Waldenstrom's Macroglobulinemia

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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.
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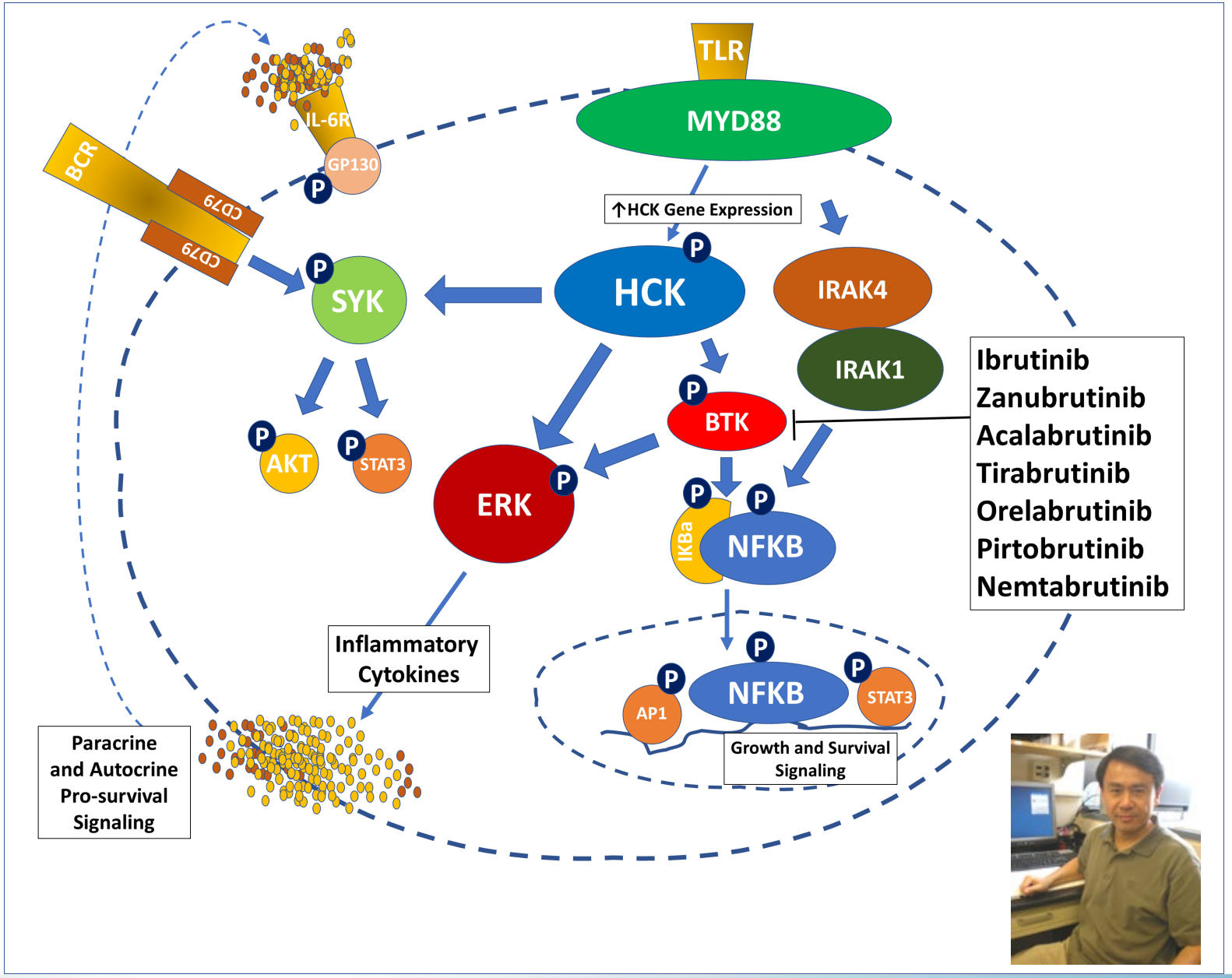

BTK-Inhibitor Trials in WM

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.
Phase 2	TN, R/R	Zanubrutinib	77	2.8 mo.	96% / 82%	45%	76% @ 36 mo.
ASPEN-1 ($MYD88^{Mut}$)	TN, R/R	Ibrutinib	99	2.9 mo.	94% / 80%	25%	85% @ 42 mo.
	TN, R/R	Zanubrutinib	102	2.8 mo.	95% / 81%	36%	88% @ 42 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% (cBTKi naïve)	24% (prior cBTKi) 29% (cBTKi naïve)	57% @ 18 mo. (for prior cBTKi) N/A for cBTKi naïve.

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]

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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]

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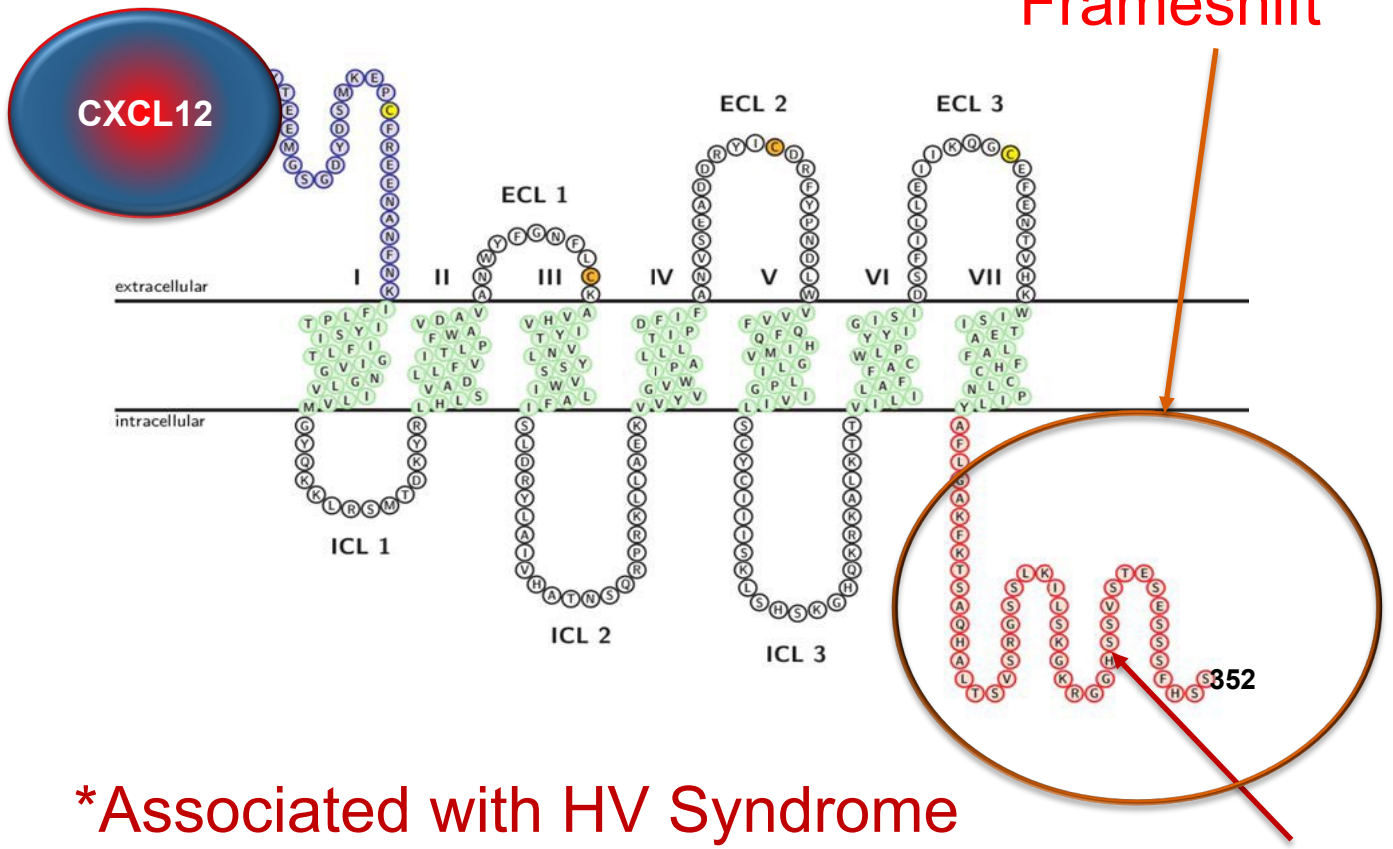
30-40% of WM patients have CXCR4 mutations

CXCR4 mutations
Non-sense (S338X)*
Frameshift



*Associated with HV Syndrome

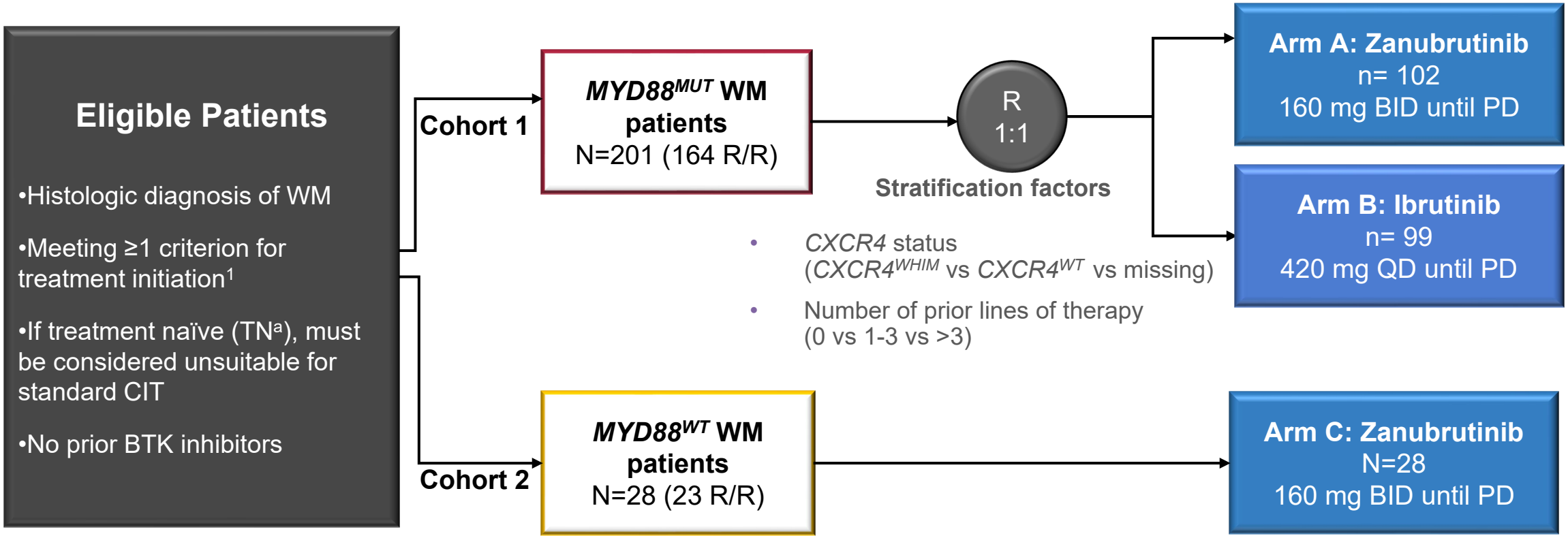
Adapted from Kahler et al. *AIMS Biophysics.* 2016, 3(2): 211-231.

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.

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.)
INNOVATE Arm C	R/R	Ibrutinib	3.6 vs. 1.0 mo.	71% vs. 88%	14% vs. 41%	18 mo. vs. NR (@ 60 mo.)
Phase 2	TN	Ibrutinib	7.3 vs. 1.8 mo.	78% vs. 94%	14% vs. 44%	59% vs. 92% (@ 48 mo.)
INNOVATE Arms A, B	TN, R/R	Ibrutinib Rituximab	3 vs. 2 mos.	77% vs. 81%	23% vs. 41%	63% vs. 72% (@ 54 mo.)
Phase 2	R/R	Zanubrutinib	N/A	91% vs. 87%	27% vs. 59%	~90% vs. ~78% (@ 42 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.)

Zanubrutinib vs Ibrutinib in WM
Phase 3 ASPEN



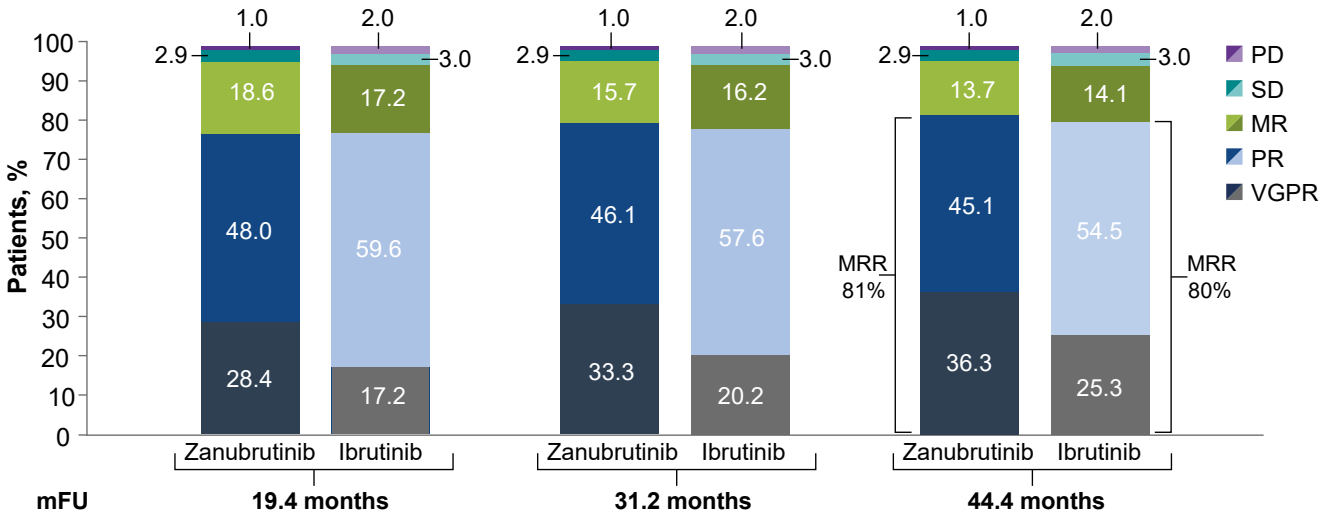
BID, twice daily; BTK, Bruton tyrosine kinase; CIT, chemoimmunotherapy; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88^{MUT}, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naïve; WM, Waldenström Macroglobulinemia;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

[a]Up to 20% of the overall population

ClinicalTrials.gov Identifier: NCT03053440

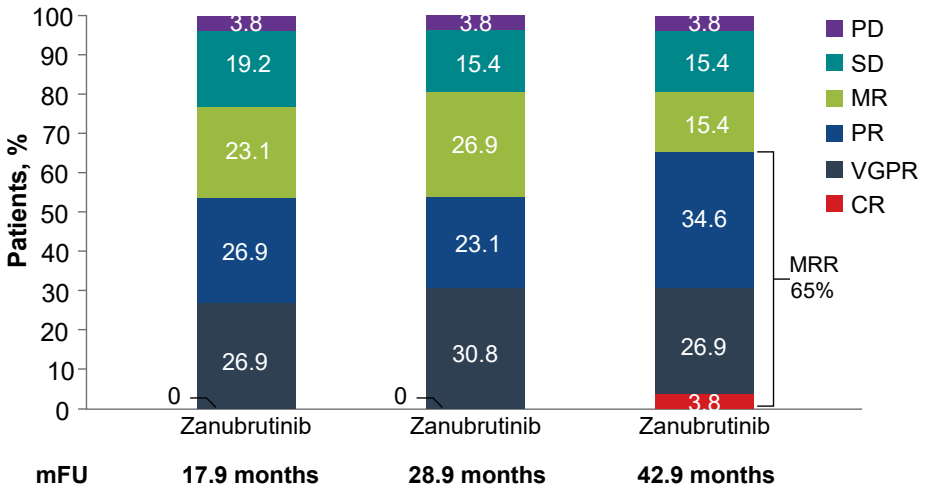
ASPEN: Best Overall Response and PFS by Investigator Assessment

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

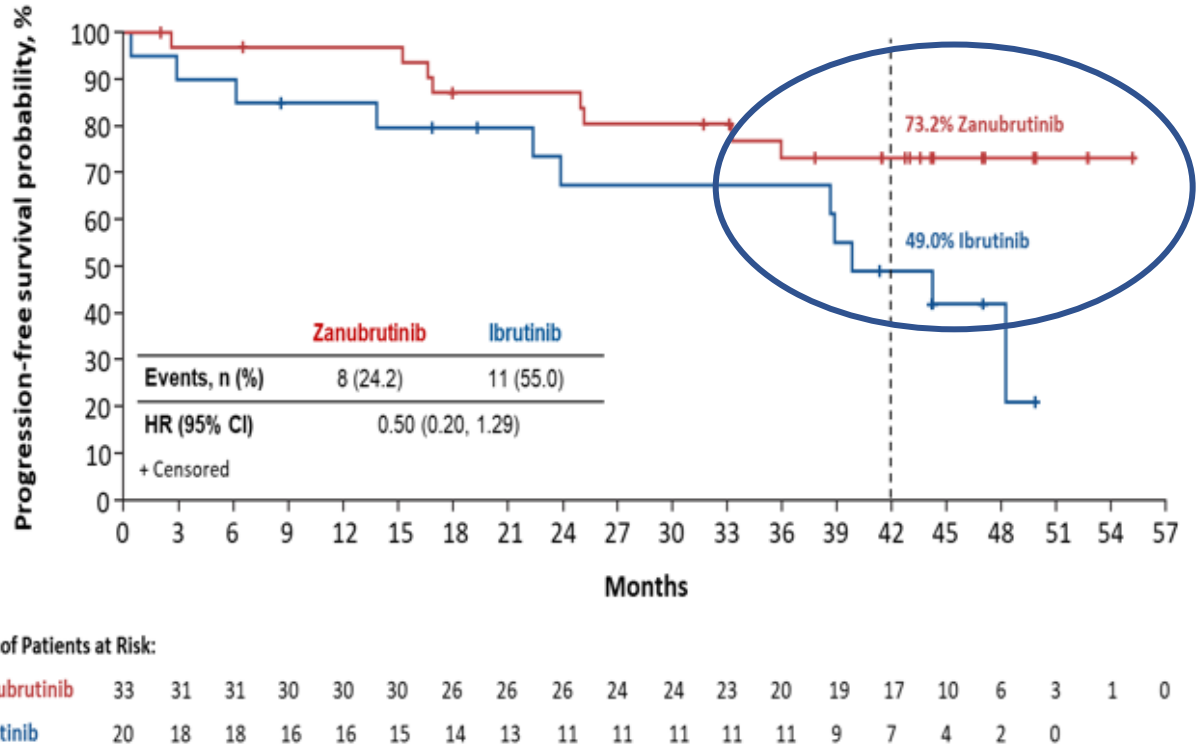
Response and PFS in Patients With *MYD88*^{MUT} by *CXCR4*^{MUT} Status

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}

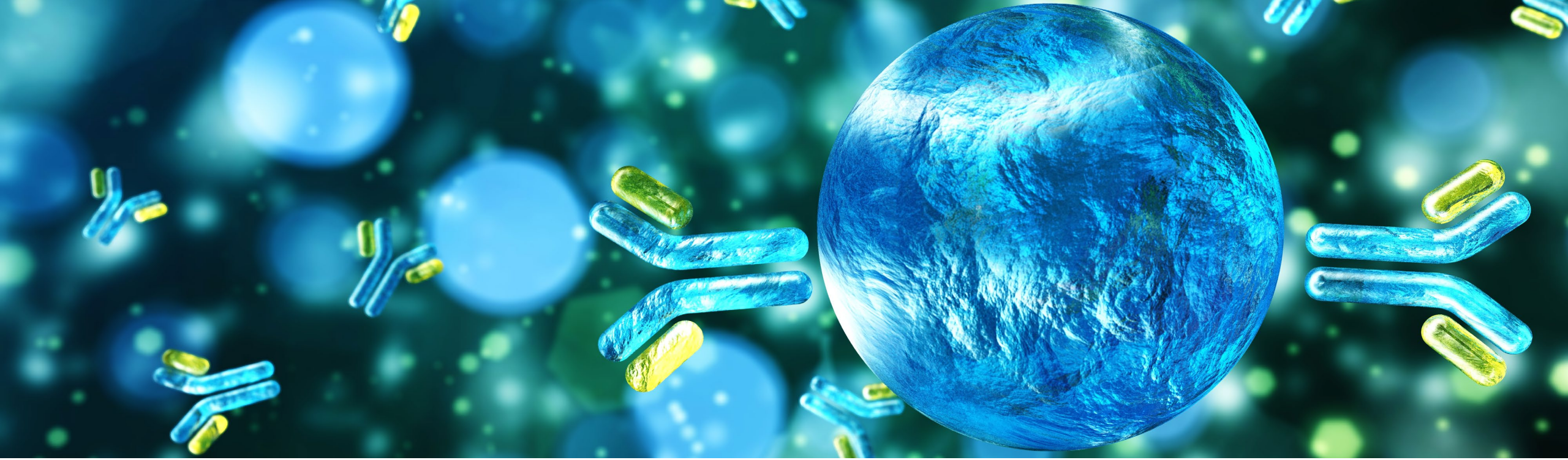


[a]*CXCR4* mutation determined by NGS. Ninety-two ibrutinib patients and 98 zanubrutinib patients had NGS results available.
Data cutoff: October 31, 2021.
CI, confidence Interval; *CXCR4*, C-X-C chemokine receptor type 4 gene; HR, hazard ratio; MR, major response; MUT, mutant; PFS, progression-free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

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.



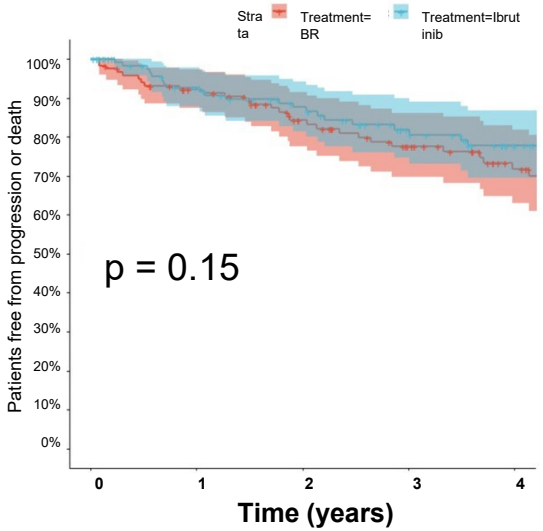
Do we give BTK-inhibitors or chemoimmunotherapy first in treatment naïve patients?

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

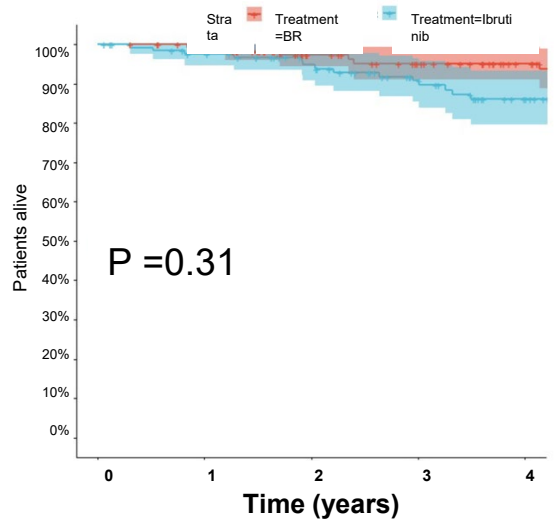
Jithma P. Abeykoon[1], Shaji Kumar[1], Jorge J. Castillo[2], Shirley D'sa[3], Efstathios Kastritis[4], Eric Durot[5], Encarl Uppal[3], Morel Pierre[6], Jonas Paludo[1], Reema Tawfiq[1], Shayna R Sarosiek[7], Olabisi Ogunbiyi[8], Pascale Cornillet-Lefebvre[9], Robert A. Kyle[1], Alain Delmer[10], Morie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

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



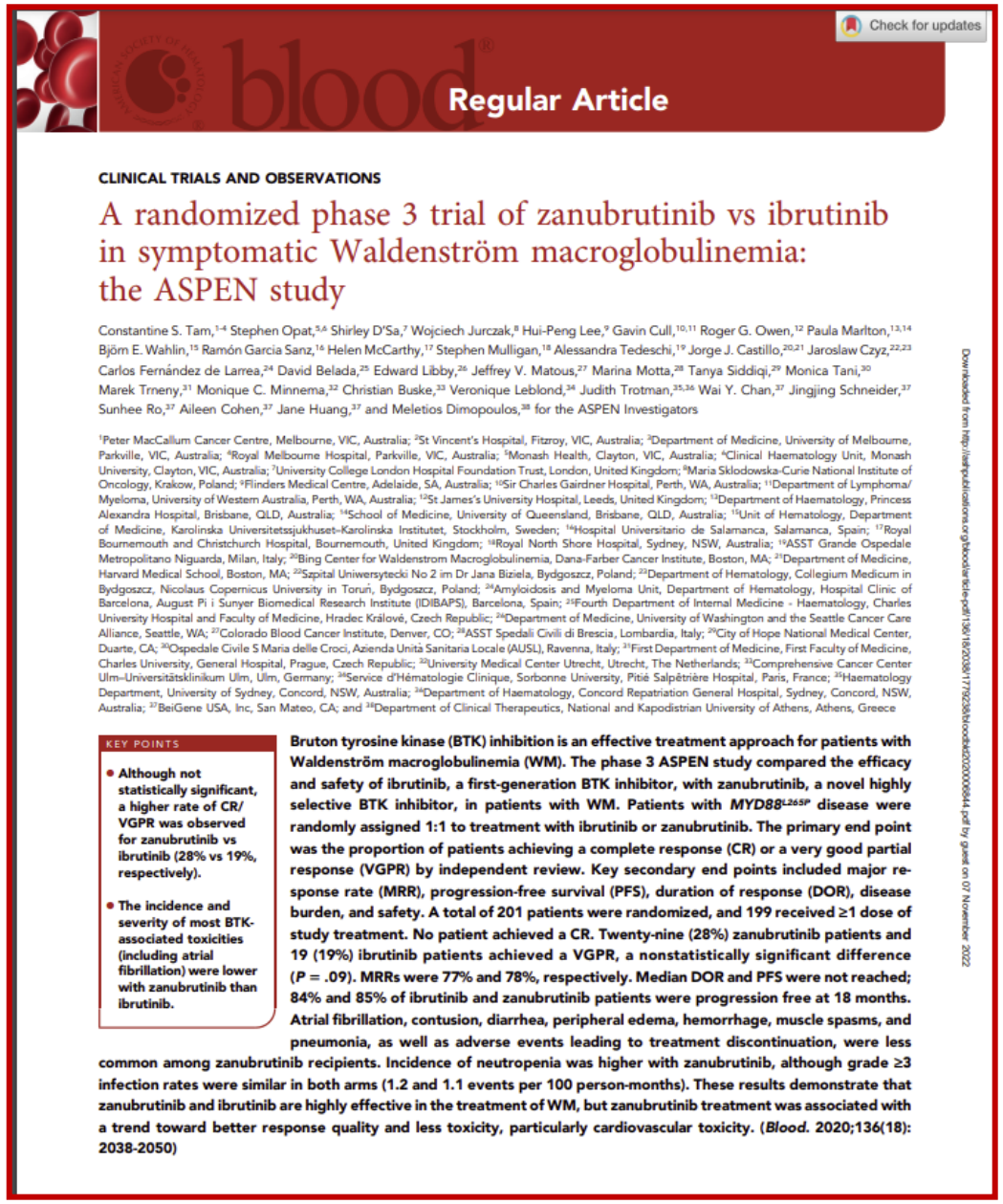
- Bivariate analysis of age matched patients who received either Benda-R or Ibrutinib (N=246)
- 77% of Benda-R patients received 6 cycles
- MYD88 WT patients excluded
- Median Follow-Up: 4.2 years

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%)

Abstracted from Tam et al, IWWM-12, Madrid Spain 2022



blood

Regular Article

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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

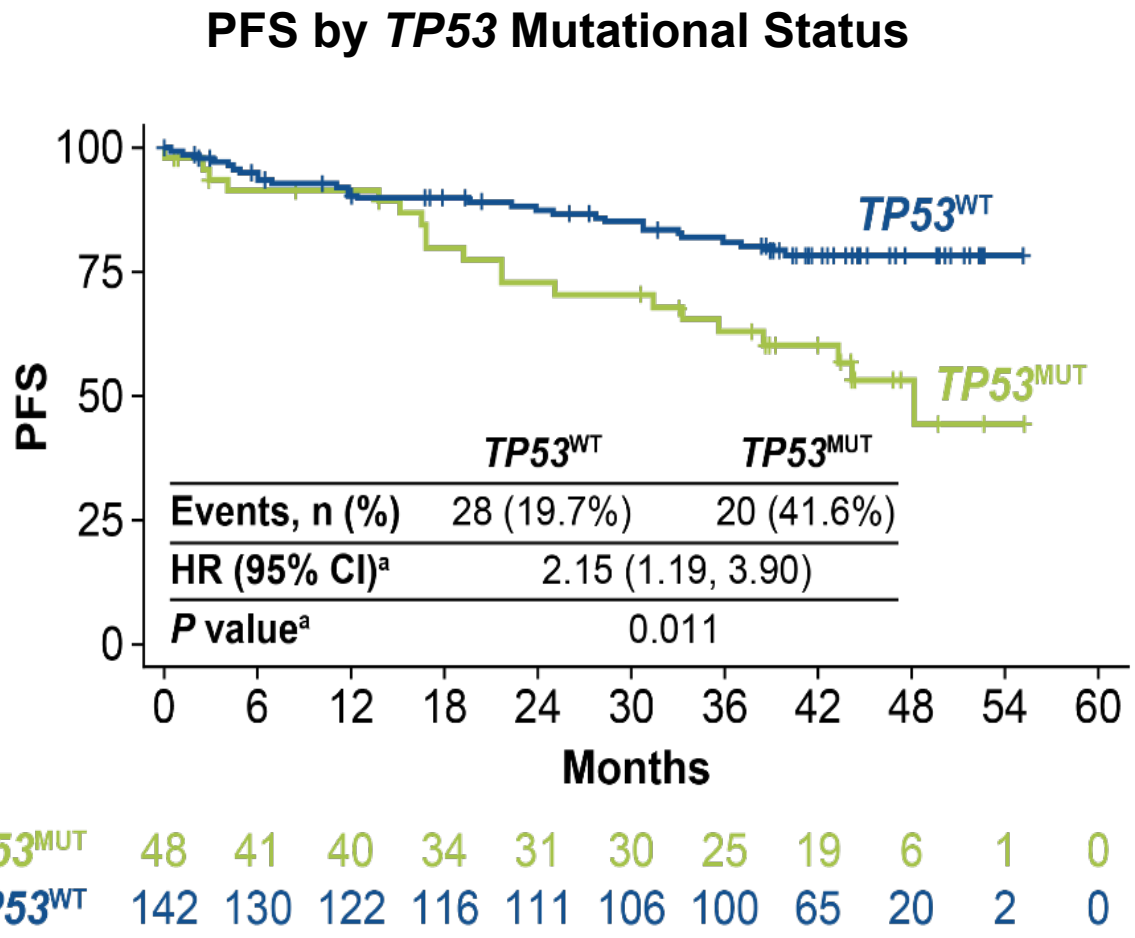
- Although not statistically significant, a higher rate of CR/VGPR was observed for zanubrutinib vs ibrutinib (28% vs 19%, respectively).
- The incidence and severity of most BTK-associated toxicities (including atrial fibrillation) were lower with zanubrutinib than ibrutinib.

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)

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)

Tam et al, Blood 2020; Updated IWWM-11, 2022

ASPEN: PFS in Patients With *TP53*^{MUT}



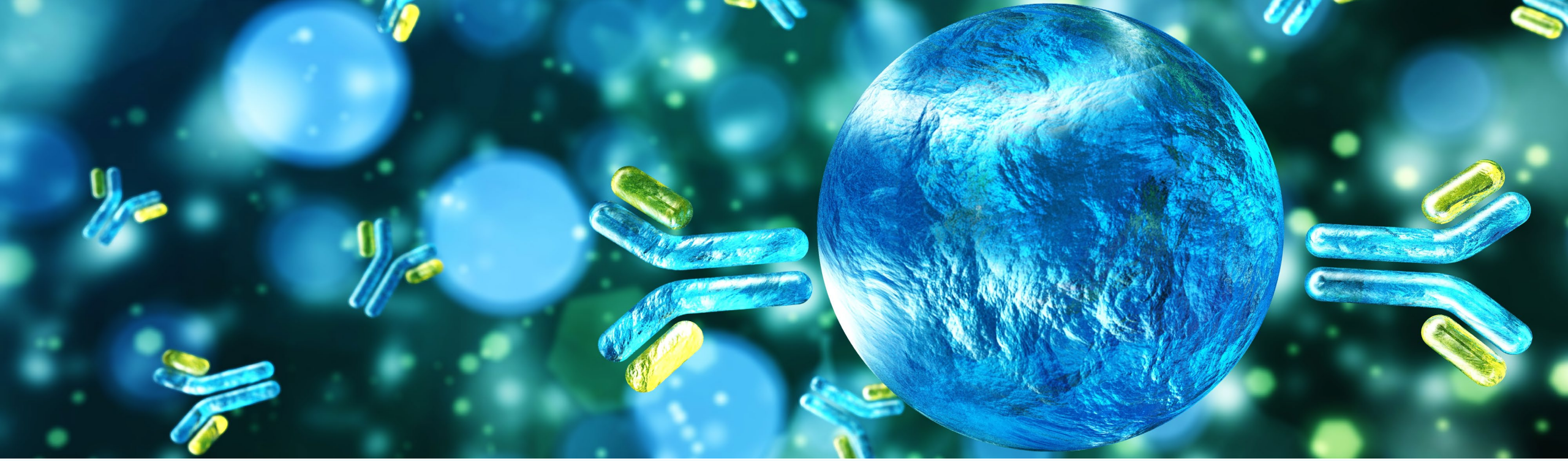
Tam et al, IWWM-11, 2022

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.



How do we optimize first line therapy with BTK-inhibitors?

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

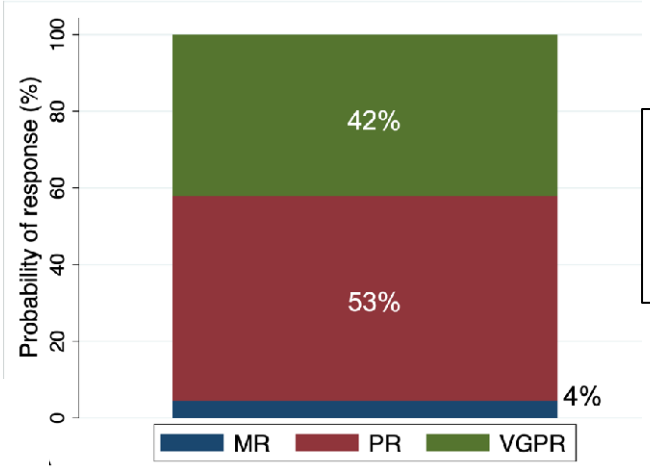
Stop therapy

Follow-up

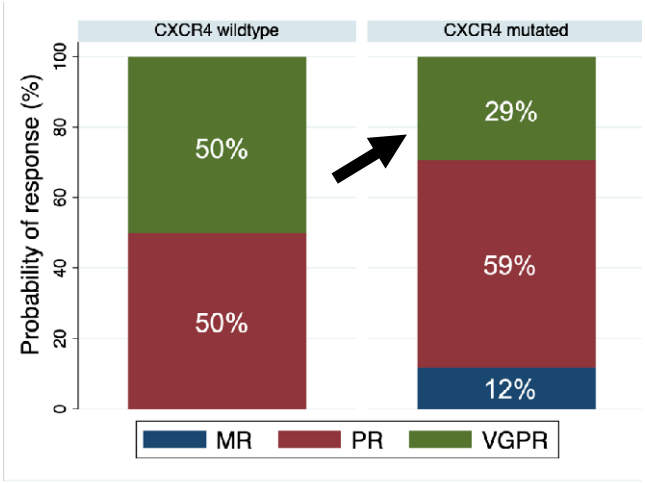
Continue therapy until completion

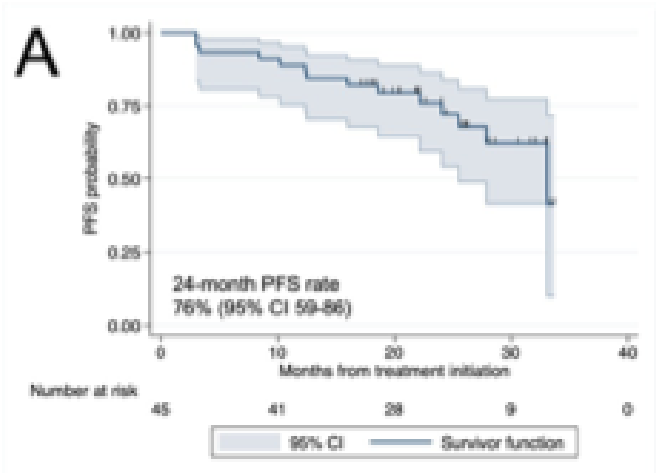
Castillo et al, Blood 2023 (in press)

Combination of Ibrutinib and Venetoclax in Treatment-Naïve WM

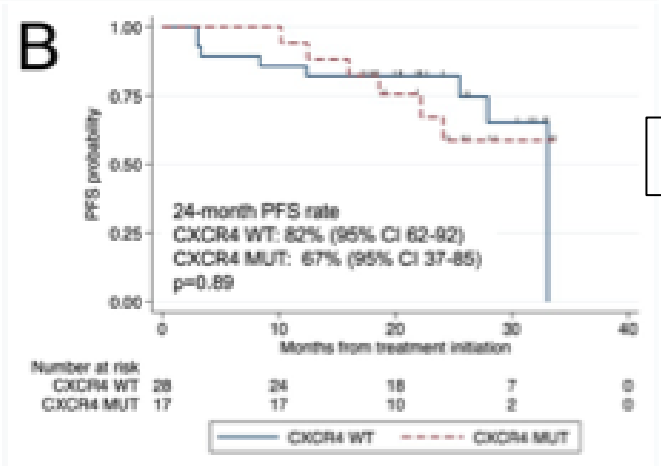


ORR 100%
Major RR 96%
VGPR 42%





24 mo. PFS: 79%



CXCR4 Mut Status

Median follow-up: 24 months

Castillo et al, BLOOD 2023 (In press)

Safety

Study therapy stopped due to unexpectedly high incidence (9%) of ventricular arrythmias, including 2 grade 5 events.

Adverse event	Grade 2	Grade 3	Grade 4	Grade 5
Alanine aminotransferase increase		1		
Anemia		1		
Anorexia	1			
Arthralgia	5	1		
Atrial fibrillation	1	2		
Bruising	2			
Diarrhea	11	3		
Fatigue	2	1		
Gastroesophageal reflux disease	12			
Headache		1		
Hematoma	1			
Hematuria	1			
Hyperphosphatemia	8			
Hypertension	2	1		
Hyponatremia	1			
Intracranial hemorrhage		1		
Lung infection	2			
Malaise	1			
Mucositis	9	4		
Myalgia	3			
Nausea	5			
Neutropenia	2	13	4	
Platelet decrease		1		
Skin rash	5			
Soft tissue infection	2	1		
Tumor lysis syndrome		3		
Upper respiratory infection	4			
Urinary tract infection	5			
Ventricular arrhythmia	1		1	2

Castillo et al, Blood 2023 (in press)

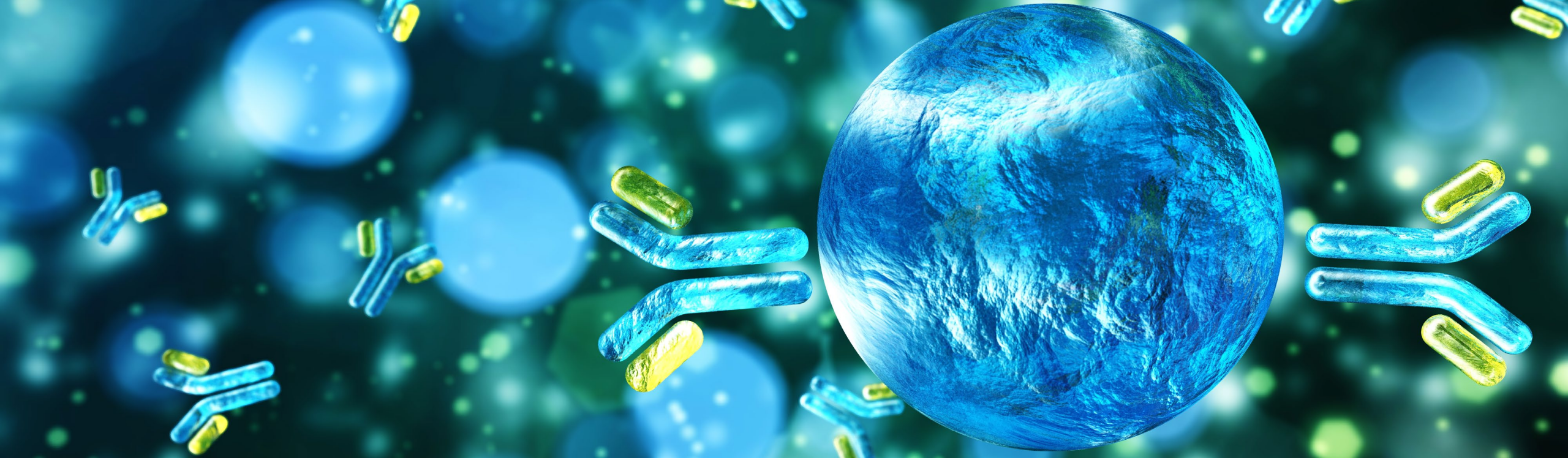
A Multi-Center, Open-Label, Single-Arm Phase II Trial of ***Bendamustine, Rituximab and the Next Generation BTK Inhibitor Acalabrutinib*** in Treatment Naïve WM - BRAWM

- 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

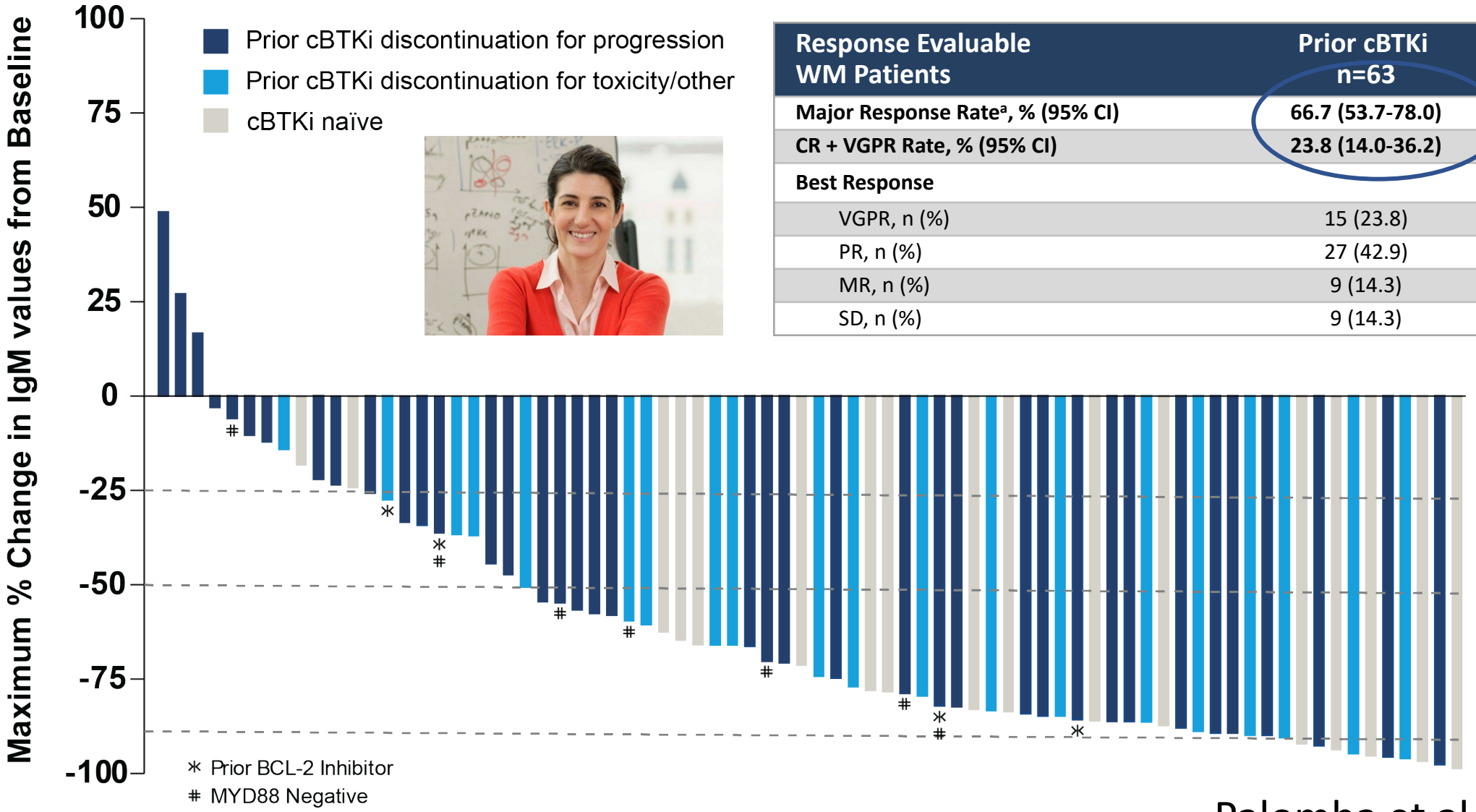
ClinicalTrials.gov Identifier: NCT04624906

Sunnybrook RESEARCH INSTITUTE



How do we manage BTK-inhibitor resistant disease?

Non-covalent BTK-I Pirtobrutinib Efficacy in WM Patients



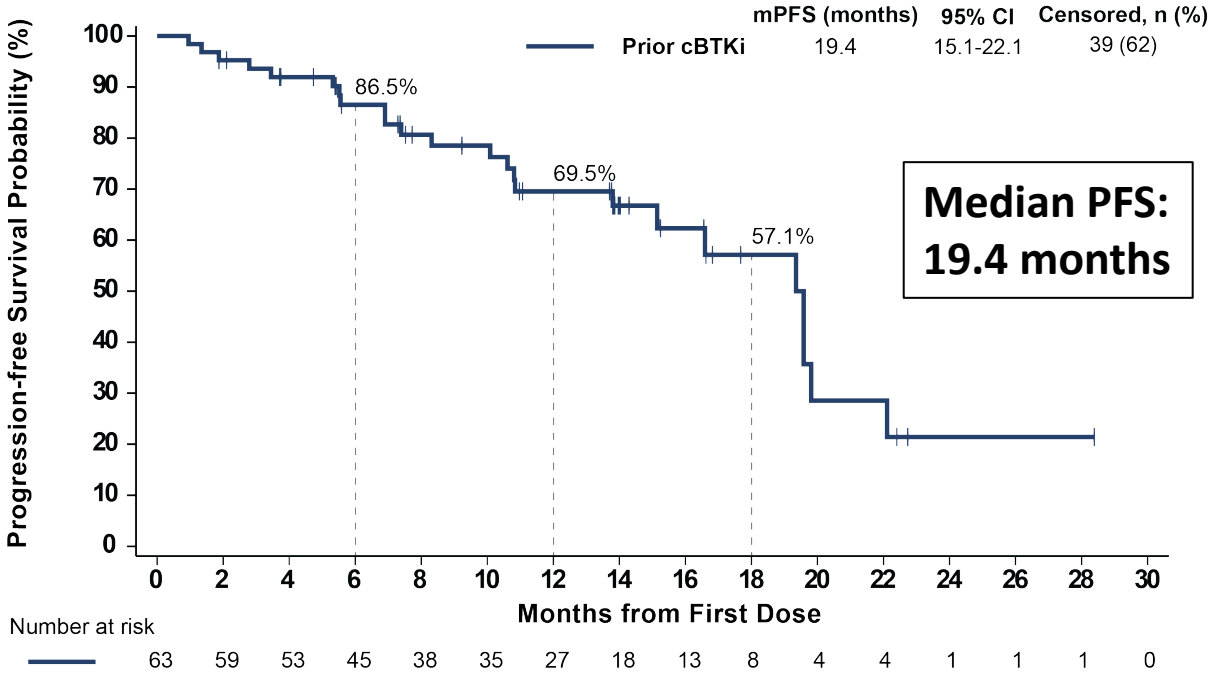
Response Evaluable WM Patients	Prior cBTKi n=63	cBTKi Naïve n=17
Major Response Rate[a], % (95% CI)	**66.7 (53.7-78.0)**	**88.2 (63.6-98.5)**
CR + VGPR Rate, % (95% CI)	**23.8 (14.0-36.2)**	**29.4 (10.3-56.0)**
Best Response		
VGPR, n (%)	15 (23.8)	5 (29.4)
PR, n (%)	27 (42.9)	10 (58.8)
MR, n (%)	9 (14.3)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

Palomba et al, IWWM-11

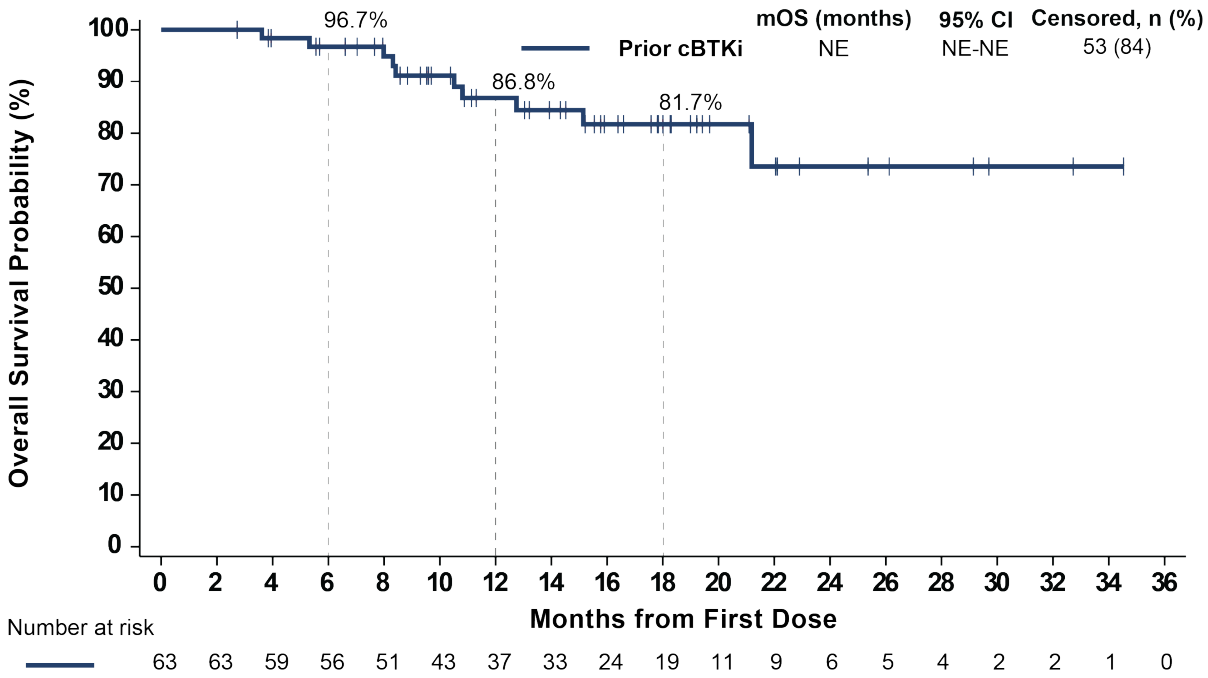
Data cutoff date of 29 July 2022. Data for 4 patients are not shown in the waterfall plot due to missing IgM values at baseline or response assessment. Response as assessed by investigator based on Modified IWWM6 (Owen's) criteria. Under modified IWWM6 criteria, a PR is upgraded to VGPR if corresponding 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 months, respectively
- 55.6% (35/63) of patients who received prior cBTKi remain on pirtobrutinib

Palomba et al, IWWM-11

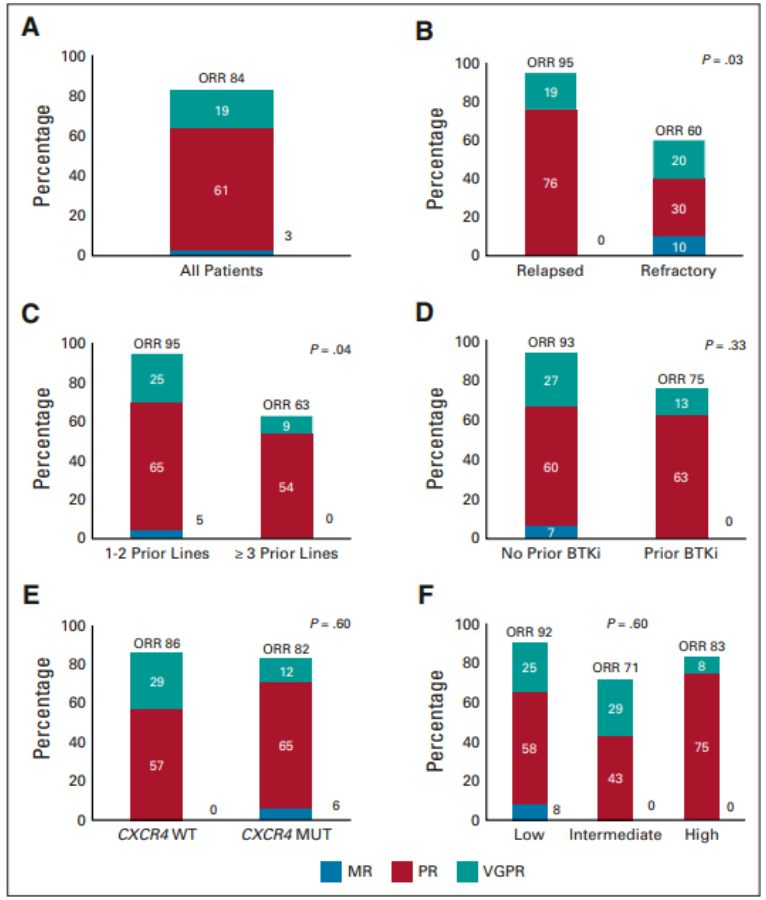
Data cutoff date of 29 July 2022. Response as assessed by investigator based on modified IWWM6 criteria.

original reports

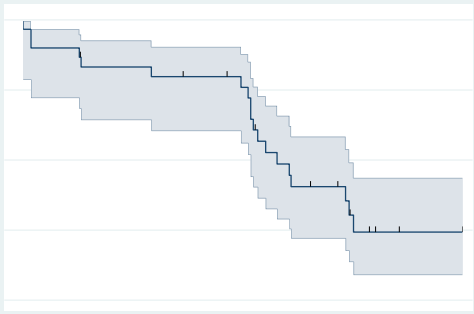
Venetoclax in Previously Treated Waldenström Macroglobulinemia

Journal of Clinical Oncology®

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]



ORR: 84%; Major RR: 81%



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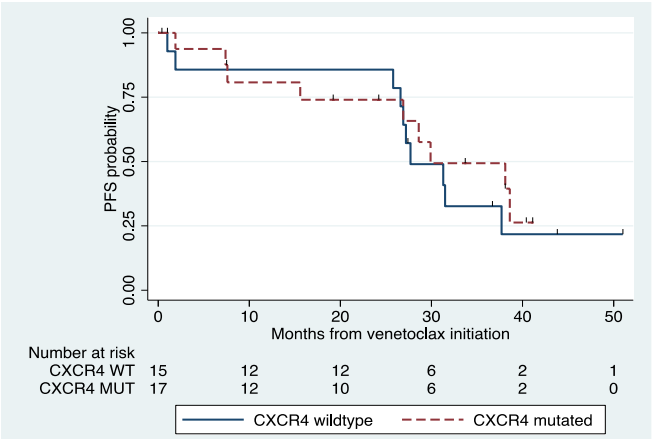
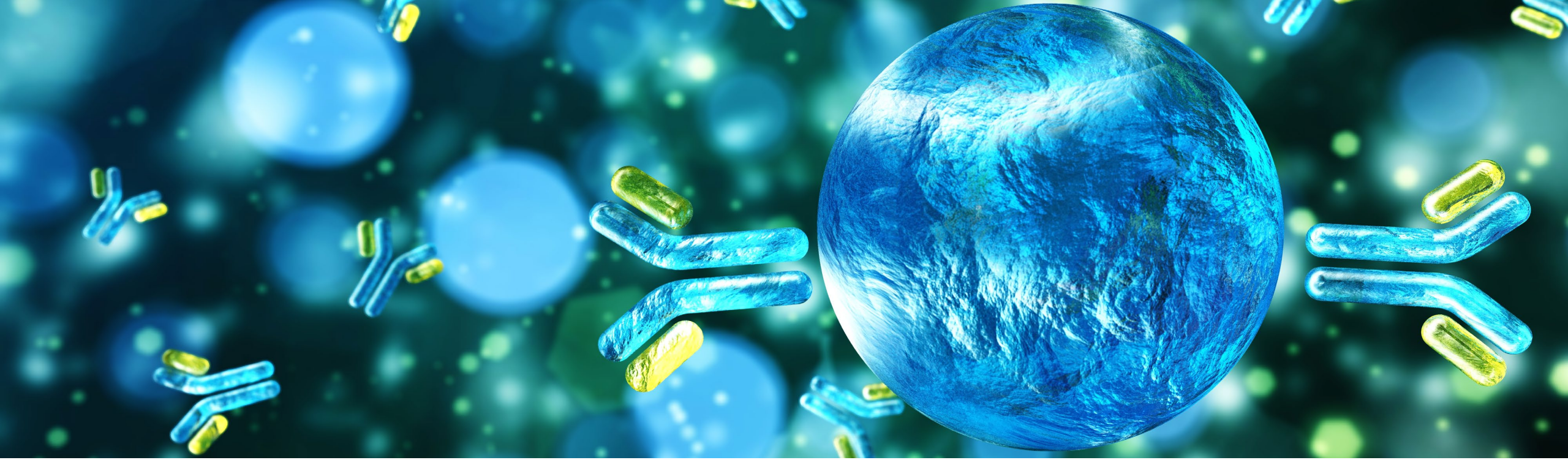


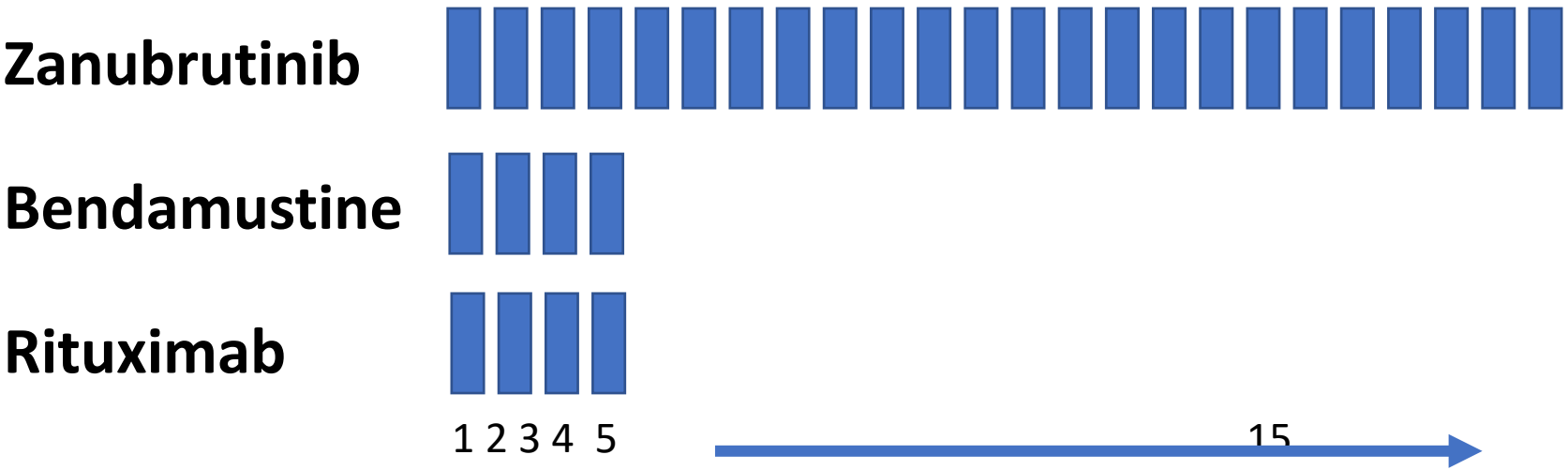
Median f/u: 33 mos; Median PFS: 30 mos.
Not impacted by CXCR4 mutation status.
Grade ≥3 neutropenia: 45%

Castillo et al, JCO 2021



What does the future hold for WM therapy?

Zanubrutinib, Bendamustine and Rituximab in Treatment Naïve WM (ZeBRa Trial)



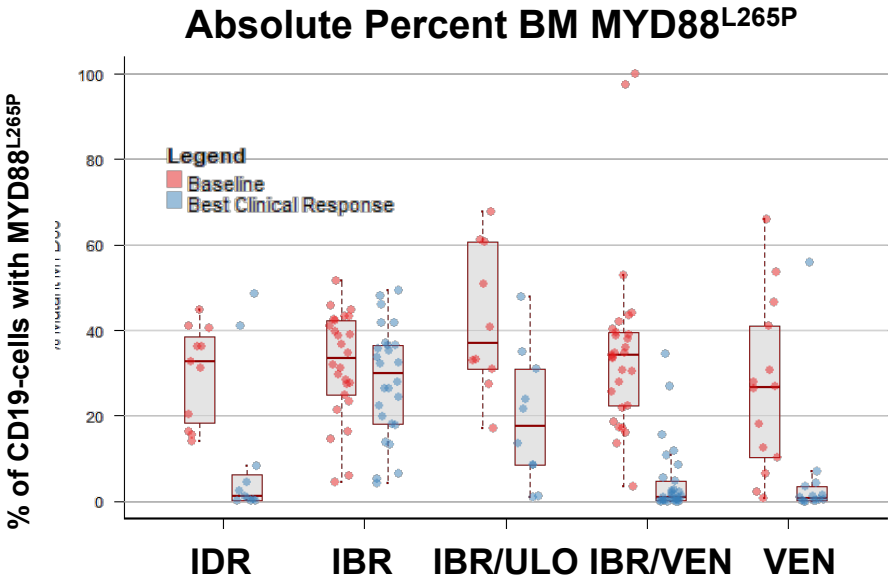
Andrew Branagan

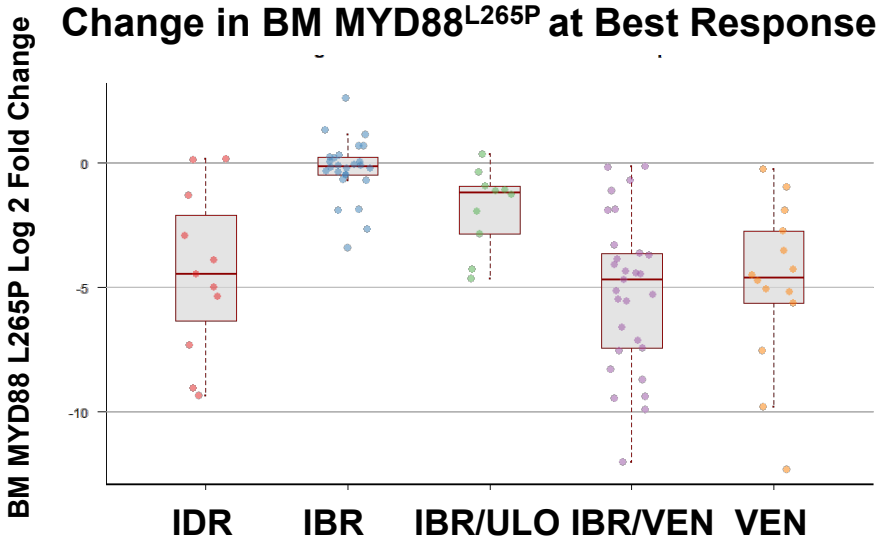
MASSACHUSETTS GENERAL HOSPITAL

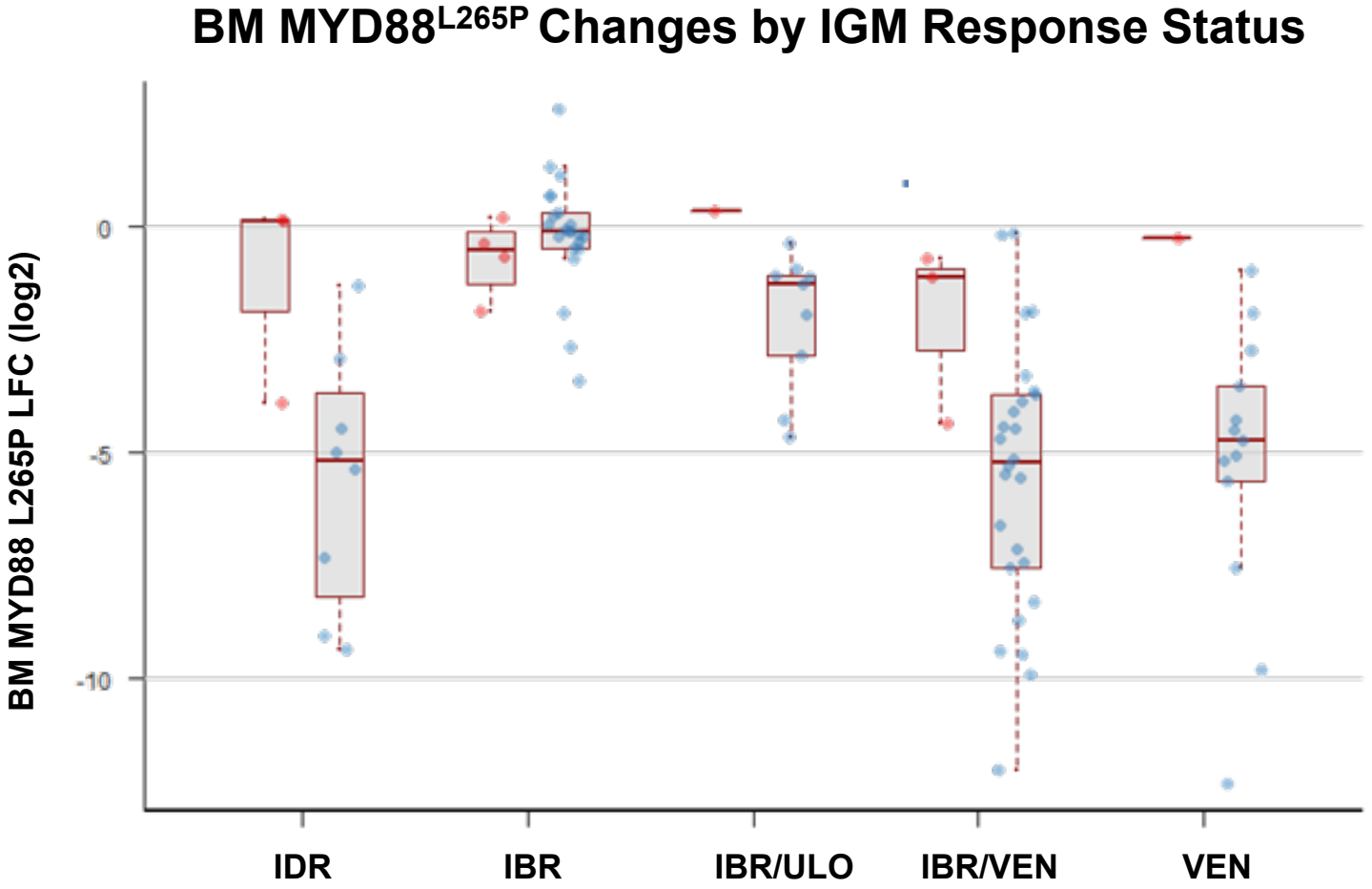
Dana-Farber Cancer Institute

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

DIFFERENTIAL IMPACT OF TREATMENT TYPE ON BM MYD88^{L265P} CHANGES





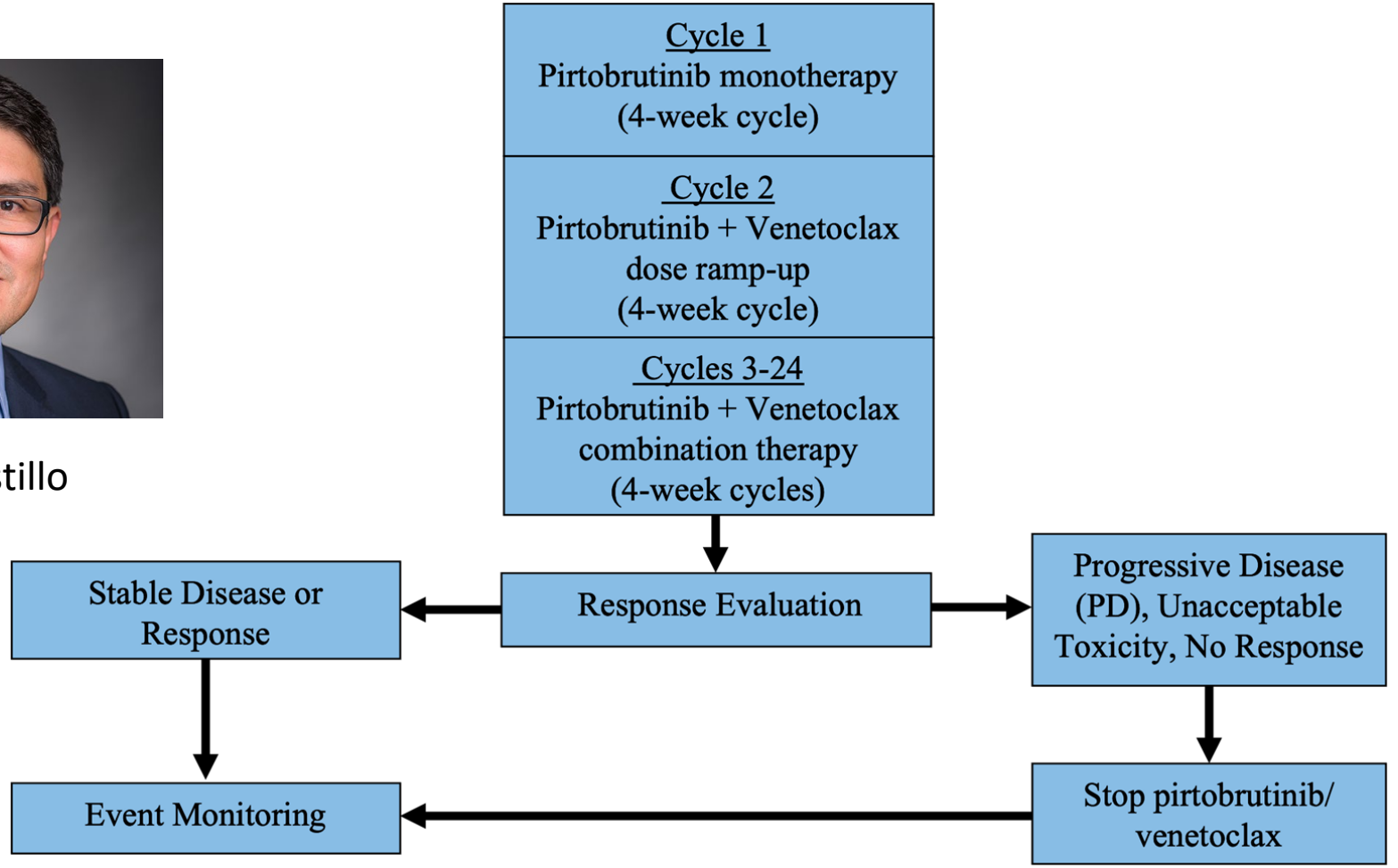


Non-Major responders: <50% reduction in serum IgM

Major responders: >= 50% reduction in serum IgM

Pirtobrutinib and Venetoclax Study in Relapsed/Refractory WM

Jorge Castillo



ClinicalTrials.gov Identifier: NCT05734495

Efficacy of Sonrotoclax as Monotherapy and Zanubrutinib

BGB-11417-101 – NHL or WM

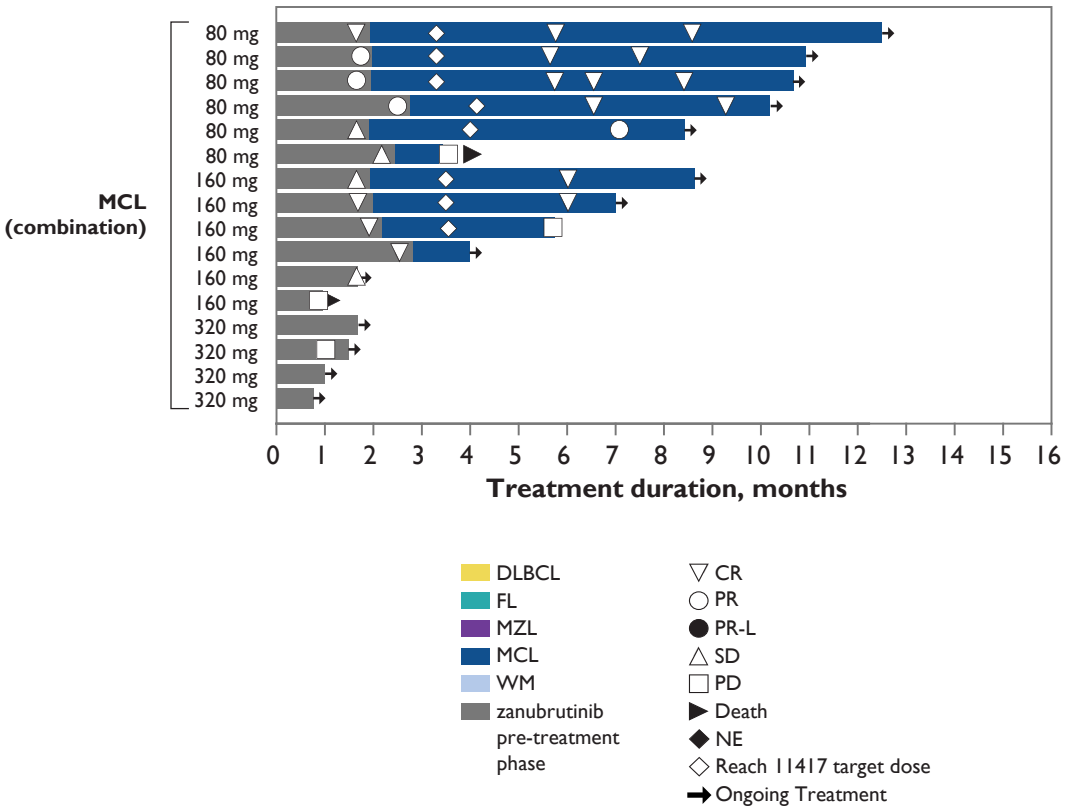
Response, n (%)	BGB-11417 monotherapy (N=43)		BGB-11417 + zanubrutinib combination (N=16)
	R/R NHL, DLBCL, MZL, FL, tFL, MCL (N=34)[a]	R/R WM (N=9)[b]	R/R MCL (N=16)[c]
Treated with BGB-11417	34	9	10
Efficacy evaluable	29[d]	7	9
Best overall response[e]	3 (10)	3 (43)	7 (78)
CR	1 (3)	0	6 (67)
PR	2 (7)	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)

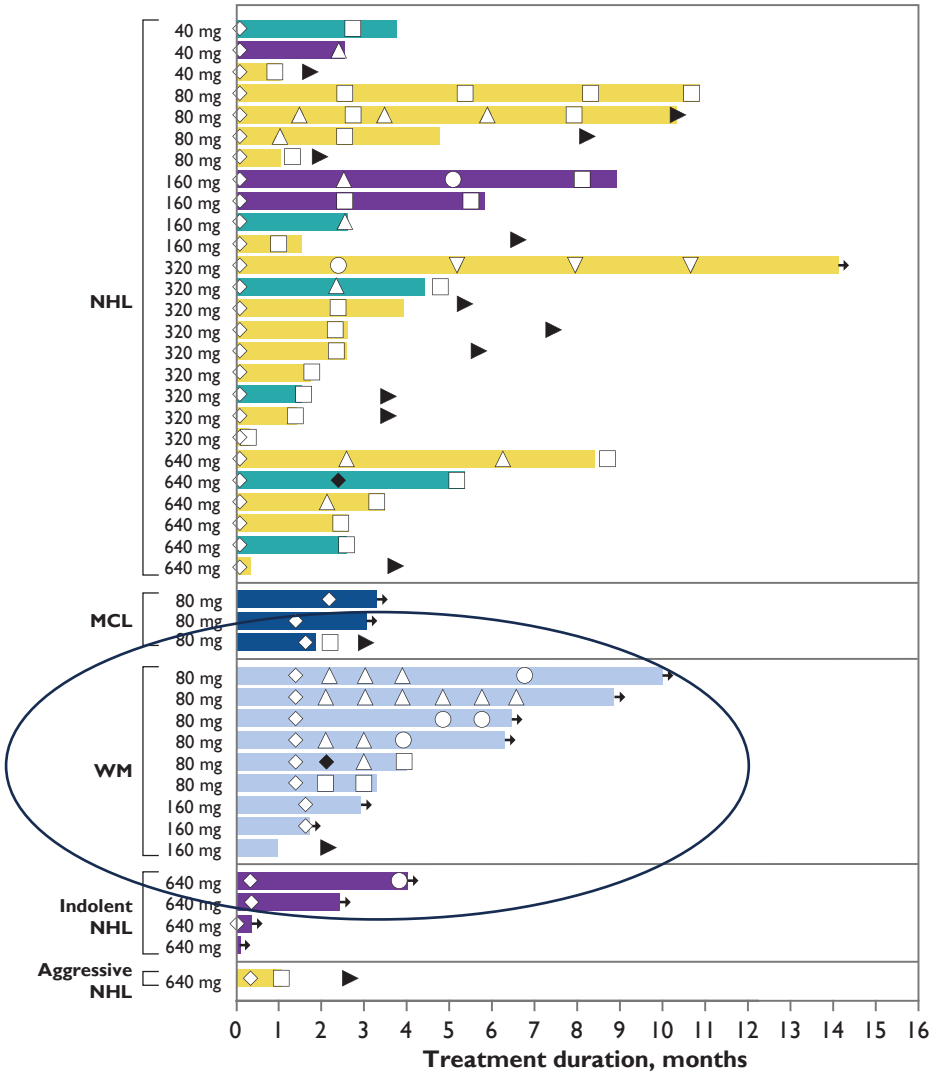
Major RR 86%

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

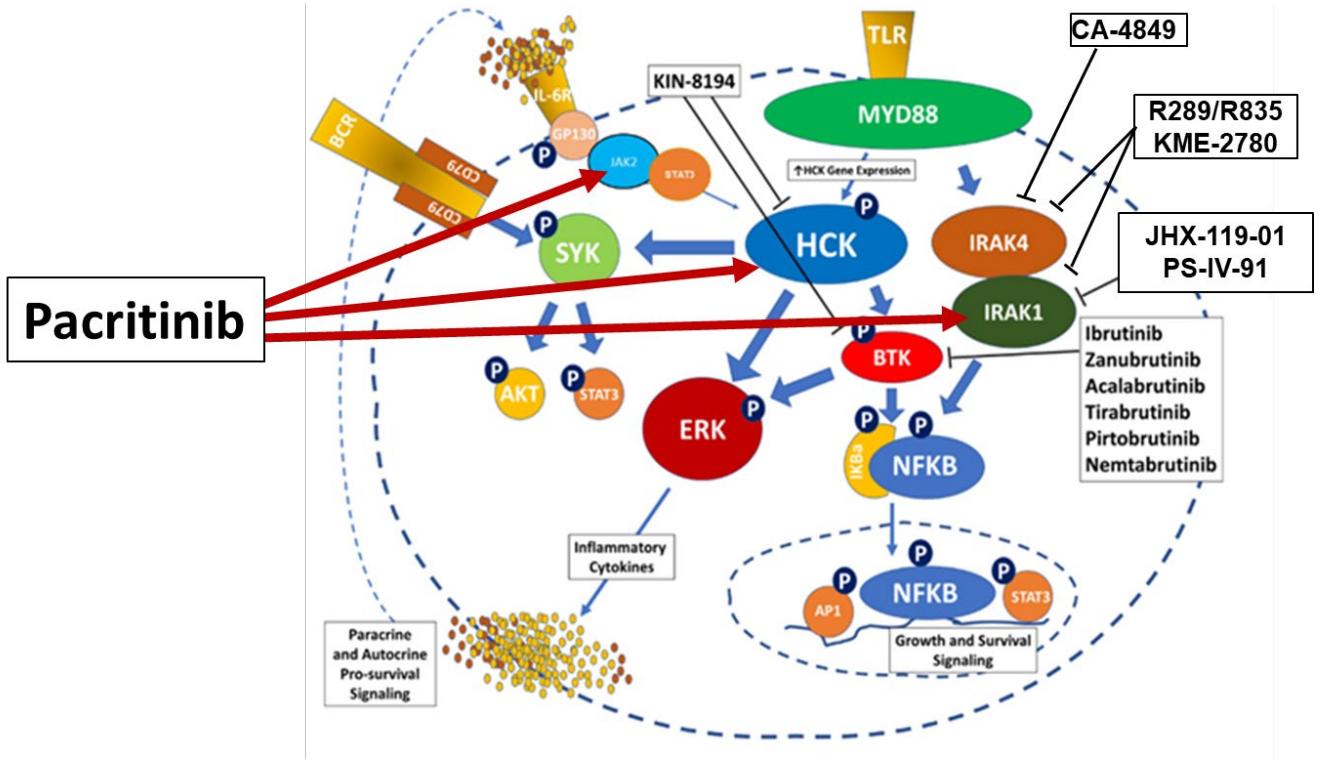


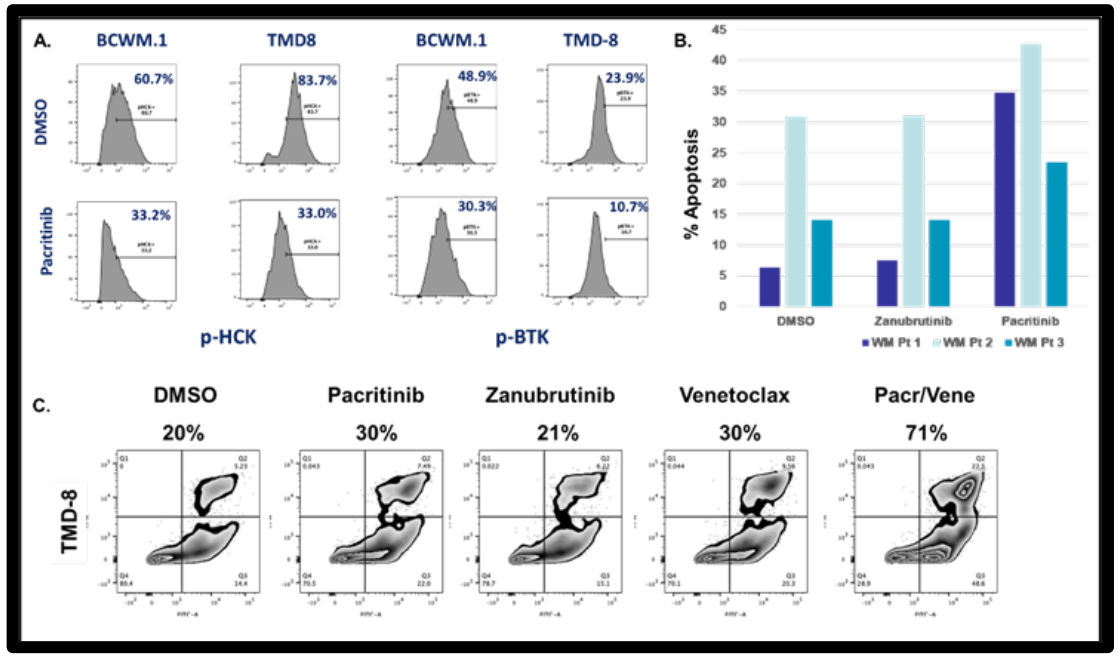


Data cutoff: 1 September 2022.
aSafety analysis set.
All received treatments were monotherapy except patients in part 3B, which were combo MCL
CR=complete response, DLBCL=diffuse large B-cell lymphoma, FL=follicular lymphoma, MCL=mantle cell lymphoma, MZL=marginal zone lymphoma, NHL=non-Hodgkin's lymphoma, 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

Novel Treatment Approaches: Pacritinib

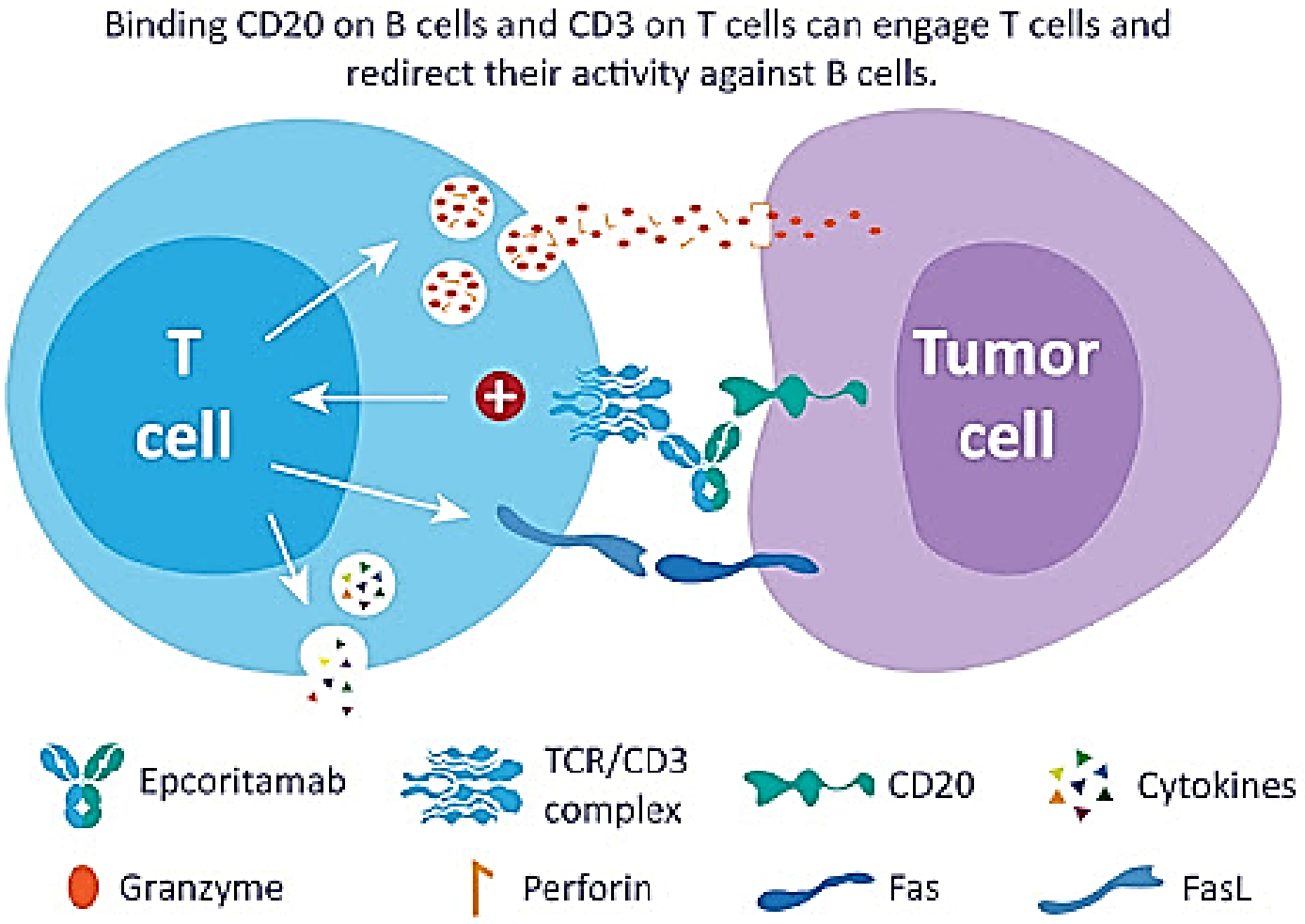
Shayna Sarosiek





Liu et al, ASH 2023

Bispecific Antibody Therapy for Waldenstrom's Macroglobulinemia



Gottfried Von Keudell

Study approved by Sponsor

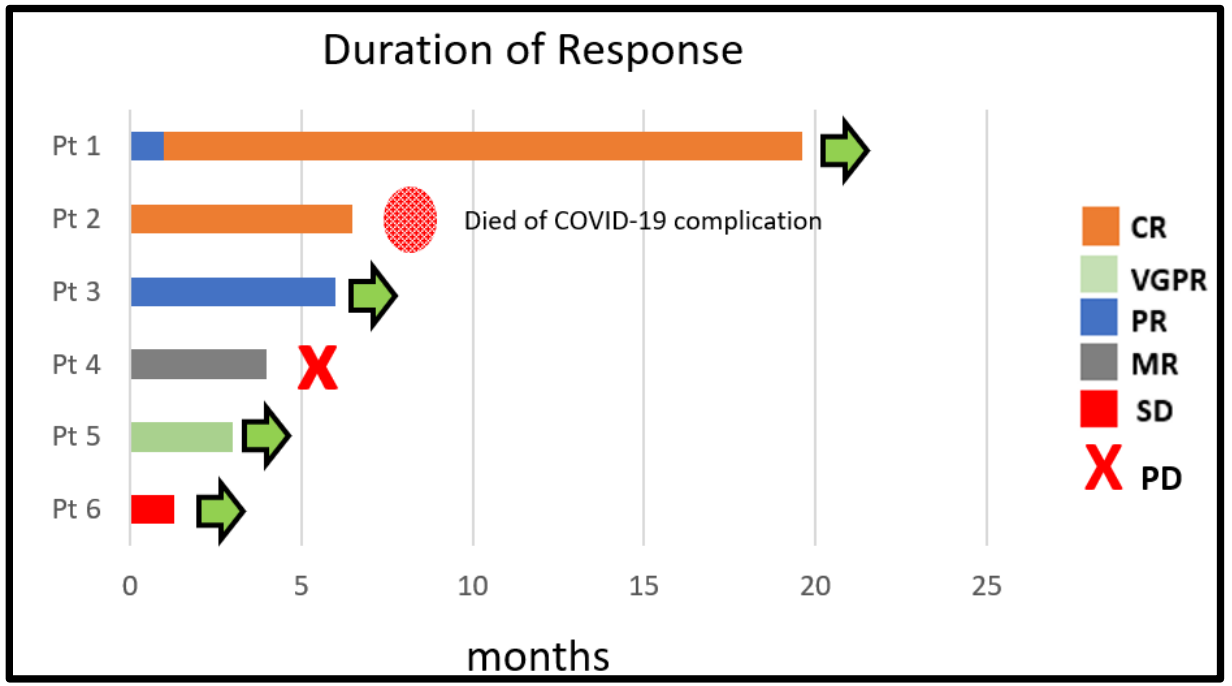
CD20 CAR-T Cell Therapy

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%



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

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

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