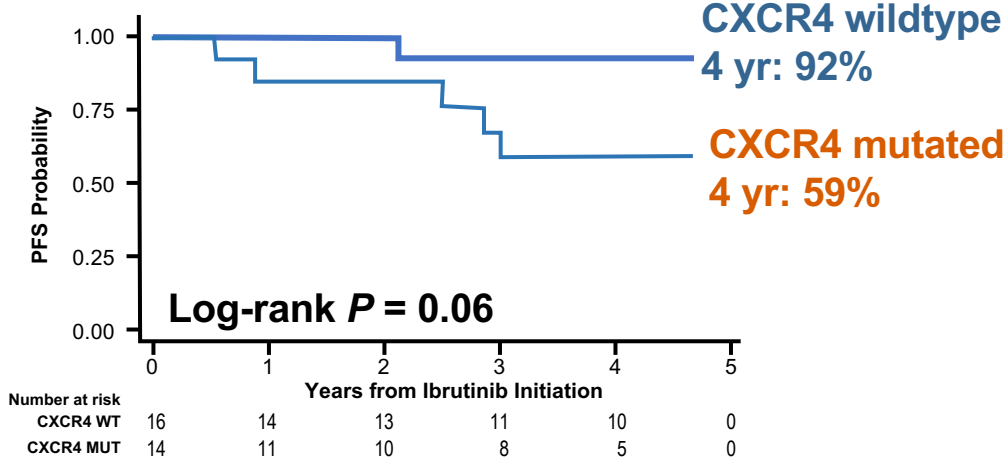
	CXCR4^{WT}	CXCR4^{MUT}
Time to Minor Response (mos).[1]	0.9	1.7
Time to Major Response (mos).[2]	1.8	7.3

1. p=0.07; 2. p=0.01

All patients were MYD88 mutated.

Median f/u: 50 months





Treon SP, et al. *J Clin Oncol*. 2018;36(27):2755-2761. Castillo, et al. *Leukemia. 2022;*36:532–539.

Impact of Mutated CXCR4 in WM BTKi Trials

Comparisons for **CXCR4^{Mut}** vs. **CXCR4^{WT}**

Study	Regimen	Time to Major Response	Major RR	VGPR	PFS
Treon et al[1] R/R WM	Ibrutinib	4.7 vs.1.8 mos.	68% vs. 97%	9% vs. 47%	38% vs. 70% (5 yrs)
Trotman et al[2] R/R WM	Ibrutinib	N/A	71% vs. 88%	14% vs. 41%	NR vs. 18 mo. (5 yrs)
Castillo et al[3] TN WM	Ibrutinib	7.3 vs. 1.8 mos.	78% vs. 94%	14% vs. 44%	59% vs. 90% (4 yrs)
Buske et al[4] TN, R/R WM	Ibrutinib plus Rituximab	3 vs. 2 mos.	77% vs. 81%	23% vs. 41%	63% vs. 72% (54 mos.)
Trotman et al[5] TN, R/R WM	Zanubrutinib	N/A	91% vs. 87%	27% vs. 59%	N/A
Tam et al[6] TN, RR	Ibrutinib	2.8 mos.	65% vs. 82%	10% vs. 24%	N/A
	Zanubrutinib	4.6 mos.	70% vs. 82%	18% vs. 34%	N/A

1. Treon et al, JCO 2021; 39(6):565-575 2. Trotman et al, CCR 2021; 3. Castillo et al, Leukemia 2022; 36(2):532-539
4. Buske et al JCO 2022; 40(1):52-62; 5. Trotman et al, Blood 2020; 136(18):2027-37. 6. Tam et al, Blood 2020; 136(18):2038-2050

All patients are MYD88 mutated.

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

Phase II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

Schema

Dose Level	Ibrutinib	Ulocuplumab Cycle 1	Ulocuplumab Cycles 2-6
Level 1 –Starting dose	420mg PO DQ	400 mg weekly	800 mg every other week
Level 2	420mg PO DQ	800 mg weekly	1200 mg every other week
Level 3	420mg PO DQ	800 mg weekly	1600 mg every other week

ClinicalTrials.gov Identifier: NCT03225716

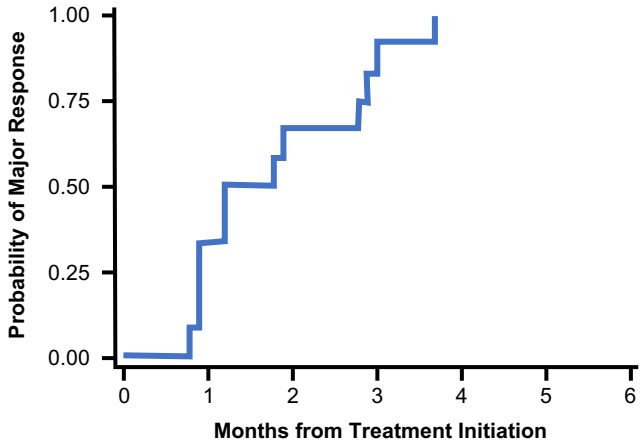
Phase I Trial of CXCR4 antagonist Ulocuplumab and Ibrutinib in CXCR4-mutated Patients with Symptomatic WM

Median follow-up : 22.4 mos.

Baseline

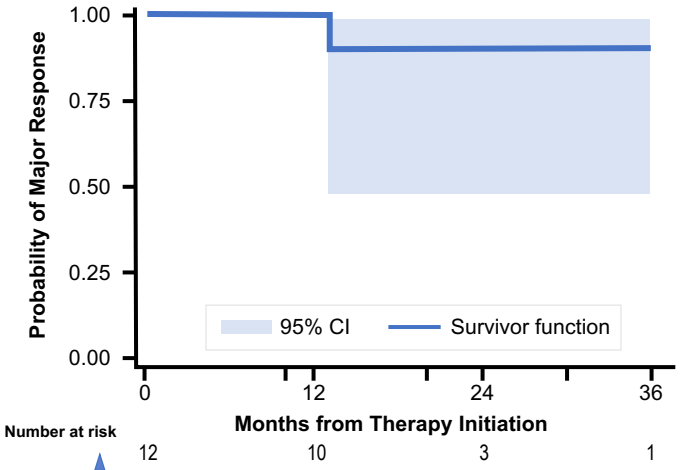
	Median
Age (yr)	61.5
sIgM (mg/dL)	5241
BM Involved	65%
Hb (g/dL)	9.1
Prior Rx	0 (0-2)
Sx HV	42%

Median Time to Major Response



1.2 (95% CI 0.9-2.8) months

Median Time to PFS

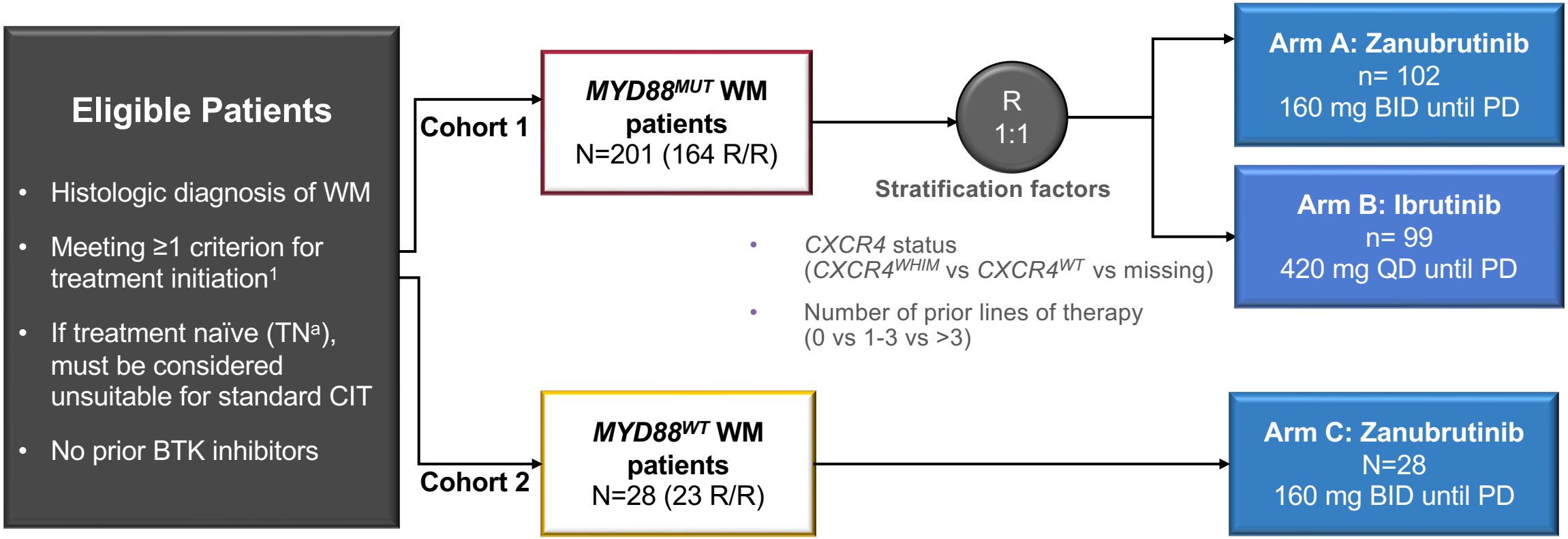


2-year 90% estimated

Major RR: 100%
VGPR: 33%

Treon S, et al. *Blood*. 2021; 138 (17): 1535–1539.

Zanubrutinib vs Ibrutinib in WM
Phase 3 ASPEN



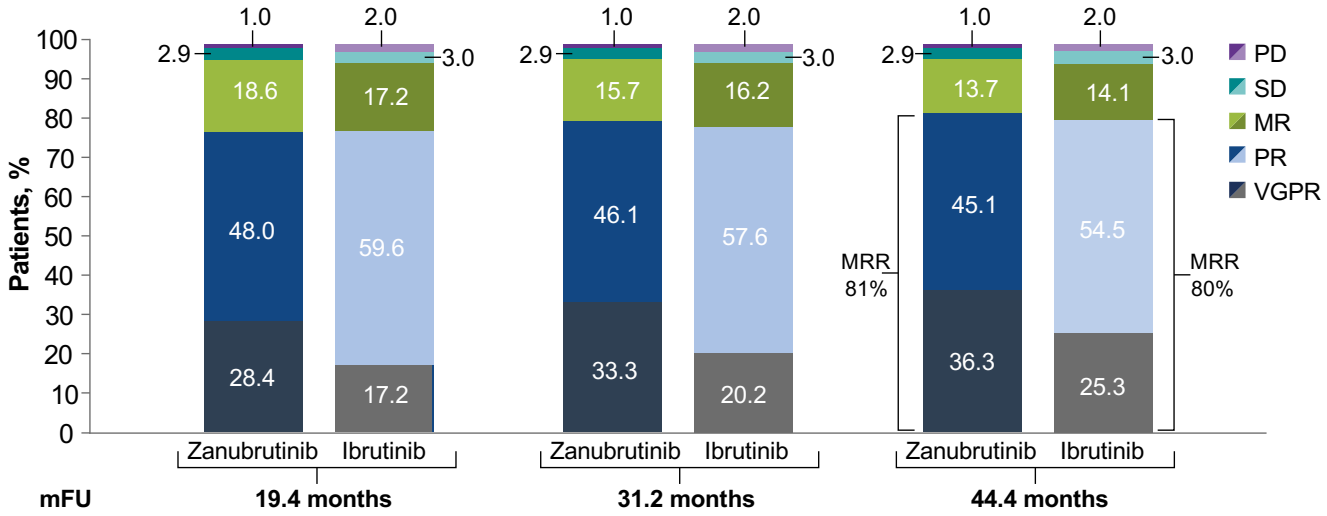
BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia; WT, wild-type.

[a]Up to 20% of the overall population

ClinicalTrials.gov Identifier: NCT03053440

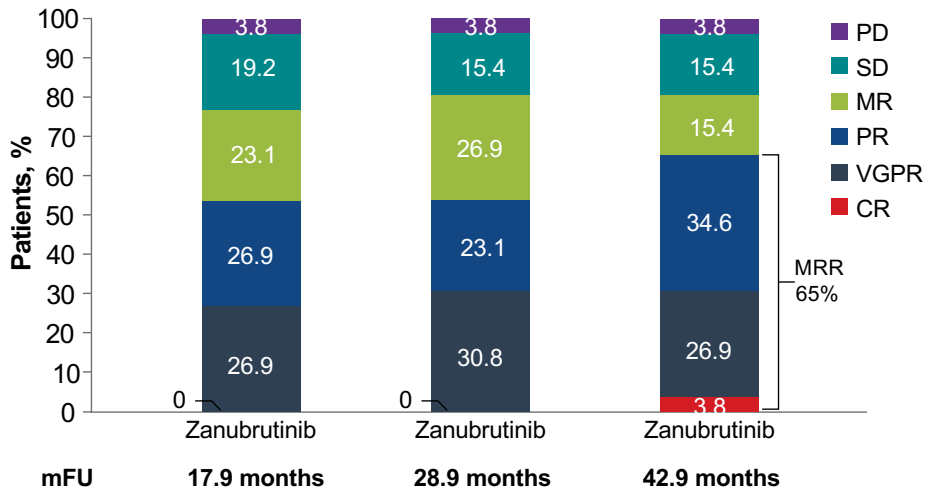
ASPEN: Best Overall Response and PFS by Investigator Assessment

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.

Data cutoff: October 31, 2021.

CR, complete response; *CXCR4*, C-X-C chemokine receptor type 4 gene; mFU, median follow-up; MR, major response; MRR, major response rate; MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response; WT, wild type.

Dimopoulos MA et al, 11th International Workshop on WM, Madrid Spain, 2022

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)

Bold blue text indicates rate of AEs with ≥10% (all grades) or ≥5% (grade ≥3) difference between arms.
Data cutoff: October 31, 2021.
*Descriptive purposes only, 1-sided $P < 0.025$ in rate difference in all grades and/or grade ≥3. [a]Grouped terms. [b]Including preferred terms of neutropenia, neutrophil count decreased, febrile neutropenia, and neutropenic sepsis.
AE, adverse event.

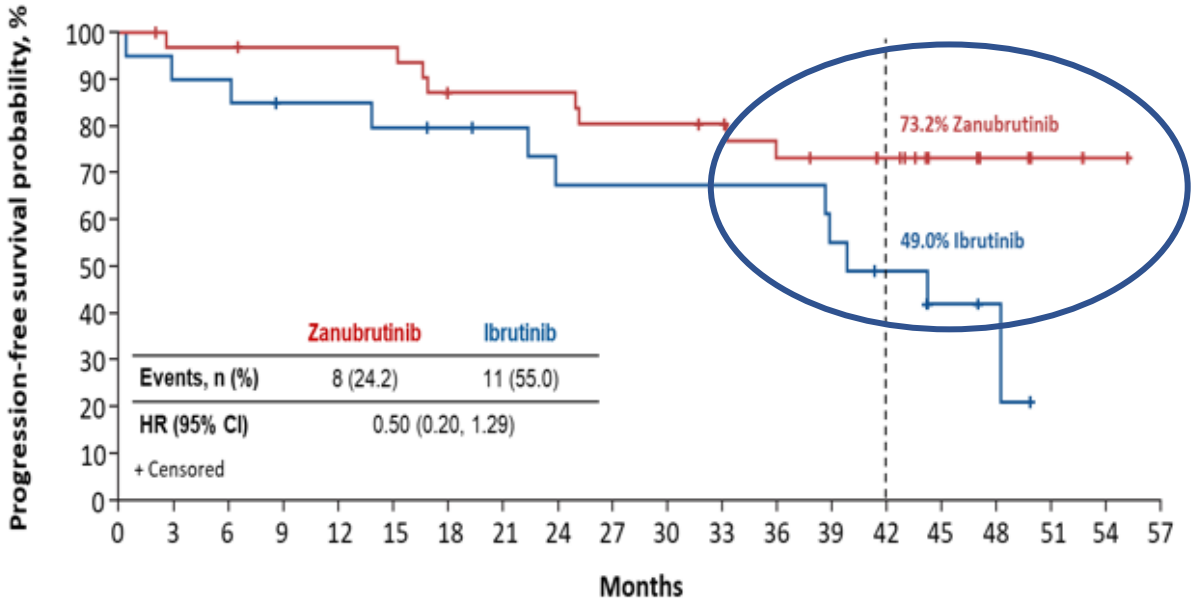
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

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}



No. of Patients at Risk:

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

[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.
Data cutoff: October 31, 2021.
CI, confidence Interval; *CXCR4*, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MR, major response; MUT, mutant; PFS, progression-free survival; VGPR, very good partial response.

Ibrutinib and Venetoclax (IVEN) in Treatment Naïve WM

Screening

Informed Consent and Registration

www.clinicaltrials.gov: NCT04273139

Cycle 1
Ibrutinib 420 mg PO QD

Cycle 2
Ibrutinib 420 mg PO QD
Venetoclax weekly ramp up
100-200-400 mg PO QD

Cycle 3-24
Ibrutinib 420 mg PO QD
Venetoclax 400 mg PO QD

Dose reductions were allowed for toxicity

Progressive Disease or Unacceptable Toxicity

Stable Disease or Response

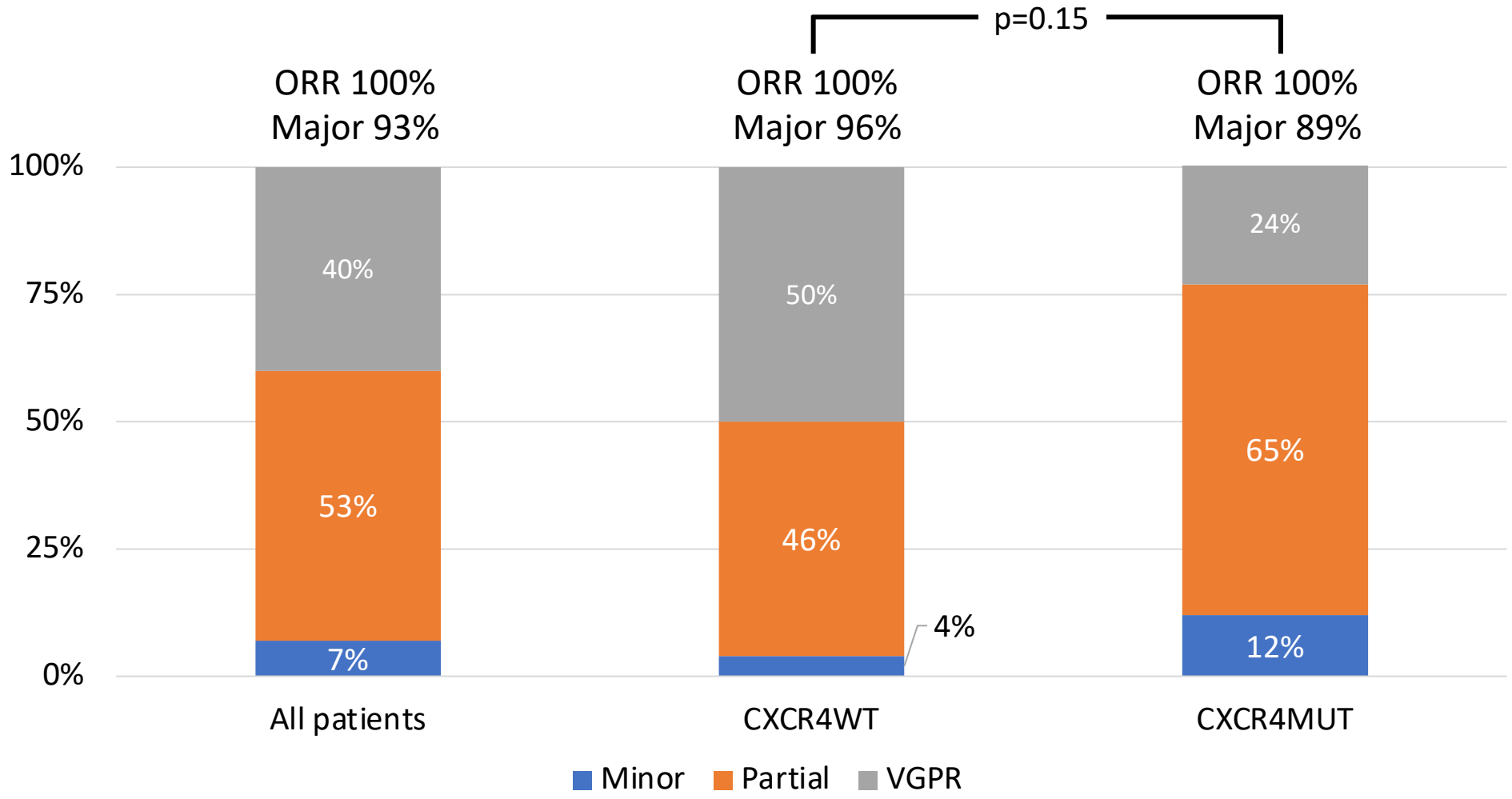
Stop therapy

Follow-up

Continue therapy until completion

Castillo et al, ASH 2022

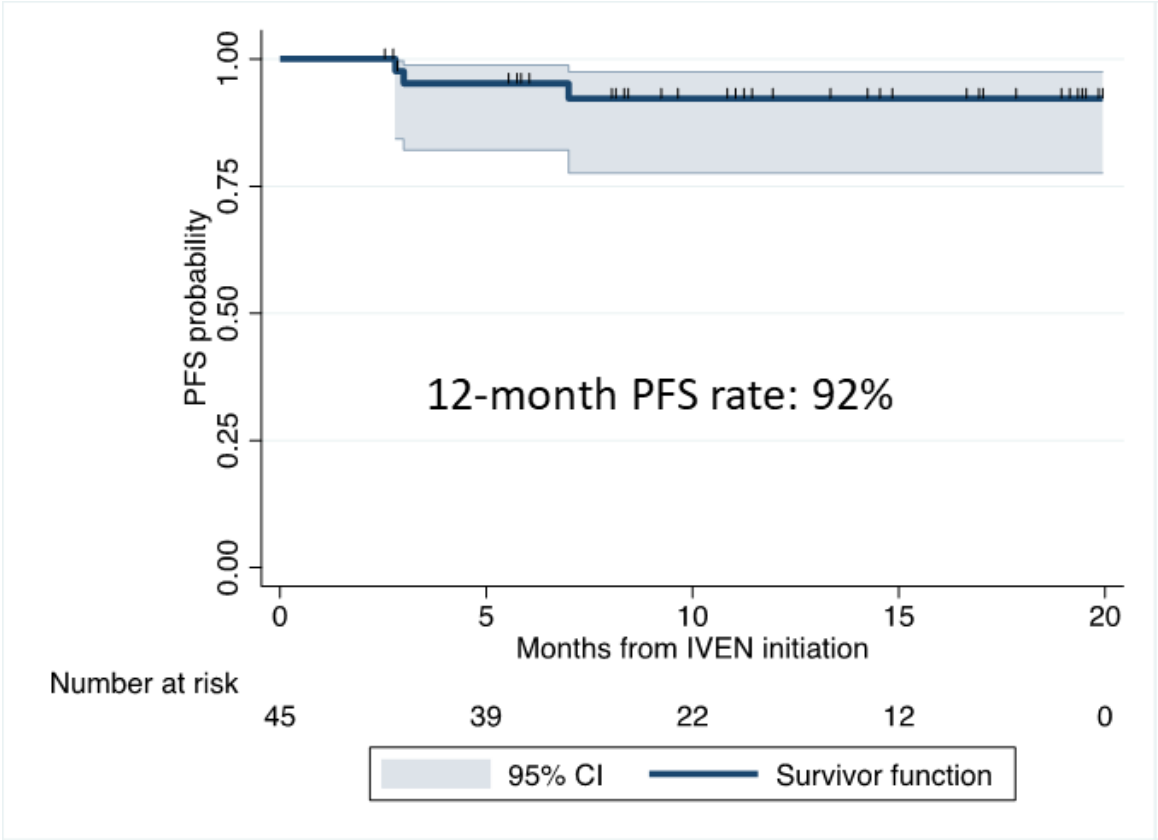
IVEN: Response to therapy

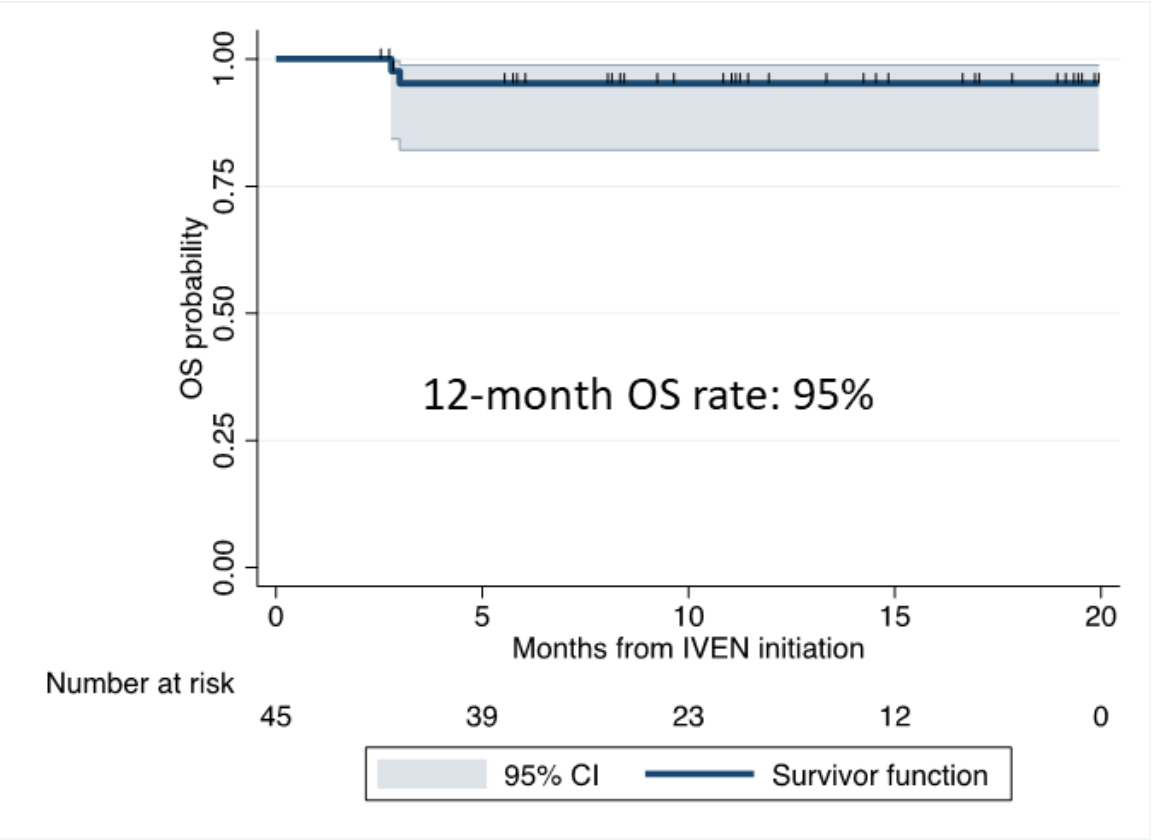


Castillo et al, ASH 2022

IVEN: Survival analysis

Median follow-up: 11 months





Castillo et al, ASH 2022

Safety

Adverse events observed in ≥3 patients and of clinical importance

n=45

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

TLS: tumor lysis syndrome

Castillo et al, ASH 2022

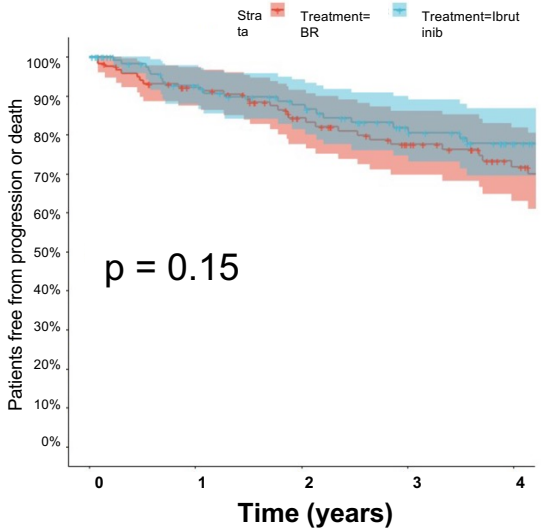
So how do we position BTK-inhibitors relative to Bendamustine-R in treatment naïve patients?

Bendamustine Rituximab v. Ibrutinib as Primary Therapy for WM: An International Collaborative Study

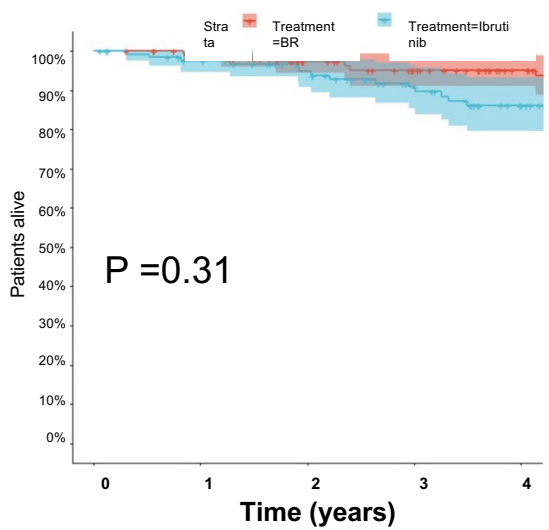
CONQUER CANCER® THE ASCO FOUNDATION MERIT AWARD RECIPIENT

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



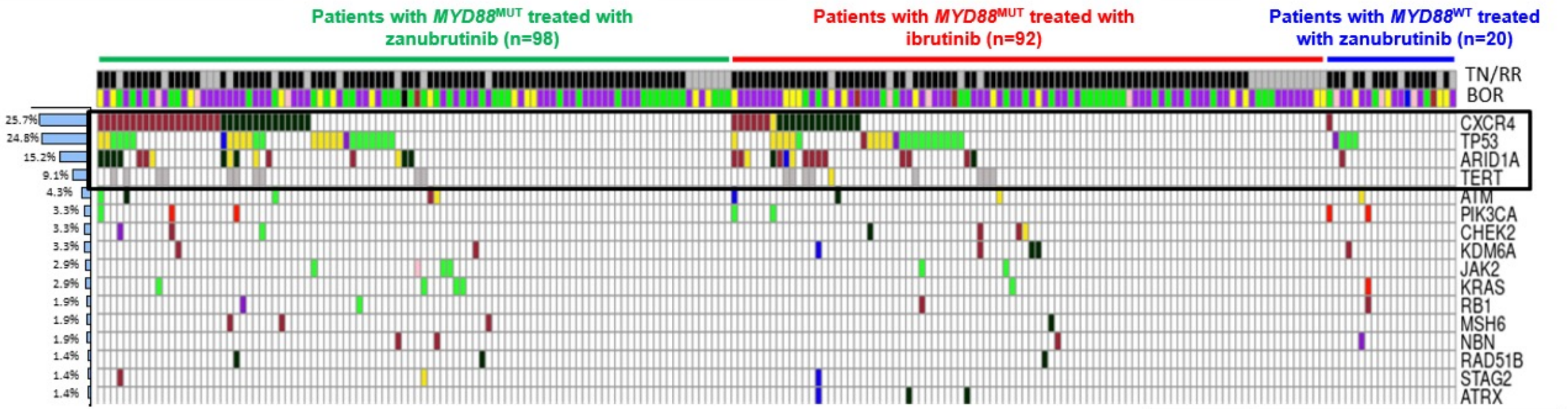
Overall survival



- 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, Eur. Hematol. Assoc. June 2022
Updated IWWM-11, 2022.

High Rate of TP53^{MUT}, TERT^{MUT} were found in ASPEN Study[a] and more often detected in Patients with MYD88^{MUT} or CXCR4^{MUT}



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

Bold text indicates >10% difference between MUT and WT in 210 NGS evaluable WM pts. [a]Including 190 patients with *MYD88*^{MUT} (98 treated by zanubrutinib and 92 treated by ibrutinib) and 20 patients with *MDY88*^{WT} (all zanubrutinib), *MYD88* status was assessed by a PCR-based assay which was used for patients' enrollment. *CXCR4* status was evaluated by NGS. BOR, best overall response; MR, major response; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; *TERT*, telomerase reverse transcriptase gene; TN, treatment-naïve; *TP53*, tumor protein P53 gene.

TP53 Mutations in ASPEN Study

	N=	Total $TP53^{Mut}$	Treatment Naïve $TP53^{Mut}$	Previously Treated $TP53^{Mut}$	p= (TN vs prev. treated)
$MYD88^{Mut}$	190	48/190 (25.2%)	6/190 (3.2%)	42/190 (22.1%)	<0.00001
$MYD88^{WT}$	20	4/20 (20%)	1/20 (5%)	3/20 (15%)	NS

Tam C et al, 11th International Workshop on WM, Madrid Spain, 2022

blood® Regular Article

CLINICAL TRIALS AND OBSERVATIONS

A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenström macroglobulinemia: the ASPEN study

Constantine S. Tam,[1-4] Stephen Opat,[5,6] Shirley D'Sa,[7] Wojciech Jurczak,[8] Hui-Peng Lee,[9] Gavin Cull,[10,11] Roger G. Owen,[12] Paula Marlton,[13,14] Björn E. Wahlin,[15] Ramón Garcia Sanz,[16] Helen McCarthy,[17] Stephen Mulligan,[18] Alessandra Tedeschi,[19] Jorge J. Castillo,[20,21] Jaroslaw Czyz,[22,23] Carlos Fernández de Larrea,[24] David Belada,[25] Edward Libby,[26] Jeffrey V. Matous,[27] Marina Motta,[28] Tanya Siddiqi,[29] Monica Tani,[30] Marek Trneny,[31] Monique C. Minnema,[32] Christian Buske,[33] Veronique Leblond,[34] Judith Trotman,[35,36] Wai Y. Chan,[37] Jingjing Schneider,[37] Sunhee Ro,[37] Aileen Cohen,[37] Jane Huang,[37] and Meletios Dimopoulos,[38] for the ASPEN Investigators

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]St Vincent's Hospital, Fitzroy, VIC, Australia; [3]Department of Medicine, University of Melbourne, Parkville, VIC, Australia; [4]Royal Melbourne Hospital, Parkville, VIC, Australia; [5]Monash Health, Clayton, VIC, Australia; [6]Clinical Haematology Unit, Monash University, Clayton, VIC, Australia; [7]University College London Hospital Foundation Trust, London, United Kingdom; [8]Maria Sklodowska-Curie National Institute of Oncology, Krakow, Poland; [9]Flinders Medical Centre, Adelaide, SA, Australia; [10]Sir Charles Gairdner Hospital, Perth, WA, Australia; [11]Department of Lymphoma/Myeloma, University of Western Australia, Perth, WA, Australia; [12]St James's University Hospital, Leeds, United Kingdom; [13]Department of Haematology, Princess Alexandra Hospital, Brisbane, QLD, Australia; [14]School of Medicine, University of Queensland, Brisbane, QLD, Australia; [15]Unit of Hematology, Department of Medicine, Karolinska Universitetssjukhuset–Karolinska Institutet, Stockholm, Sweden; [16]Hospital Universitario de Salamanca, Salamanca, Spain; [17]Royal Bournemouth and Christchurch Hospital, Bournemouth, United Kingdom; [18]Royal North Shore Hospital, Sydney, NSW, Australia; [19]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy; [20]Bing Center for Waldenstrom Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA; [21]Department of Medicine, Harvard Medical School, Boston, MA; [22]Szpital Uniwersytecki No 2 im Dr Jana Biziela, Bydgoszcz, Poland; [23]Department of Hematology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland; [24]Amyloidosis and Myeloma Unit, Department of Hematology, Hospital Clinic of Barcelona, August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Barcelona, Spain; [25]Fourth Department of Internal Medicine - Haematology, Charles University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [26]Department of Medicine, University of Washington and the Seattle Cancer Care Alliance, Seattle, WA; [27]Colorado Blood Cancer Institute, Denver, CO; [28]ASST Spedali Civili di Brescia, Lombardia, Italy; [29]City of Hope National Medical Center, Duarte, CA; [30]Ospedale Civile S Maria delle Croci, Azienda Unità Sanitaria Locale (AUSL), Ravenna, Italy; [31]First Department of Medicine, First Faculty of Medicine, Charles University, General Hospital, Prague, Czech Republic; [32]University Medical Center Utrecht, Utrecht, The Netherlands; [33]Comprehensive Cancer Center Ulm–Universitätsklinikum Ulm, Ulm, Germany; [34]Service d'Hématologie Clinique, Sorbonne University, Pitié Salpêtrière Hospital, Paris, France; [35]Haematology Department, University of Sydney, Concord, NSW, Australia; [36]Department of Haematology, Concord Repatriation General Hospital, Sydney, Concord, NSW, Australia; [37]BeiGene USA, Inc, San Mateo, CA; and [38]Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece

KEY POINTS

- Although not statistically significant, a higher rate of CR/VGPR was observed for zanubrutinib vs ibrutinib (28% vs 19%, respectively).
- The incidence and severity of most BTK-associated toxicities (including atrial fibrillation) were lower with zanubrutinib than ibrutinib.

Bruton tyrosine kinase (BTK) inhibition is an effective treatment approach for patients with Waldenström macroglobulinemia (WM). The phase 3 ASPEN study compared the efficacy and safety of ibrutinib, a first-generation BTK inhibitor, with zanubrutinib, a novel highly selective BTK inhibitor, in patients with WM. Patients with *MYD88*^{L265P} disease were randomly assigned 1:1 to treatment with ibrutinib or zanubrutinib. The primary end point was the proportion of patients achieving a complete response (CR) or a very good partial response (VGPR) by independent review. Key secondary end points included major response rate (MRR), progression-free survival (PFS), duration of response (DOR), disease burden, and safety. A total of 201 patients were randomized, and 199 received ≥1 dose of study treatment. No patient achieved a CR. Twenty-nine (28%) zanubrutinib patients and 19 (19%) ibrutinib patients achieved a VGPR, a nonstatistically significant difference ($P = .09$). MRRs were 77% and 78%, respectively. Median DOR and PFS were not reached; 84% and 85% of ibrutinib and zanubrutinib patients were progression free at 18 months. Atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia, as well as adverse events leading to treatment discontinuation, were less common among zanubrutinib recipients. Incidence of neutropenia was higher with zanubrutinib, although grade ≥3 infection rates were similar in both arms (1.2 and 1.1 events per 100 person-months). These results demonstrate that zanubrutinib and ibrutinib are highly effective in the treatment of WM, but zanubrutinib treatment was associated with a trend toward better response quality and less toxicity, particularly cardiovascular toxicity. (*Blood*. 2020;136(18): 2038-2050)

Most previously treated patients received alkylators

Prior therapy, n (%)	Ibrutinib (n=81)	Zanubrutinib (n=83)
Number of prior systemic regimens		
1	46 (57)	47 (57)
2	15 (19)	15 (18)
3	13 (16)	14 (17)
4	2 (2)	4 (5)
5	3 (4)	0
≥6	2 (3)	3 (4)
Anti-CD20 (rituximab, ofatumumab)	74 (91)	75 (90)
Alkylating agents (cyclophosphamide, chlorambucil, bendamustine, ifosamide, lomustine, melphalan, cisplatin)	66 (82)	73 (88)
Glucocorticoids (dexamethasone, prednisone, prednisolone, methylprednisone, methylprednisolone, hydrocortisone)	50 (62)	60 (72)
Nucleoside analogues (fludarabine, cladribine, cytarabine, gemcitabine,)	18 (22)	20 (24)
Vinca alkaloids (vincristine, vinblastine, vinorelbine)	18 (22)	23 (28)
Proteasome inhibitors (bortezomib, ixazomib)	10 (12)	10 (12)
Anthracyclines (doxorubicin, epirubicin)	9 (11)	9 (11)
Kinase inhibitors (idelalisib, everolimus)	3 (4)	2 (2)
Immunomodulators (lenalidomide, thalidomide)	1 (1)	1 (1)
Topoisomerase inhibitors (etoposide)	1 (1)	2 (2)
Multi-agent regimens, including anti-CD20	0	1 (1)
Others (interferon, bleomycin, belimumab, methotrexate)	0	4 (5)

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 major response rate (*P* value[c] = 0.11) in *TP53*^{MUT}

Data cutoff: October 31, 2021.

Bold text indicates >10% difference between MUT and WT. **Bold red** text highlights P value < 0.05.

**P* value <0.05, based on a logistic regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and TERT (WT, MUT) statuses as covariates. WT is the reference group.

[a]Mutation determined by NGS and available for 92 patients in the ibrutinib arm and 98 patients in the zanubrutinib arm. [b]Estimated using a Cox regression model with CXCR4 (WT, FS, NS), TP53 (WT, MUT), and *TERT* (WT, MUT) mutational status as covariates. WT is the reference group. [c]Estimated using a logistic regression model with treatment group, *TERT* (WT, MUT) and *CXCR4* (WT, FS, NS) mutational status as covariates within the respective subgroups(† P value <0.05).

MUT, mutant; *MYD88*, myeloid differentiation primary response 88 gene; NGS, next-generation sequencing; PFS, progression-free survival; *TP53*, tumor protein P53 gene; VGPR, very good partial response; WT, wild type.

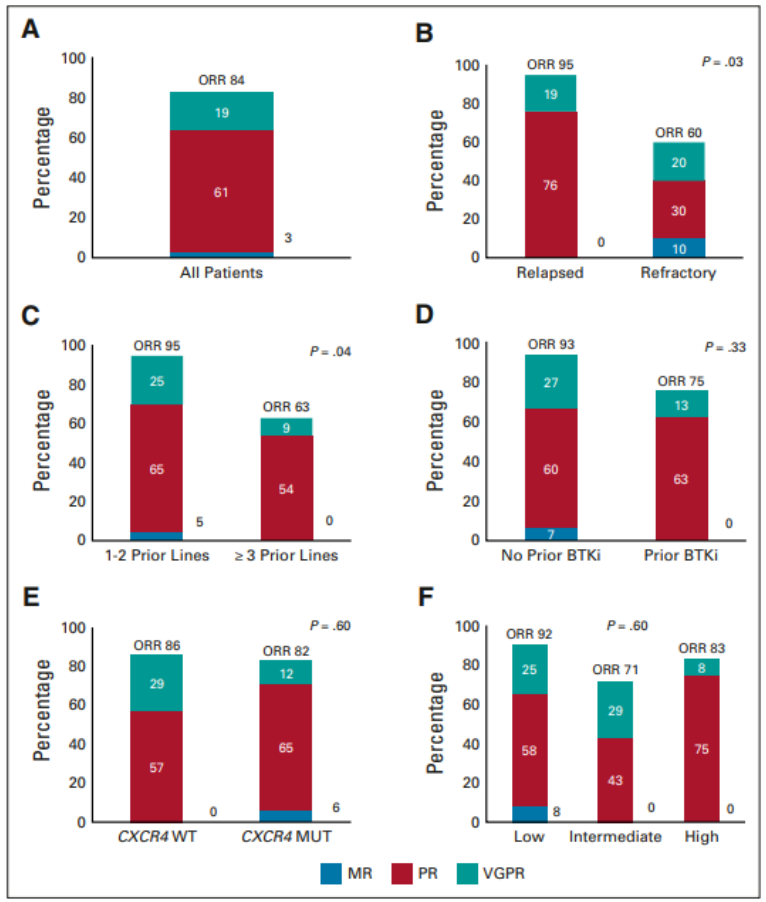
So how do we manage BTK-inhibitor resistant disease?

original reports

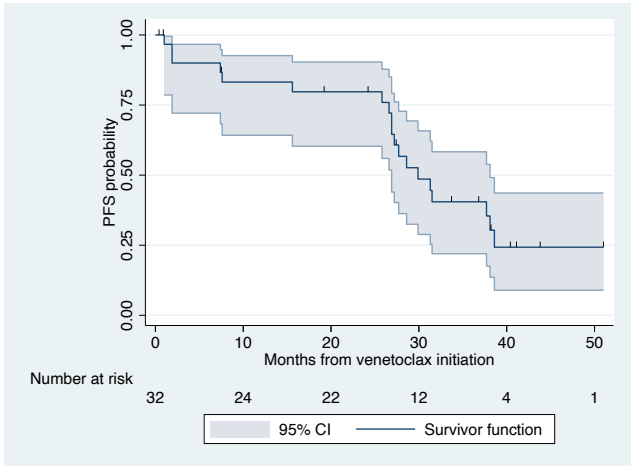
Venetoclax in Previously Treated Waldenström Macroglobulinemia

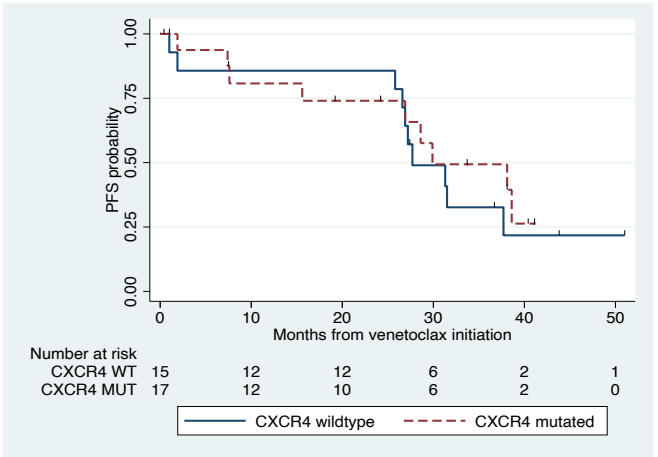
Jorge J. Castillo, MD[1,2]; John N. Allan, MD[3]; Tanya Siddiqi, MD[4]; Ranjana H. Advani, MD[5]; Kirsten Meid, MPH[1]; Carly Leventoff, BA[1]; Timothy P. White, BA[1]; Catherine A. Flynn, NP[1]; Shayna Sarosiek, MD[1,2]; Andrew R. Branagan, MD[2,6]; Maria G. Demos, BA[1]; Maria L. Guerrera, MD[1]; Amanda Kofides, BA[1]; Xia Liu, BA[1]; Manit Munshi, BA[1]; Nicholas Tsakmaklis, BA[1]; Lian Xu, BA[1]; Guang Yang, BA[1]; Christopher J. Patterson, BA[1]; Zachary R. Hunter, PhD[1,2]; Matthew S. Davids, MD[2,7]; Richard R. Furman, MD[3]; and Steven P. Treon, MD, PhD[1,2]

Journal of Clinical Oncology®



ORR: 84%; Major RR: 81%

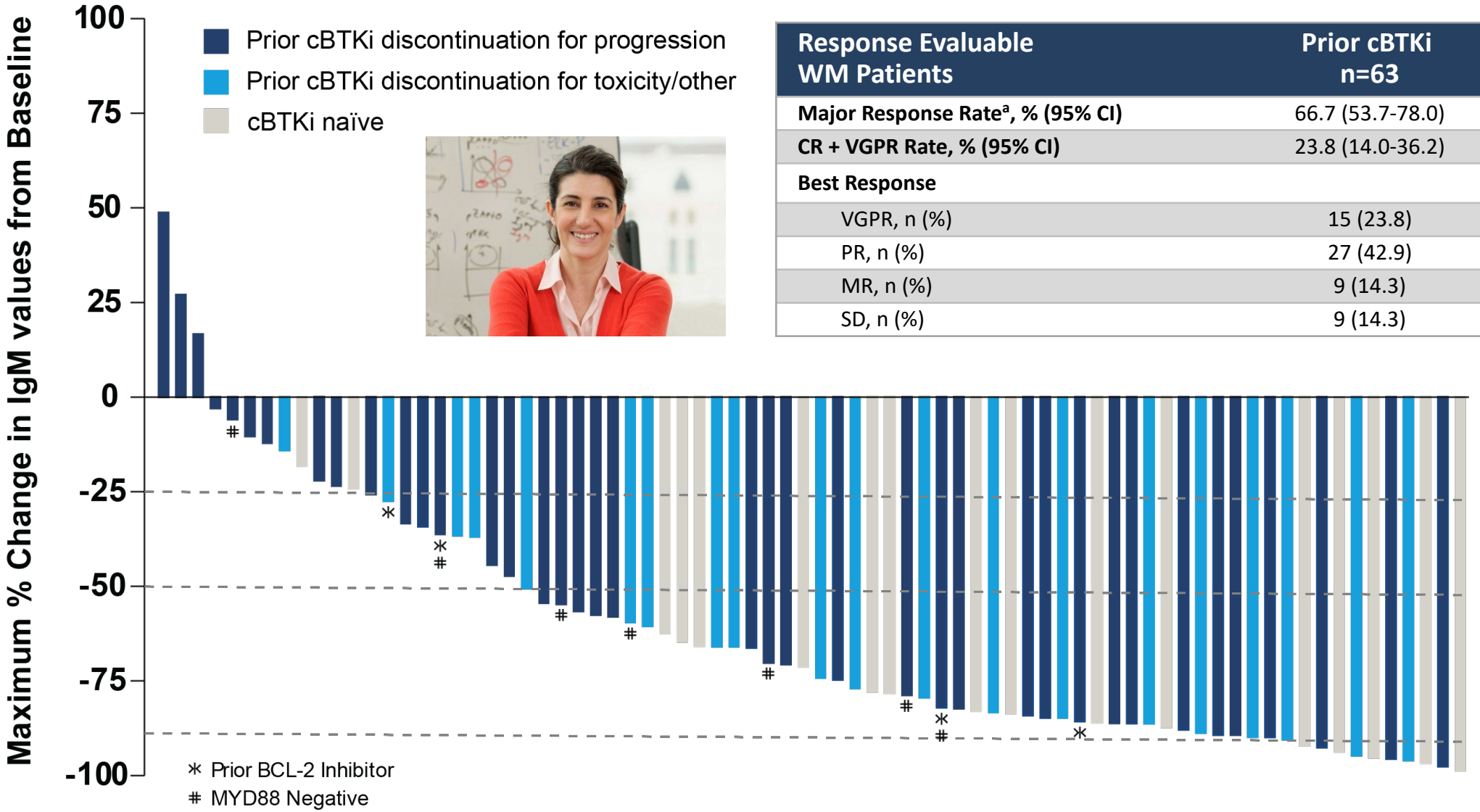




Median f/u: 33 mos; Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

Castillo et al, JCO 2021

Pirtobrutinib Efficacy in WM Patients

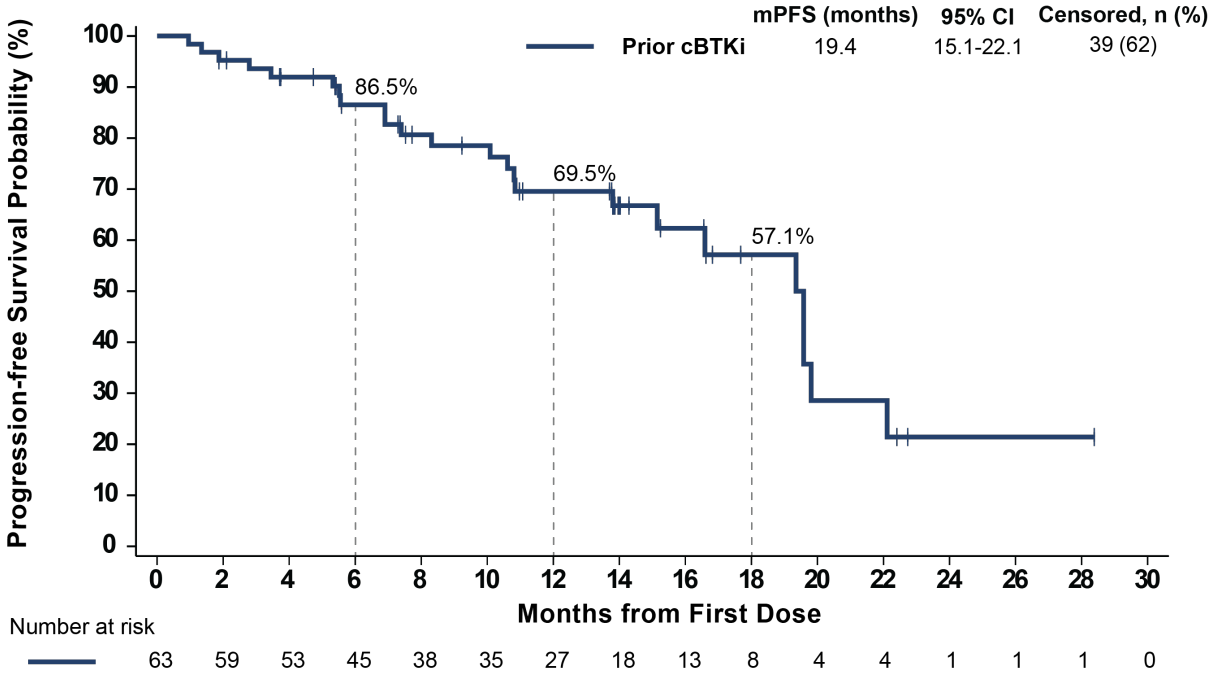


Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	66.7 (53.7-78.0)	88.2 (63.6-98.5)
CR + VGPR Rate, % (95% CI)	23.8 (14.0-36.2)	29.4 (10.3-56.0)
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)	0 (0)
SD,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

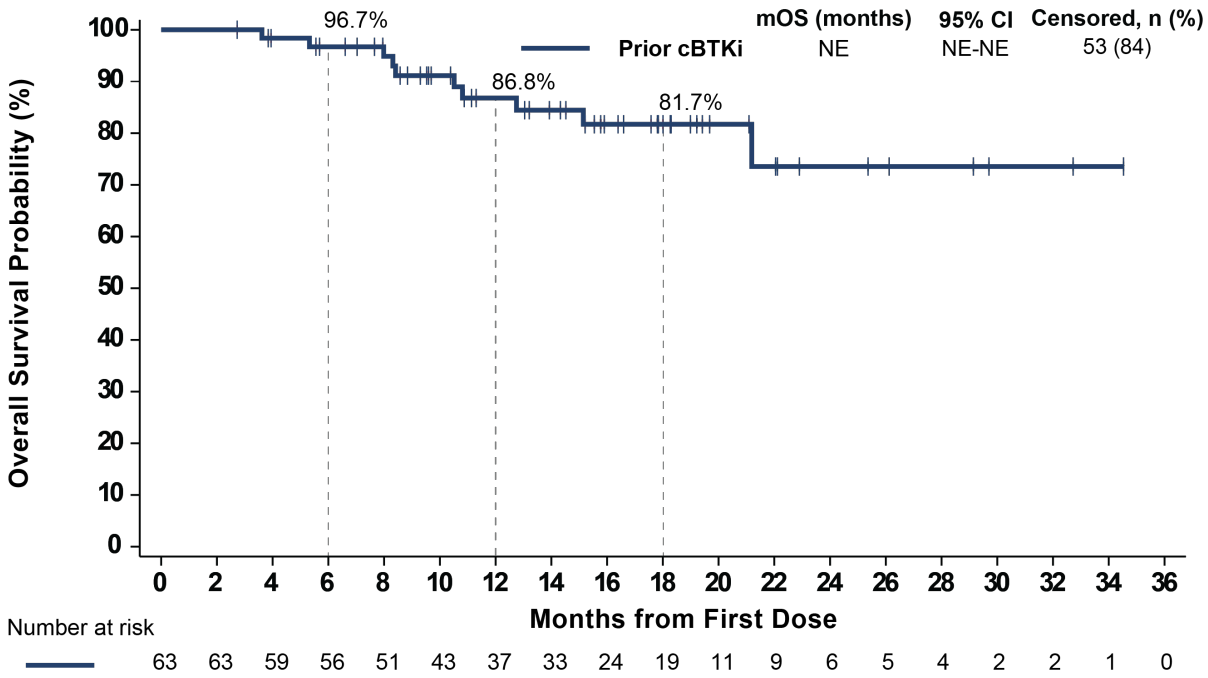
Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding 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.

Progression-Free Survival and Overall Survival **in** Prior cBTKi Patients

Progression-Free Survival



Overall Survival



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

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

Pirtobrutinib Safety Profile

	All Doses and Patients (N=773)			
	Treatment-Emergent AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event (AEs)	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Fatigue	28.7%	2.1%	9.3%	0.8%
Diarrhea	24.2%	0.9%	9.3%	0.4%
Neutropenia[a]	24.2%	20.4%	14.7%	11.5%
Contusion	19.4%	0.0%	12.8%	0.0%
Cough	17.5%	0.1%	2.3%	0.0%
Covid-19	16.7%	2.7%	1.3%	0.0%
Nausea	16.2%	0.1%	4.7%	0.1%
Dyspnea	15.5%	1.0%	3.0%	0.1%
Anemia	15.4%	8.8%	5.2%	2.1%
AEs of Special Interest[b]	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Bruising[c]	23.7%	0.0%	15.1%	0.0%
Rash[d]	12.7%	0.5%	6.0%	0.4%
Arthralgia	14.4%	0.6%	3.5%	0.0%
Hemorrhage/Hematoma[e]	11.4%	1.8%	4.0%	0.6%
Hypertension	9.2%	2.3%	3.4%	0.6%
Atrial fibrillation/flutter[f,g]	2.8%	1.2%	0.8%	0.1%

Median time on treatment for the overall safety population was 9.6 months
Discontinuations due to treatment-related AEs occurred in 2.6% (n=20) of all patients
Dose reductions due to treatment-related AEs occurred in 4.5% (n=35) of all patients
Overall and WM safety profiles are generally consistent[h]

Data cutoff date of 29 July 2022. [a]Aggregate of neutropenia and neutrophil count decreased. [b]AEs of special interest are those that were previously associated with covalent BTK inhibitors. [c]Aggregate of contusion, petechiae, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hematoma or hemorrhage. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of the 22 total afib/aflutter TEAEs in the overall safety population, 7 occurred in patients with a prior medical history of atrial fibrillation. [h]WM safety population data can be found via QR code. Constipation is more commonly seen as a TEAE in the WM population than in all patients.

Pirtobrutinib shows synergistic interactions with venetoclax in MYD88 mutated lymphoma cells.

BCWM.1 - BTK^{WT}

Pirtobrutinib

Venetoclax	3.1600	1.0000	0.3160	0.1000
3.1600	0.4320	0.7140	0.8960	1.3630
1.0000	0.5030	0.7230	0.6520	0.6430
0.3160	0.4900	0.6060	0.3140	0.4490
0.1000	0.6970	0.7870	0.2590	0.2400

BCWM.1 - BTK^{Cys481Ser}

Pirtobrutinib

Venetoclax	3.1600	1.0000	0.3160	0.1000
3.1600	0.6610	1.0630	2.0900	0.9140
1.0000	0.3940	0.2860	0.2270	0.1650
0.3160	0.3190	0.2520	0.1010	0.0950
0.1000	0.7470	0.4430	0.4550	0.2850

TMD8 - BTK^{WT}

Pirtobrutinib

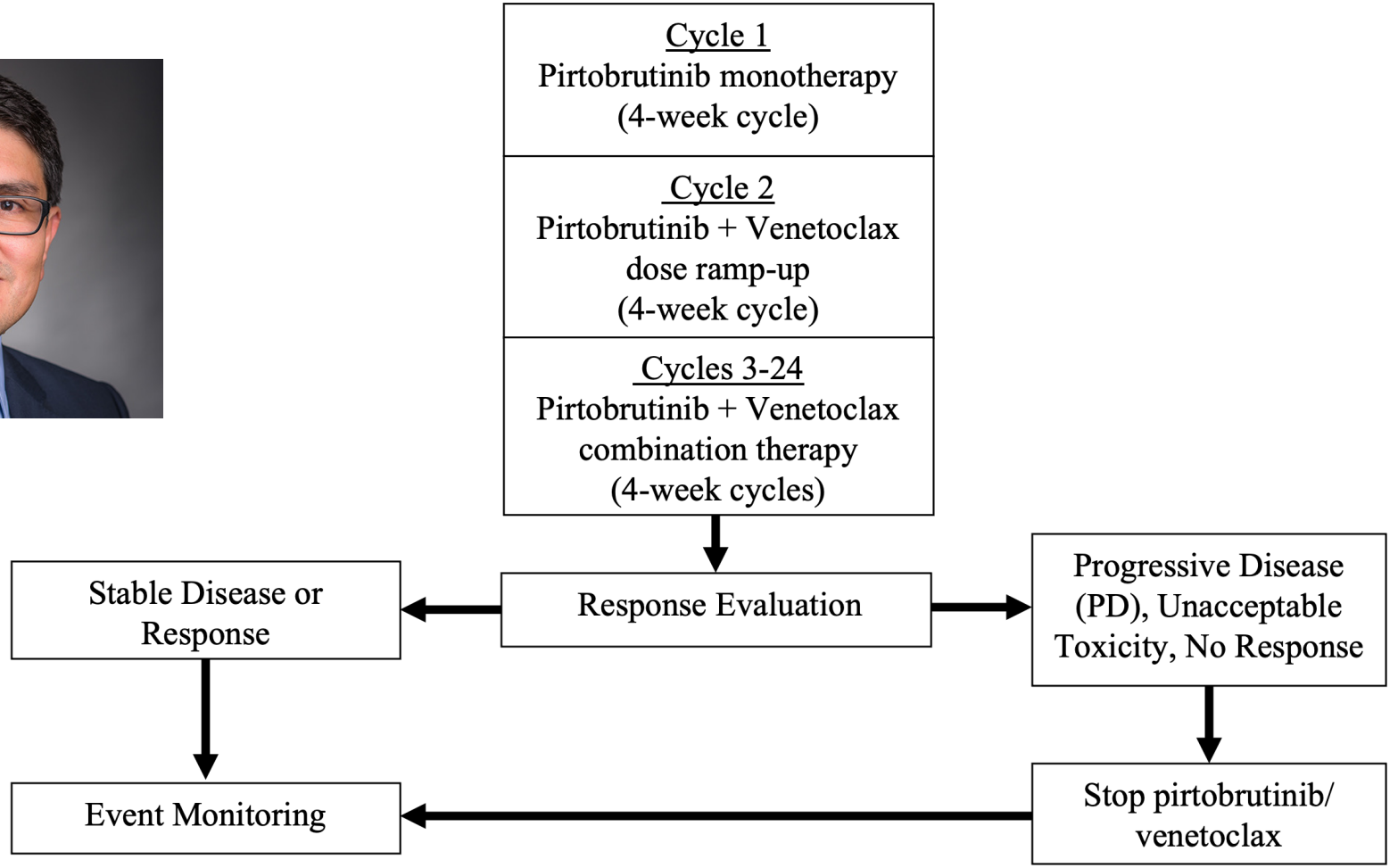
Venetoclax	0.0316	0.0100	0.0032	0.0010
3.1600	0.1830	0.1170	0.0930	0.0810
1.0000	0.2370	0.1290	0.1310	0.0800
0.3160	0.2600	0.2300	0.2600	0.2740
0.1000	0.3490	0.4030	0.3790	0.4750

TMD8 - BTK^{Cys481Ser}

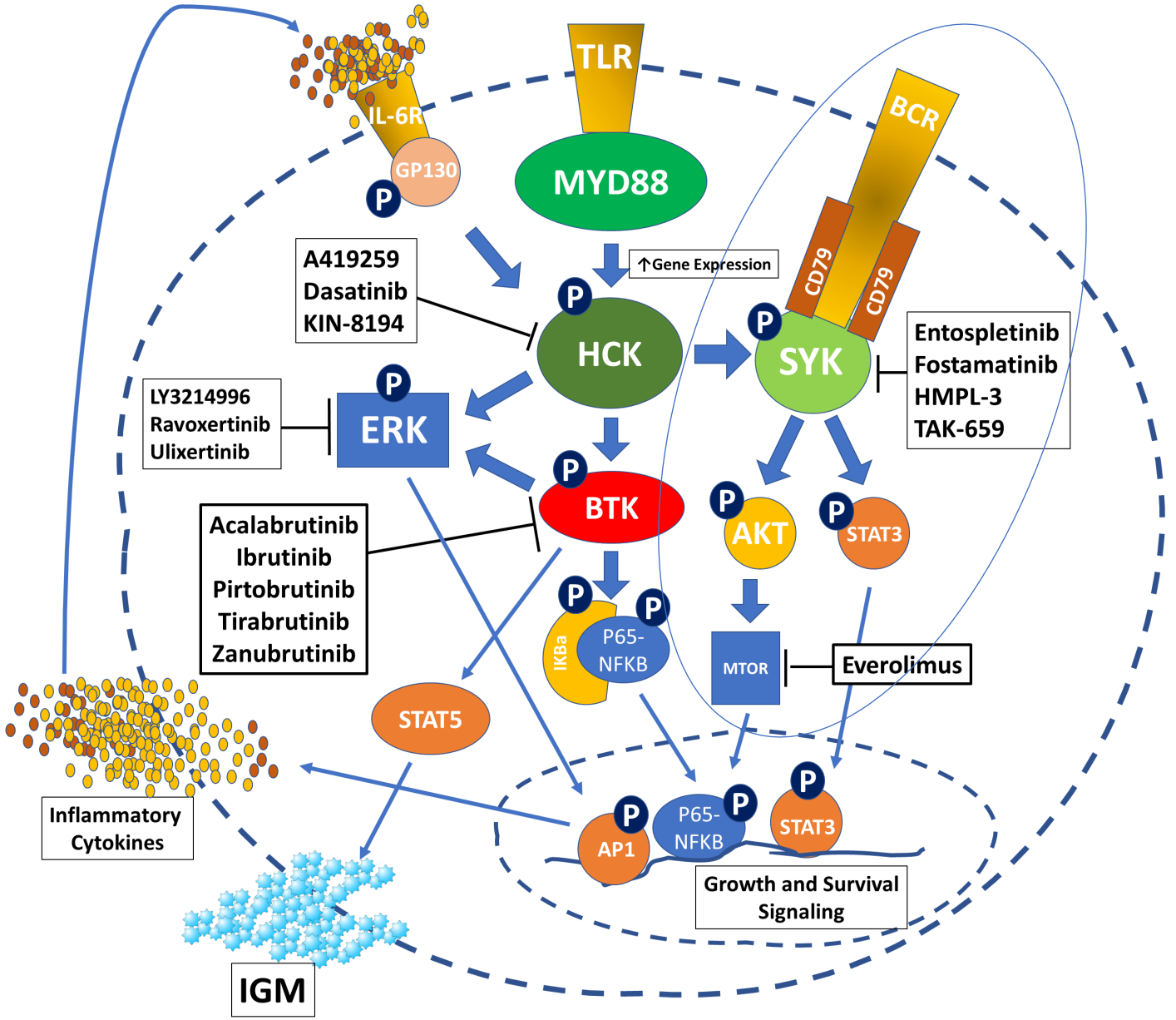
Pirtobrutinib

Venetoclax	0.0316	0.0100	0.0032	0.0010
3.1600	0.3370	0.2120	0.2070	0.2980
1.0000	0.4240	0.2730	0.1920	0.2440
0.3160	0.5060	0.3640	0.2520	0.3030
0.1000	0.6710	0.4950	0.3560	0.6750

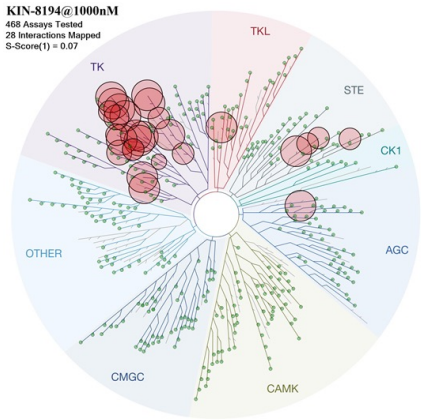
Schema for Pirtobrutinib and Venetoclax Study in Relapsed/Refractory WM



Targeting HCK in MYD88 Driven Lymphomas

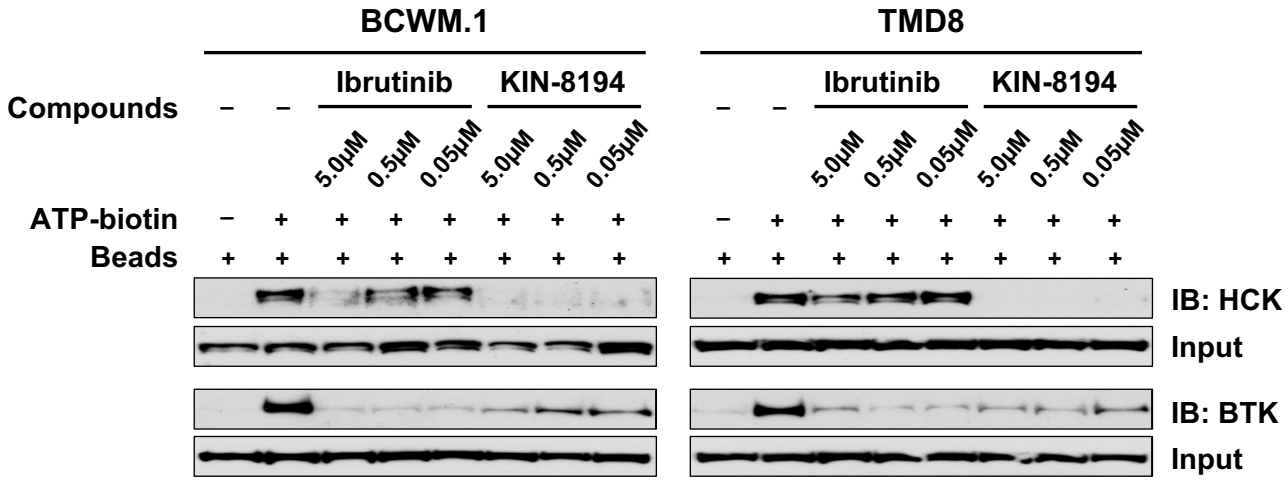


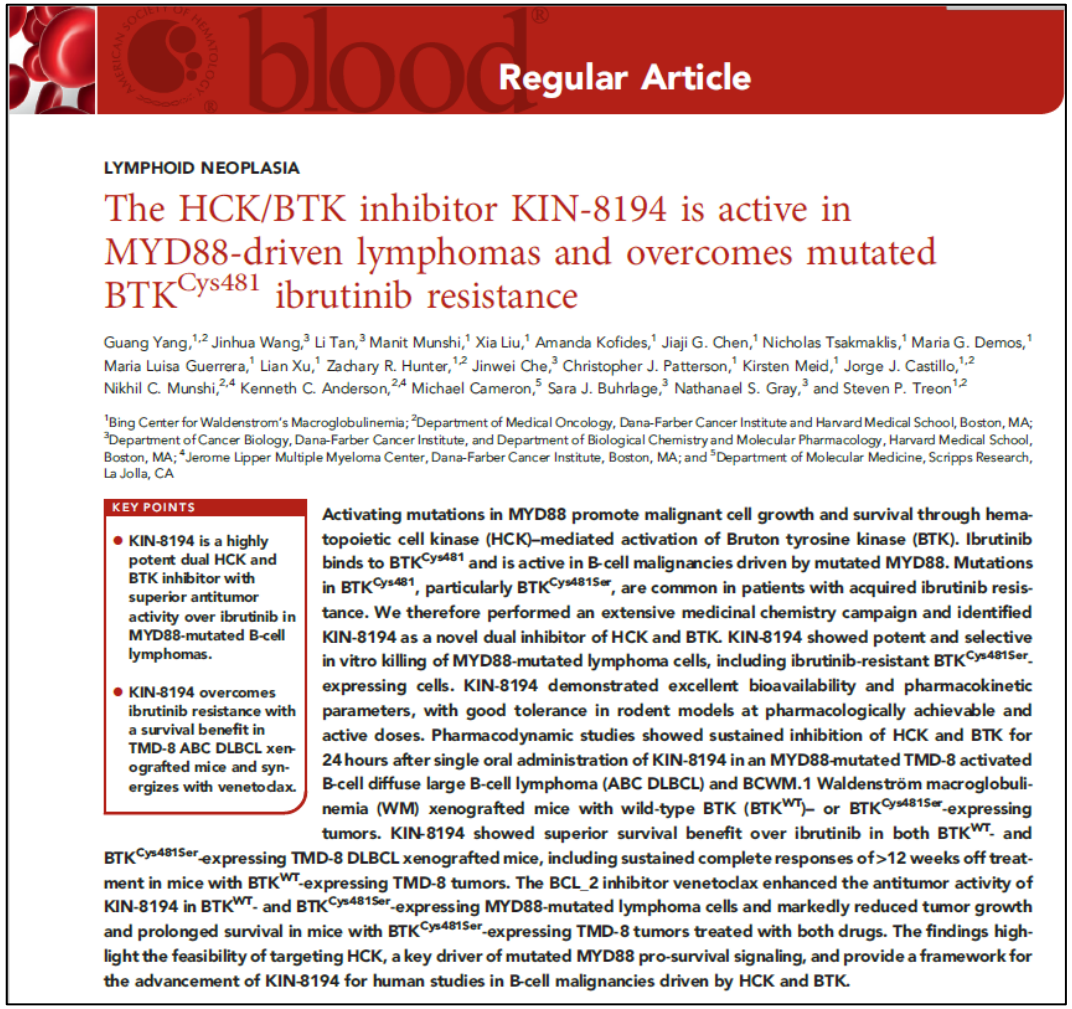
KIN-8194 is a highly potent, dual HCK/BTK Inhibitor



KINOMEscan® against a panel of 468 kinases. KIN-8194 at 1.0 uM showed good selectivity (S10=0.07)

Kinases	Enzymatic IC50 (nM)	Kinase group	Kinase family
HCK	<0.495	TK	SRC
BLK	<0.495	TK	SRC
BTK	0.915	TK	TEC
LYN	1.150	TK	SRC
FRK	1.400	TK	SRC
ACK (TNK2)	7.780	TK	ACK
CSK	16.100	TK	CSK
ErbB2	52.600	TK	EPH
ABL	98.600	TK	ABL




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

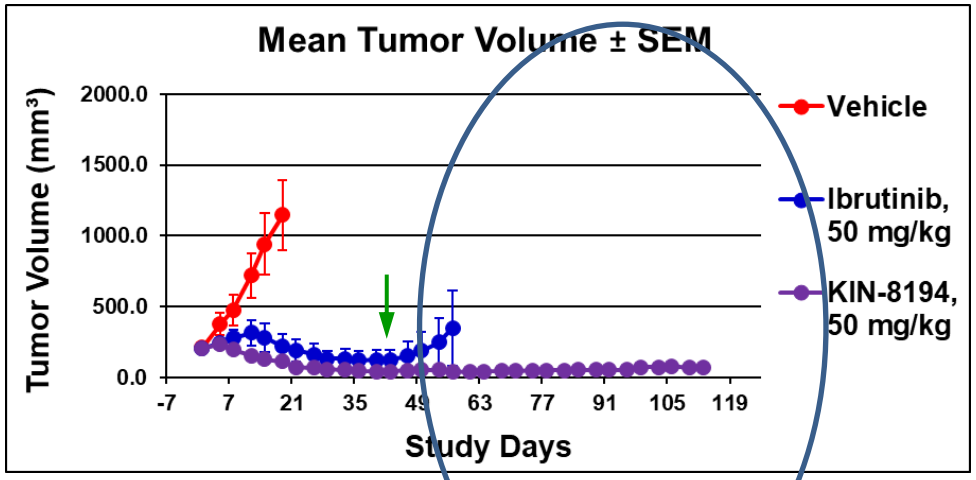
KEY POINTS

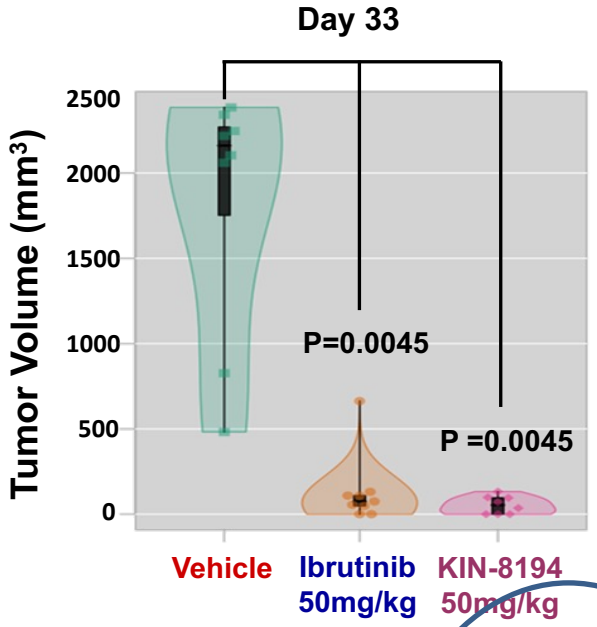
- KIN-8194 is a highly potent dual HCK and BTK inhibitor with superior antitumor activity over ibrutinib in MYD88-mutated B-cell lymphomas.
- KIN-8194 overcomes ibrutinib resistance with a survival benefit in TMD-8 ABC DLBCL xenografted mice and synergizes with venetodax.

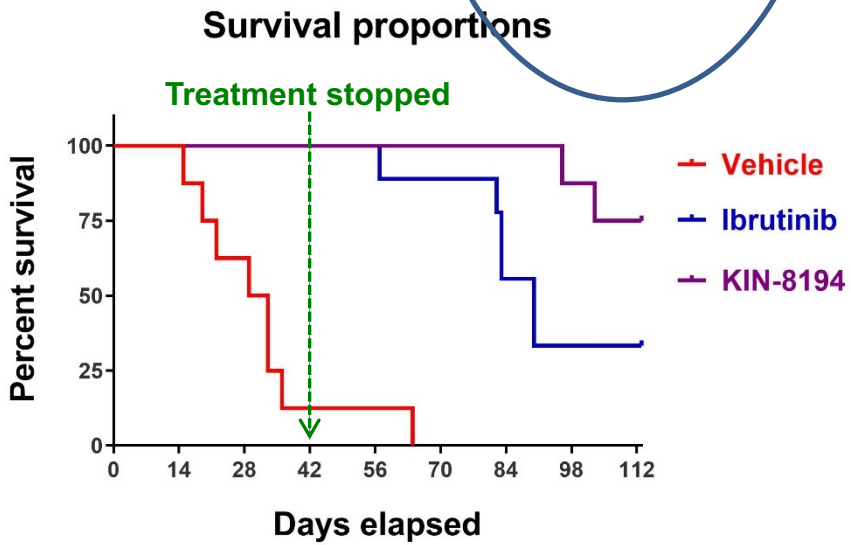
Activating mutations in MYD88 promote malignant cell growth and survival through hematopoietic cell kinase (HCK)–mediated activation of Bruton tyrosine kinase (BTK). Ibrutinib binds to BTK^{Cys481} and is active in B-cell malignancies driven by mutated MYD88. Mutations in BTK^{Cys481}, particularly $BTK^{Cys481Ser}$, 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.

Yang et al, Blood 2021

KIN-8194 Efficacy Studies in BTK wild-type TMD8 xenografted mice





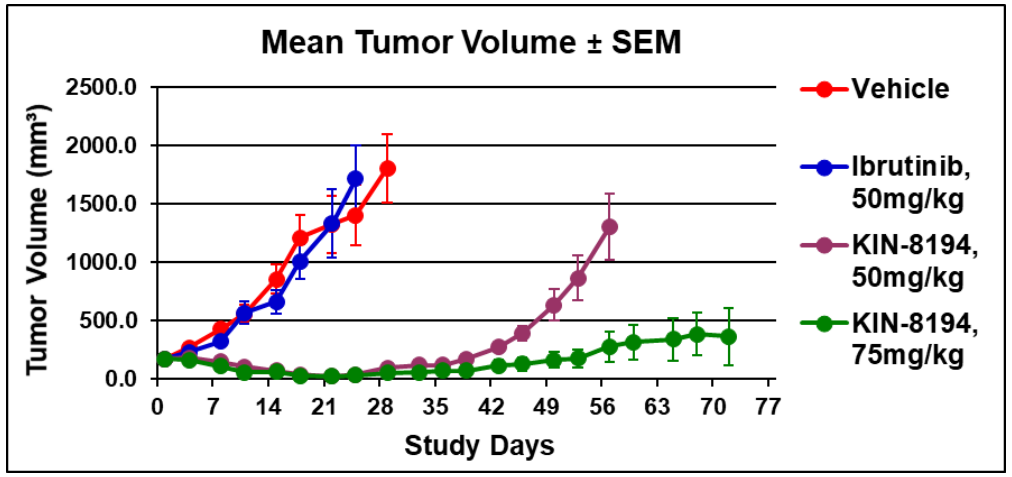


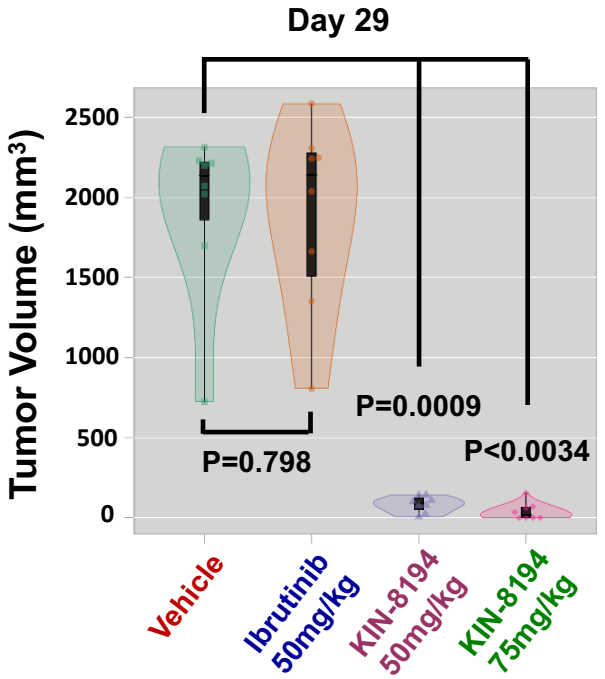
Median Survival	Vehicle	Ibrutinib (50mg/kg)	KIN-8194 (50mg/kg)
(days)	31	90	Undefined

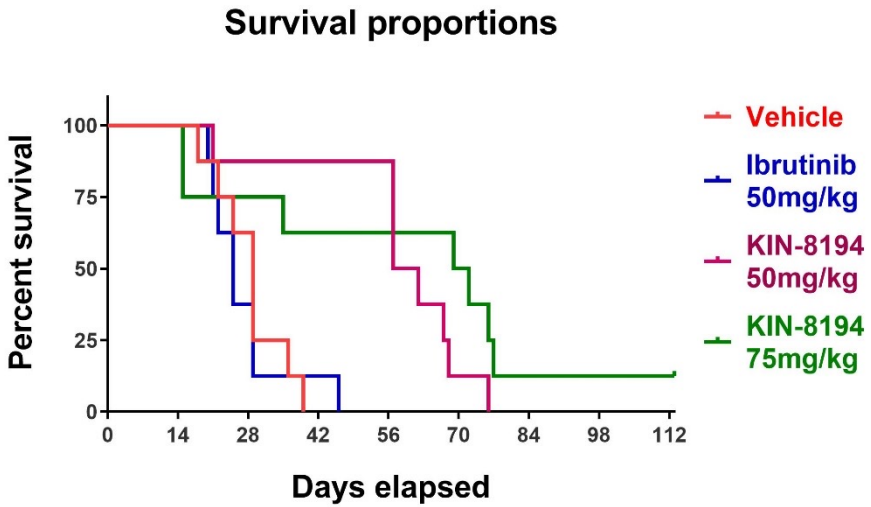
Log-rank (Mantel-Cox) test, P<0.0001

Yang et al, Blood 2021

KIN-8194 Efficacy Studies in BTK Cys481 mutated TMD8 xenografted mice





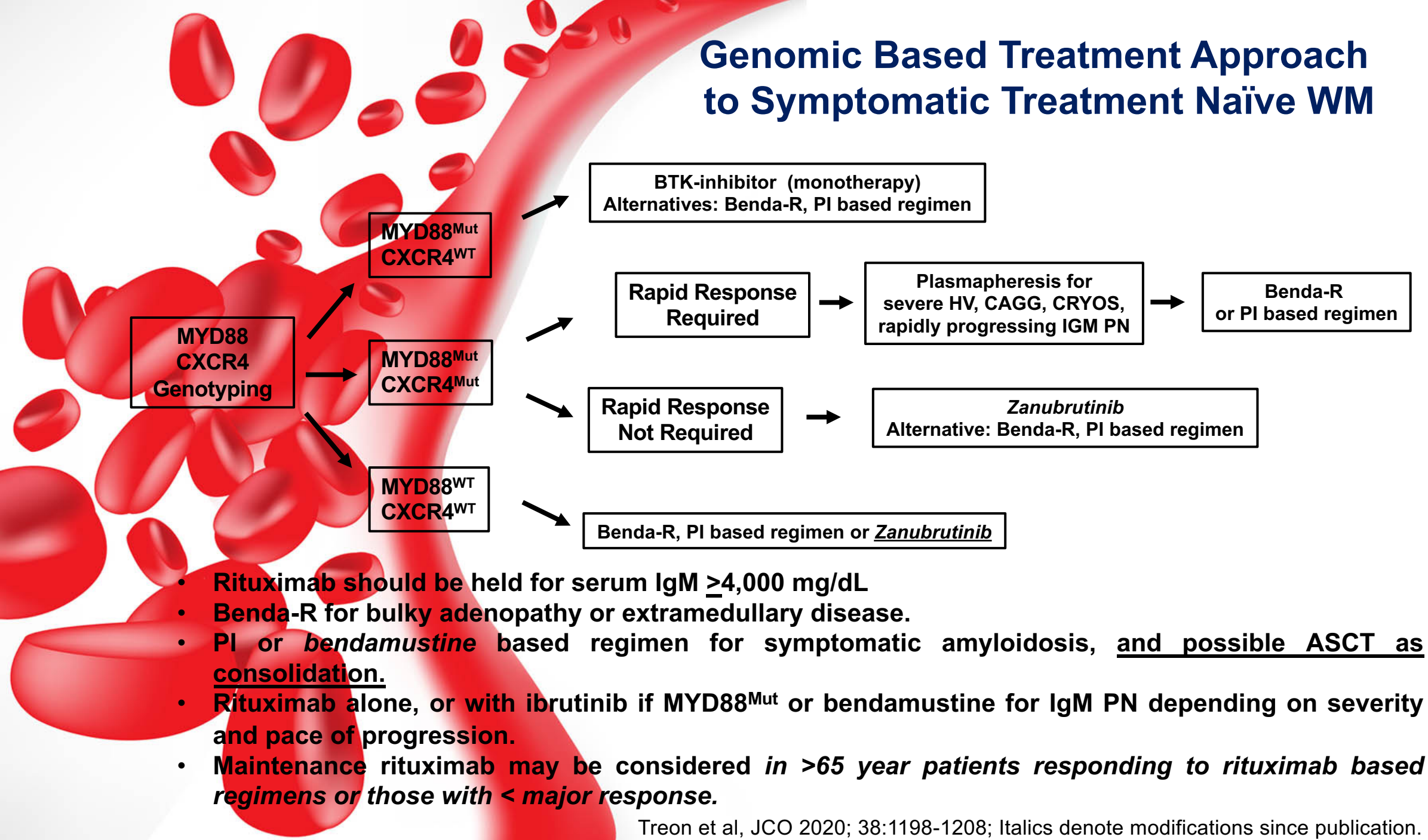


Median Survival	Vehicle	Ibrutinib 50mg/kg	KIN-8194 50mg/kg	KIN-8194 75mg/kg
(days)	29	25	57.5	70.5

Log-rank (Mantel-Cox) test, P=0.0007

Yang et al, Blood 2021

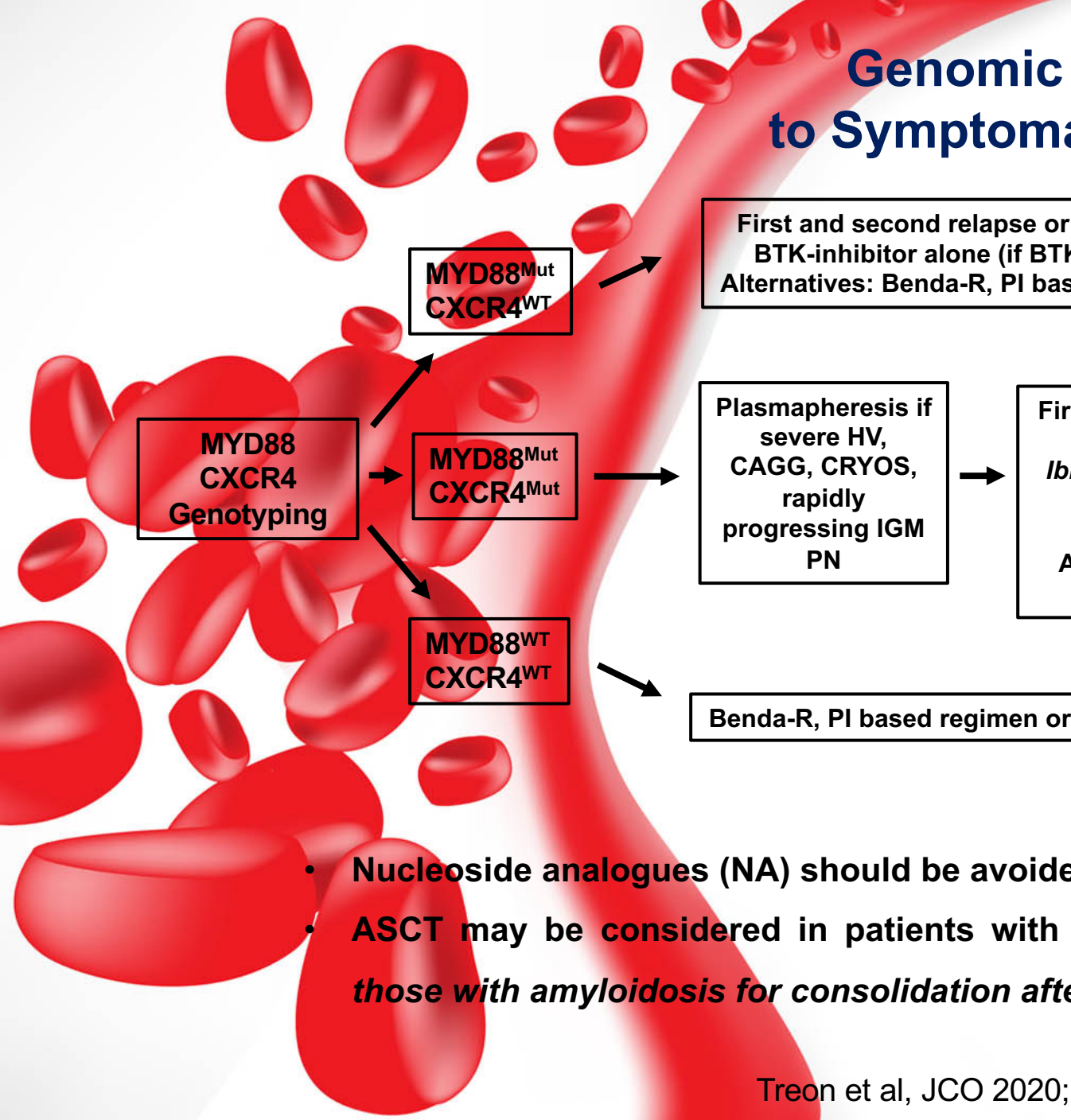
Genomic Based Treatment Approach to Symptomatic Treatment Naïve WM



- Rituximab should be held for serum IgM ≥4,000 mg/dL
- Benda-R for bulky adenopathy or extramedullary disease.
- PI or *bendamustine* based regimen for symptomatic amyloidosis, and possible ASCT as consolidation.
- Rituximab alone, or with ibrutinib if MYD88^{Mut} or bendamustine for IgM PN depending on severity and pace of progression.
- Maintenance rituximab may be considered *in >65 year patients responding to rituximab based regimens or those with < major response.*

Treon et al, JCO 2020; 38:1198-1208; Italics denote modifications since publication.

Genomic Based Treatment Approach to Symptomatic Relapsed or Refractory WM



MYD88 CXCR4 Genotyping

MYD88^{Mut} CXCR4^{WT}

First and second relapse or refractory BTK-inhibitor alone (if BTK-I naïve)
Alternatives: Benda-R, PI based regimen

→ Third or later relapse or refractory BTK-inhibitor alone (if BTK-I naïve)
Alternatives: *Venetoclax*, NA[1], everolimus

MYD88^{Mut} CXCR4^{Mut}

Plasmapheresis if severe HV, CAGG, CRYOS, rapidly progressing IGM PN

→ First and second relapse or refractory *Ibrutinib plus rituximab or zanubrutinib* (if BTK-I naïve)
Alternative: Benda-R, PI based regimen

→ Third or later relapse or refractory *Ibrutinib plus rituximab or zanubrutinib* (if BTK-I naïve)
Alternatives: venetoclax, NA[1], everolimus

MYD88^{WT} CXCR4^{WT}

Benda-R, PI based regimen or *zanubrutinib*

- **Nucleoside analogues (NA) should be avoided in younger patients, and candidates for ASCT.[1]**
- **ASCT may be considered in patients with multiple relapses, and chemosensitive disease, *and those with amyloidosis for consolidation after PI or bendamustine based therapy.***

Treon et al, JCO 2020; 38:1198-1208; Italics denote modifications since publication.

Bing Center for WM